A SILAC-Based Approach Elicits the Proteomic Responses to Vancomycin-Associated Nephrotoxicity in Human Proximal Tubule Epithelial HK-2 Cells

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Abstract: Vancomycin, a widely used antibiotic, often induces nephrotoxicity, however, the molecular targets and underlying mechanisms of this side effect remain unclear. The present study aimed to examine molecular interactome and analyze the signaling pathways related to the vancomycin-induced nephrotoxicity in human proximal tubule epithelial HK-2 cells using the stable isotope labeling by amino acids in cell culture (SILAC) approach. The quantitative proteomic study revealed that there were at least 492 proteins interacting with vancomycin and there were 290 signaling pathways and cellular functions potentially regulated by vancomycin in HK-2 cells. These proteins and pathways played a critical role in the regulation of cell cycle, apoptosis, autophagy, EMT, and ROS generation. These findings suggest that vancomycin-induced proteomic responses in HK-2 cells involve functional proteins and pathways that regulate cell cycle, apoptosis, autophagy, and redox homeostasis. This is the first systemic study revealed the networks of signaling pathways and proteomic responses to vancomycin treatment in HK-2 cells, and the data may be used to discriminate the molecular and clinical subtypes and to identify new targets and biomarkers for vancomycin-induced nephrotoxic effect. Further studies are warranted to explore the potential of quantitative proteomic analysis in the identification of new targets and biomarkers for drug-induced renal toxicity.

Keywords: vancomycin; nephrotoxicity; SILAC; proteomics

1. Introduction

Neonatal sepsis is common and is a major cause of morbidity and mortality [1]. Vancomycin is the preferred treatment for several neonatal staphylococcal infections. It remains the primary antibiotic treatment for multi-resistant Gram-positive infections, such as methicillin-resistant Staphylococcus aureus (MRSA) and Enterococcus faecium [2]. Vancomycin pharmacokinetic estimates, which are different in neonates compared with adults, also exhibit extensive inter-neonatal variability [3]. In neonates, several vancomycin dosing schedules have been proposed, mainly based on age (i.e., postmenstrual and postnatal), body weight, or serum creatinine level. Although vancomycin has historically been linked to various toxicities, in particular nephrotoxicity, it was largely attributed to drug impurities in early formulations [4,5]. The incidence of such toxicities was drastically reduced after refinement of purification methods and the risk of nephrotoxicity was considered relatively low at less than 5% [5–7].
However, the molecular targets for vancomycin-associated nephrotoxicity are unclear. There is a lack of study which reveals the global targets of vancomycin with regard to its renal toxicity, although the characterization and identification of individual targets and related signaling pathways have provided important evidence for the mechanism of actions of vancomycin in vitro and in vivo. Stable isotope labeling by amino acids in cell culture (SILAC) is a practical and powerful approach to uncover the global proteomic responses to drug treatment and other interventions [8,9]. In particular, it can be used to systemically and quantitatively assess the target network of drugs, evaluate drug toxicity, and identify new biomarkers for the diagnosis and treatment of importance diseases such as cancer and Alzheimer’s disease [8,10,11].

In this regard, in order to uncover the comprehensive and global understanding on the effect of vancomycin, we investigated the molecular targets of vancomycin in human proximal tubule epithelial HK-2 cells with a focus on cell cycle, apoptosis, autophagy, and epithelial to mesenchymal transition (EMT) pathways.

2. Results

2.1. Overview of Proteomic Response to Vancomycin Treatment in HK-2 Cells

First, we performed a SILAC-based proteomic study to quantitatively determine the interactome of vancomycin in HK-2 cells treated with vancomycin at 50 µg/mL. There were 492 protein molecules identified as the potential targets of vancomycin in HK-2 cells (Table 1). These included a number of molecules involved in cell proliferation, cell metabolism, cell migration, cell invasion, cell survival, and cell death. Vancomycin increased the expression level of 178 protein molecules, but decreased the expression level of 314 protein molecules in HK-2 cells. Subsequently, these proteins were subject to IPA pathway analysis. A total of 486 molecular proteins were mapped using IPA (Table 2). Furthermore, as shown in and Table 3 and Figures 1 and 2 there were 290 signaling pathways and cellular functions that were potentially regulated by vancomycin in HK-2 cells. Additionally, there were 24 networks of molecular signaling pathways that were regulated in HK-2 cells when treated with vancomycin (Table 4 and Figures 3–26).

2.2. Vancomycin Alters a Number of Cellular Functions in HK-2 cells

Since we have identified numerous molecular targets which were regulated by vancomycin in HK-2 cells, we predicted the modulating effects of vancomycin on cellular functions in HK-2 cells by functional analysis using IPA software. As shown in Table 5, there were 500 categories of cellular functions which were altered by vancomycin in HK-2 cells. Treatment of vancomycin induced marked alterations in cell growth, cell proliferation, cell metabolism, cell morphology, gene expression, RNA post-translational modification, DNA replication and repair, cell-to-cell signaling and interaction, and cell death and survival. These cellular functional alterations are closely related to disease development. Notably, the functional analysis showed that vancomycin induced remarkable abnormalities in renal tissues and caused injury, probably resulting in renal tissue damage and cancer (Table 6), with the involvement of molecular proteins of AHNAK, ANLN, BASP1, EDC4, NUMA1, PDXK, PNP, SDHAF2, SMARCA4, SNRNP200, and TUBA1C. Moreover, vancomycin induced the inflammation, degradation, and fibrosis of renal tubules involving PSAP and APRT. Taken together, the functional analysis of vancomycin suggests that vancomycin has a damaging effect on cellular functions and thus cause renal injuries.
Table 1. 492 molecular proteins regulated by vancomycin in HK-2 cells.

| Protein ID | Protein Name | Gene Names                                      | Average (H/L) |
|------------|--------------|-------------------------------------------------|---------------|
| P04264     | Keratin, type II cytoskeletal 1 | KRT1                                             | 0.172905      |
| P35527     | Keratin, type I cytoskeletal 9  | KRT9                                            | 0.224193      |
| E9PCX2     | Aldose reductase                       | AKR1B1                                           | 0.272265      |
| P02751     | Fibronectin                               | FN1                                             | 0.286053      |
| Q517C4     | High mobility group protein B1         | HMGB1; HMGB1P1                                   | 0.315275      |
| Q13185     | Chromobox protein homolog 3            | CBX3                                            | 0.34326       |
| P40261     | Nicotinamide N-methyltransferase       | NNMT                                            | 0.397895      |
| P29966     | Myristoylated alanine-rich C-kinase substrate | MARCKS                                           | 0.400377      |
| F57H7V     | Tenasin                                  | TNC                                             | 0.40316       |
| Q9Y2V2     | Calcium-regulated heat stable protein 1 | CARHSP1                                         | 0.41335       |
| K7ERT7     | Synaptic vesicle membrane protein VAT-1 homolog | VAT1                                           | 0.434395      |
| P51858     | Hepatoma-derived growth factor          | HDGF                                            | 0.453443      |
| E9PEJ4     | Dihydrolipooylsine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial | DLAT                                      | 0.4645        |
| H0YK49     | Electron transfer flavoprotein subunit α, mitochondrial | ETPA                                       | 0.46645       |
| E7ES10     | Calpastatin                              | CAST                                            | 0.46797       |
| Q6830      | Peroxiredoxin-1                          | PRDX1                                           | 0.486445      |
| Q9H87I     | Calcyclin-binding protein                | CACYBP                                          | 0.49843       |
| H0YX6      | Protein arginine N-methyltransferase 5  | PRMT5                                           | 0.50622       |
| O7957      | DNAJ homolog subfamily C member 8       | DNAJC8                                          | 0.50726       |
| P49915     | GMP synthase [glutamine-hydrolyzing]    | GMP5                                           | 0.513415      |
| H0YFA4     | Cysteine-rich protein 2                 | CRIP2                                           | 0.51363       |
| P04792     | Heat shock protein β-1                  | HSPB1                                           | 0.51522       |
| E9PLK3     | Puromycin-sensitive aminopeptidase       | NPEPPS                                          | 0.535463      |
| P49773     | Histidine triad nucleotide-binding protein 1 | HINT1                                        | 0.5365        |
| Q6323      | Proteasome activator complex subunit 1  | PSME1                                          | 0.541965      |
| B8ZZQ6     | Prethymosin α                            | PTMA                                           | 0.547615      |
| Q9Y696     | Chloride intracellular channel protein 4 | CLIC4                                        | 0.55066       |
| P16403     | Histone H1.2                             | HIST1H1C; HIST1H1D; HIST1H1T; HIST1H1A          | 0.55312       |
| H7C469     | Cathepsin D                              | CTSD                                            | 0.554823      |
| Q12792     | Twinfilin-1                              | TWF1                                            | 0.55623       |
| J3KTF8     | Rho GDP-dissociation inhibitor 1         | ARHGIDIA                                        | 0.5657        |
| P28482     | Mitogen-activated protein kinase 1       | MAPK1                                           | 0.57903       |
| Q6C005     | Protein DPY-30 homolog                   | DPY30                                           | 0.57974       |
| Q9UK27     | Protein CDV3 homolog                     | CDV3                                            | 0.582217      |
| B4E022     | Transketolase                            | TKT                                            | 0.58253       |
| Q99497     | Protein DJ-1                             | PARK7                                           | 0.584365      |
| P18669     | Phosphoglycerate mutase 1                | PGAM1                                           | 0.587947      |
| P09104     | γ-Enolase                                | ENO2                                            | 0.58879       |
| Protein ID | Protein Name | Gene Names | Average (H/L) |
|------------|--------------|------------|---------------|
| P20042     | Eukaryotic translation initiation factor 2 subunit 2 | EIF2S2     | 0.60232       |
| Q01995     | Transgelin   | TAGLN      | 0.60334       |
| C9J9W2     | LIM and SH3 domain protein 1 | LASP1     | 0.60464       |
| P37837     | Transaldolase | TALDO1     | 0.60516       |
| F8VZ29     | Ubiquitin-conjugating enzyme E2 N | UBE2N     | 0.60813       |
| Q9H4M9     | EH domain-containing protein 1 | EHD1      | 0.60702       |
| Q86Q1K1    | Vacuolar protein sorting-associated protein 35 | VPS35     | 0.609495      |
| P49321     | Nuclear autoantigenic sperm protein | NASP      | 0.6098        |
| P40925     | Malate dehydrogenase, cytoplasmic | MDH1      | 0.61013       |
| P31150     | Rab GDP dissociation inhibitor α | GDP1      | 0.61355       |
| Q16836     | Hydroxyacyl-coenzyme A dehydrogenase, mitochondrial | HADH     | 0.61513       |
| P60174     | Triosephosphate isomerase | TPI1      | 0.617187      |
| Q92616     | Translational activator GCN1 | GCN1L1    | 0.62355       |
| Q99714     | 3-Hydroxyacyl-CoA dehydrogenase type-2 | HSD17B10 | 0.630585      |
| P31947     | 14-3-3 protein α | SFN       | 0.630867      |
| P12956     | X-ray repair cross-complementing protein 6 | XRCC6     | 0.63482       |
| Q00341     | Vigin        | HDLBP      | 0.63632       |
| O75367     | Core histone macro-H2A.1 | H2AFY     | 0.63646       |
| P07814     | Difunctional glutamate/proline-tRNA ligase | EPRS     | 0.6377        |
| P27016     | Microtubule-associated protein 4 | MAP4      | 0.64062       |
| P05141     | ADP/ATP translocase 2 | SLC25A5  | 0.641425      |
| Q04917     | 14-3-3 protein η | YWHAH     | 0.641525      |
| O43175     | D-3-phosphoglycerate dehydrogenase | PHGDH    | 0.644225      |
| P30086     | Phosphatidylethanolamine-binding protein 1 | PEKP1    | 0.644533      |
| Q0182      | Spectrin β chain, non-erythrocytic 1 | SPTBN1   | 0.64709       |
| Q13907     | Isopentenyl-diphosphosphate δ-isomerase 1 | IDE1    | 0.64705       |
| P53621     | Coatomer subunit α | COPA     | 0.65046       |
| O89884     | DNAJ homolog subfamily A member 2 | DNAJA2   | 0.65208       |
| Q9JNR4     | Transforming protein RhoA | RHOA     | 0.65726       |
| P11413     | Glucose-6-phosphate 1-dehydrogenase | G6PD    | 0.664673      |
| P26196     | Probable ATP-dependent RNA helicase DDX6 | DDX6 | 0.66701       |
| Q08945     | FACT complex subunit SSRP1 | SSRP1  | 0.66756       |
| Q13283     | Ras GTPase-activating protein-binding protein 1 | G3BP1 | 0.66807       |
| Q15365     | Poly(rC)-binding protein 1 | PCBP1 | 0.66967       |
| P42166     | Lamina-associated polypeptide 2, isoform α | TMPO | 0.6721        |
| K7ELL7     | Glucosidase 2 subunit β | PRKCSH | 0.67451       |
| P32119     | Peroxiredoxin-2 | PRDX2 | 0.67591       |
| P23381     | Tryptophan-tRNA ligase, cytoplasmic | WARS | 0.677045      |
| P33991     | DNA replication licensing factor MCM4 | MCM4 | 0.6794       |
| P05787     | Keratin, type II cytoskeletal 8 | KRT8 | 0.680803      |
Table 1. Cont.

| Protein ID | Protein Name                                         | Gene Names       | Average(H/L) |
|------------|------------------------------------------------------|------------------|--------------|
| C9JJ34     | Ran-specific GTPase-activating protein               | RANBP1           | 0.68427      |
| P49327     | Fatty acid synthase                                  | FASN             | 0.687997     |
| P09936     | Ubiquitin carboxyl-terminal hydrolase isozyme L1     | UCHL1            | 0.688333     |
| A2A2D0     | Stathmin                                             | STMN1            | 0.69224      |
| Q9ULV4     | Coronin-1C                                           | CORO1C           | 0.695522     |
| Q9Y4L1     | Hypoxia up-regulated protein 1                       | HYOU1            | 0.696023     |
| P07195     | l-lactate dehydrogenase B chain                      | LDHB             | 0.700453     |
| F8VWS0     | 60S acidic ribosomal protein P0                      | RPLP0            | 0.703667     |
| P25205     | DNA replication licensing factor MCM3                | MCM3             | 0.708945     |
| K7EJE8     | Lon protease homolog, mitochondrial                  | LONP1            | 0.70909      |
| P23528     | Cofilin-1                                            | CFL1             | 0.71004      |
| P07737     | Profilin-1                                           | PFN1             | 0.71163      |
| ESRW3      | Tubulin-specific chaperone A                         | TBCA             | 0.71218      |
| P63010     | AP-2 complex subunit β                               | AP2B1            | 0.714287     |
| P52209     | 6-Phosphogluconate dehydrogenase, decarboxylating   | PGD              | 0.715343     |
| O00151     | PDZ and LIM domain protein 1                         | PDLIM1           | 0.71603      |
| P36871     | Phosphoglucomutase-1                                 | PGM1             | 0.717643     |
| Q15056     | Eukaryotic translation initiation factor 4H          | EIF4H            | 0.721007     |
| P27797     | Calreticulin                                         | CALR             | 0.722223     |
| P23528     | Cofilin-1                                            | P25205           | 0.723653     |
| Q16777     | Histone H2A type 2-C                                 | HIST2H2AC; HIST2H2AA3 | 0.72469 |
| Q92973     | Transportin-1                                        | TPO1             | 0.72551      |
| O60506     | Heterogeneous nuclear ribonucleoprotein Q            | SYNCRIP          | 0.7259       |
| O14579     | Coatomer subunit ε                                   | COPE             | 0.72719      |
| P14324     | Farnesyl pyrophosphate synthase                      | FDPS             | 0.7323       |
| B4DQU5     | Ras-related protein Rab-11A                         | RAB11A; RAB1B    | 0.73251      |
| P00338     | l-lactate dehydrogenase A chain                      | LDHA             | 0.735003     |
| P24752     | Acetyl-CoA acetyltransferase, mitochondrial          | ACAT1            | 0.73511      |
| O73569     | Filamin-B                                            | FLNB             | 0.73513      |
| P14866     | Heterogeneous nuclear ribonucleoprotein L            | HNRNPL           | 0.735237     |
| B4DDD8     | Histidine—tRNA ligase, cytoplasmic                    | HARS             | 0.73643      |
| E9PBS1     | Multifunctional protein ADE2                        | PAICS            | 0.738453     |
| P42224     | Signal transducer and activator of transcription 1-α/β | STAT1            | 0.738843     |
| P30084     | Enoyl-CoA hydratase, mitochondrial                   | ECHS1            | 0.740183     |
| B7Z972     | Protein-l-isoaspartate O-methyltransferase           | PCMT1            | 0.7404       |
| P53618     | Coatomer subunit β                                   | COPB1            | 0.74088      |
| Q04760     | Lactoylglutathione lyase                             | GLO1             | 0.7413       |
| D6RG15     | Twinfilin-2                                          | TWF2             | 0.74232      |
| P40939     | Trifunctional enzyme subunit α, mitochondrial        | HADHA            | 0.744977     |
| Protein ID | Protein Name | Gene Names | Average(H/L) |
|------------|--------------|------------|--------------|
| P14618     | Pyruvate kinase PKM | PKM | 0.745617 |
| P07237     | Protein disulfide-isomerase | P4HB | 0.7458 |
| P30447     | HLA class I histocompatibility antigen, A-23 α chain | HLA-A; HLA-H; HLA-C | 0.74708 |
| Q10567     | AP-1 complex subunit β-1 | AP1B1 | 0.74868 |
| P21796     | Voltage-dependent anion-selective channel protein 1 | VDAC1 | 0.748783 |
| ES9PMH2    | Peptidyl-prolyl cis-trans isomerase | AIP | 0.75192 |
| F8VUA6     | 60S ribosomal protein L18 | RPL18 | 0.75214 |
| P06744     | Glucose-6-phosphate isomerase | GPI | 0.755337 |
| O60888     | Protein CutA | CUTA | 0.7555 |
| P35606     | Coatomer subunit β | COPB2 | 0.755705 |
| P10768     | S-formylglutathione hydrolase | ESD | 0.75572 |
| P27695     | DNA-(apurinic or apyrimidinic site) lyase | APEX1 | 0.75672 |
| P12004     | Proliferating cell nuclear antigen | PCNA | 0.75721 |
| Q6ZR64     | Proliferation-associated protein 2G4 | PA2G4 | 0.75738 |
| E7EU01     | DNA-dependent protein kinase catalytic subunit | PRKDC | 0.761483 |
| Q15185     | Prostaglandin E synthase 3 | PTGES3 | 0.762053 |
| P43243     | Matrin-3 | MATR3 | 0.763323 |
| Q6FW1      | Ubiquitin thioesterase OTUB1 | OTUB1 | 0.766887 |
| P31939     | Bifunctional purine biosynthesis protein PURH | ATIC | 0.766895 |
| Q96733     | Nucleosome assembly protein 1-like 4 | NAP1L4 | 0.769025 |
| P62191     | 26S protease regulatory subunit 4 | PSMC1 | 0.77016 |
| P40926     | Malate dehydrogenase, mitochondrial | MDH2 | 0.770383 |
| Q32Q12     | Nucleoside diphosphate kinase | NME1-NME2; NME2; NME2P1; NME1 | 0.770707 |
| P30044     | Peroxiredoxin-5, mitochondrial | PRDX5 | 0.77087 |
| P34997     | Serine hydroxymethyltransferase, mitochondrial | SHMT2 | 0.77093 |
| P08578     | Annexin A5 | ANXA5 | 0.772893 |
| P00558     | Phosphoglycerate kinase 1 | PGK1 | 0.776877 |
| Q92945     | Far upstream element-binding protein 2 | KHSRP | 0.778823 |
| Q01105     | Protein SET | SET | 0.779857 |
| F8W1N5     | Nascent polypeptide-associated complex subunit α | NACA | 0.78007 |
| P05386     | 60S acidic ribosomal protein P1 | RPL1P | 0.784843 |
| Q968D1     | Acetyl-CoA acetyltransferase, cytosolic | ACAT2 | 0.7849 |
| Q96824     | Far upstream element-binding protein 3 | FBP3 | 0.78507 |
| F8V2E1     | LIM domain and actin-binding protein 1 | LIMA1 | 0.786983 |
| O43852     | Calumenin | CALU | 0.787113 |
| Q02790     | Peptidyl-prolyl cis-trans isomerase FKBP4 | FKBP4 | 0.790175 |
| J3KN67     | Tropomyosin α-3 chain | TPM3 | 0.790573 |
Table 1. Cont.

| Protein ID | Protein Name | Gene Names | Average(H/L) |
|------------|--------------|------------|--------------|
| P00441     | Superoxide dismutase [Cu-Zn] | SOD1 | 0.79129 |
| Q15181     | Inorganic pyrophosphatase | PPA1 | 0.79164 |
| P20700     | Lamin-B1 | LMNB1 | 0.798267 |
| E9PK47     | Phosphorylase | PYGL | 0.79884 |
| P62136     | Serine/threonine-protein phosphatase PP1-α catalytic subunit | PPP1CA; PPP1CC | 0.79982 |
| P43686     | 26S protease regulatory subunit 6B | PSMC4 | 0.800465 |
| P07384     | Calpain-1 catalytic subunit | CAPN1 | 0.806005 |
| O14773     | Tripeptidyl-peptidase 1 | TPP1 | 0.807353 |
| Q14566     | DNA replication licensing factor MCM6 | MCM6 | 0.80749 |
| Q09666     | Neuroblast differentiation-associated protein AHNAK | AHNAK | 0.81098 |
| P84077     | ADP-ribosylation factor 1 | ARF1; ARF3; ARF4; ARF5 | 0.81248 |
| Q14444     | Caprin-1 | CAPRIN1 | 0.812877 |
| F5H018     | GTP-binding nuclear protein Ran | RAN | 0.813607 |
| Q92499     | ATP-dependent RNA helicase DDX1 | DDX1 | 0.81953 |
| Q99832     | T-complex protein 1 subunit η | CCT7 | 0.81562 |
| P68431     | Histone H3.1 | HIST1H3A; H3F3B; H3F3A; HIST3H3; H3F3C | 0.816783 |
| P33993     | DNA replication licensing factor MCM7 | MCM7 | 0.81733 |
| Q01518     | Adenyl cyclase-associated protein 1 | CAP1 | 0.818003 |
| P62258     | 14-3-3 protein | YWHA3E | 0.822137 |
| P63241     | Eukaryotic translation initiation factor 5A-1 | EIF5A; EIF5AL1 | 0.82674 |
| P26368     | Splicing factor U2AF 65 kDa subunit | U2F2 | 0.827353 |
| P49588     | Alanine-RNA ligase, cytoplasmic | AARS | 0.827427 |
| P24534     | Elongation factor 1-β | EEF1B2 | 0.82769 |
| P68104     | Elongation factor 1-α 1 | EEF1A1; EEF1A1P5 | 0.828823 |
| P39023     | 60S ribosomal protein L3 | RPL3 | 0.829365 |
| O75083     | WD repeat-containing protein 1 | WDR1 | 0.82946 |
| H0YL2C     | Proteasome subunit α type | PSMA4 | 0.83054 |
| P46778     | 60S ribosomal protein L21 | RPL21 | 0.83041 |
| P40227     | T-complex protein 1 subunit ζ | CCT6A | 0.83204 |
| Q14980     | Nuclear mitotic apparatus protein 1 | NUMA1 | 0.832107 |
| Q13263     | Transcription intermediary factor 1-β | TRIM28 | 0.832473 |
| P06733     | α-Enolase | ENO1 | 0.836683 |
| Q6UK76     | Hematological and neurological expressed 1 protein | HN1 | 0.833713 |
| P13010     | X-ray repair cross-complementing protein 5 | XRCC5 | 0.835137 |
| P67099     | Nucleosome-sensitive element-binding protein 1 | YBX1 | 0.83629 |
| Q13492     | Phosphatidylinositol-binding clathrin assembly protein | PICALM | 0.83656 |
| P26639     | Threonine-RNA ligase, cytoplasmic | TARS | 0.837765 |
| P30153     | Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A α isoform | PPP2R1A | 0.839417 |
| Protein ID  | Protein Name                                    | Gene Names           | Average(H/L) |
|------------|-------------------------------------------------|----------------------|--------------|
| P61978     | Heterogeneous nuclear ribonucleoprotein K       | HNRNPK               | 0.839853     |
| G3V1A1     | 60S ribosomal protein L8                        | RPL8                 | 0.83992      |
| R4GN98     | Protein S100-A6                                 | S100A6               | 0.840685     |
| P62081     | 40S ribosomal protein S7                        | RPS7                 | 0.84122      |
| P16899     | Y-box-binding protein 3                         | YBX3                 | 0.84325      |
| P67936     | Tropomyosin α-4 chain                           | TPM4                 | 0.84394      |
| P10809     | 60 kDa heat shock protein, mitochondrial        | HSPD1                | 0.84574      |
| E9PLD0     | Ras-related protein Rab-1B                     | RAB1B, RAB1C         | 0.84636      |
| P54136     | Arginine-tRNA ligase, cytoplasmic               | RAR5                 | 0.84759      |
| P50454     | Serpin H1                                       | SERPINH1             | 0.848623     |
| P11021     | 78 kDa glucose-regulated protein               | HSPA5                | 0.84892      |
| P67699     | β2-microglobulin                               | B2M                  | 0.849333     |
| FSCY37     | Prohibitin-2                                    | PHB2                 | 0.85107      |
| Q07666     | KH domain-containing, RNA-binding, signal transduction-associated protein 1 | KHDRBS1 | 0.85112 |
| P18206     | Vinculin                                        | VCL                  | 0.851217     |
| P62314     | Small nuclear ribonucleoprotein Sm D1           | SNRPD1               | 0.85213      |
| P49411     | Elongation factor Tu, mitochondrial             | TUFM                 | 0.85245      |
| H0Y4R1     | Inosine-5-monophosphate dehydrogenase 2         | IMPDH2               | 0.853715     |
| P04844     | Dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit 2 | RPN2 | 0.85403 |
| Q7IDB      | Histone H3.2                                    | HIST2H3A             | 0.854437     |
| P50995     | Rab GDP dissociation inhibitor β                | GD2                  | 0.855377     |
| Q00839     | Heterogeneous nuclear ribonucleoprotein U       | HNRNPU               | 0.8554       |
| Q13347     | Eukaryotic translation initiation factor 3 subunit I | EIF3I | 0.85975   |
| P40222     | α-Taxilin                                       | TXLNA                | 0.860857     |
| P09582     | Galectin-1                                      | LGALS1               | 0.861283     |
| Q15084     | Protein disulfide-isomerase A6                  | PDIα6                | 0.861437     |
| Q14247     | Src substrate cortactin                        | CTN                  | 0.86161      |
| P21333     | Filamin-A                                       | FLNA                 | 0.86397      |
| O14818     | Proteasome subunit α type-7                     | PSMA7; PSMA8         | 0.86409      |
| P13667     | Protein disulfide-isomerase A4                  | PDIα4                | 0.86544      |
| Q9UMS4     | Pre-mRNA-processing factor 19                   | PRPF19               | 0.866023     |
| E7EPW6     | Programmed cell death protein 6                 | PDCD6                | 0.87172      |
| E9PRI1     | Thioredoxin reductase 1, cytoplasmic            | TXNRD1               | 0.872513     |
| Q9UXH1     | Poly(U)-binding-splicing factor PUF60           | PUF60                | 0.872915     |
| P03556     | Integrin β-1                                    | ITGB1                | 0.873165     |
| P41021     | Macrophage-capping protein                      | CAPG                 | 0.87371      |
| Q03135     | Caveolin-1                                      | CAV1                 | 0.87427      |
| P13797     | Plastin-3                                       | PLS3                 | 0.87507      |
| P27824     | Calnexin                                        | CANX                 | 0.87692      |
### Table 1. Cont.

| Protein ID | Protein Name | Gene Names | Average(H/L) |
|------------|--------------|------------|--------------|
| Q15019     | Septin-2     |            | 0.87721      |
| Q9UNZ2     | NSFL1 cofactor p47 | NSFL1C | 0.878297     |
| Q9YSB9     | FACT complex subunit SPT16 | SUPT16H | 0.879483     |
| B1AK85     | F-actin-capping protein subunit β | CAPZB | 0.88193      |
| P68133     | Actin, α skeletal muscle | ACTA1; ACTC1; ACTG2; ACTA2 | 0.88416      |
| P06493     | Cyclin-dependent kinase 1 | CDK1 | 0.88483      |
| Q3ZCM7     | Tubulin β-8 chain | TUBB8 | 0.88649      |
| P07858     | Cathepsin B |            | 0.889247     |
| Q16555     | Dihydropyrimidinase-related protein 2 | DFPYS1L2 | 0.88961      |
| P63104     | 14-3-3 protein Ł/δ | YWHAZ | 0.890777     |
| Q14697     | Neutral α-glucosidase AB | GANAB | 0.89087      |
| P05783     | Keratin, type I cytoskeletal 18 | KRT18 | 0.891143     |
| P26640     | Valine-tRNA ligase | VAR5 | 0.89307      |
| B4DUR8     | T-complex protein 1 subunit γ | CCT3 | 0.895913     |
| Q96P70     | Importin-9 |            | 0.89849      |
| Q7KZF4     | Staphylococcal nuclease domain-containing protein 1 | SND1 | 0.899653     |
| Q16643     | Drebrin |            | 0.90207      |
| P35579     | Myosin-9 |            | 0.90543      |
| P22626     | Heterogeneous nuclear ribonucleoproteins A2/B1 | HNRNPA2B1 | 0.907457     |
| Q15942     | Zyxin |            | 0.909143     |
| Q9NQC3     | Reticulon-4 | RTN4 | 0.90961      |
| P07108     | Acyl-CoA-binding protein | DBI | 0.91033      |
| P11216     | Glycogen phosphorylase, brain form | PYGB | 0.914587     |
| A6PVH9     | Copine-1 |            | 0.914685     |
| O14980     | Exportin-1 | XPO1 | 0.91646      |
| P04075     | Fructose-bisphosphate aldolase A | ALDOA | 0.917223     |
| O43390     | Heterogeneous nuclear ribonucleoprotein R | HNRNPR | 0.91729     |
| P61158     | Actin-related protein 3 | ACTR3 | 0.91757      |
| P13639     | Elongation factor 2 | EEF2 | 0.918273     |
| P07942     | Laminin subunit β-1 | LAMB1 | 0.91949      |
| P31948     | Stress-induced-phosphoprotein 1 | STIP1 | 0.920767     |
| Q14204     | Cytoplasmic dynein 1 heavy chain 1 | DYNCL1H1 | 0.92284     |
| O60664     | Perilipin-3 | PLIN3 | 0.92903      |
| P62158     | Calmodulin | CALM1; CALM2; CALM3 | 0.923537     |
| Q96Q26     | Sodium-coupled neutral amino acid transporter 2 | SLC38A2 | 0.92438      |
| Q92575     | UBX domain-containing protein 4 | UBXN4 | 0.924495     |
| M0R0F0     | Annexin A6 | ANXA6 | 0.92615      |
| P08133     | 40S ribosomal protein S5 | RPS5 | 0.92887      |
| P62906     | 60S ribosomal protein L10a | RPL10A | 0.930083     |
Table 1. Cont.

| Protein ID | Protein Name                                      | Gene Names | Average(H/L) |
|------------|--------------------------------------------------|------------|--------------|
| O15144     | Actin-related protein 2/3 complex subunit 2      | ARPC2      | 0.932825     |
| Q9Y490     | Talin-1                                           | TLN1       | 0.933233     |
| P04406     | Glyceraldehyde-3-phosphate dehydrogenase          | GAPDH      | 0.934323     |
| P25786     | Proteasome subunit α type-1                      | PSMA1      | 0.93491      |
| P25787     | Proteasome subunit α type-2                      | PSMA2      | 0.93574      |
| P34932     | Heat shock 70 kDa protein 4                      | HSPA4      | 0.935983     |
| E7EQR4     | Ezrin                                             | EZR        | 0.93788      |
| P46777     | 60S ribosomal protein L5                          | RPL5       | 0.939327     |
| P05387     | 60S acidic ribosomal protein P2                   | RPLP2      | 0.94137      |
| P25398     | 40S ribosomal protein S12                         | RPS12      | 0.941813     |
| P42704     | Leucine-rich PPR motif-containing protein, mitochondrial | LRPPRC | 0.944687     |
| P55072     | Transitional endoplasmic reticulum ATPase        | VCP        | 0.945267     |
| P62937     | Peptidyl-prolyl cis-trans isomerase A            | PPLA       | 0.94628      |
| P68863     | Tubulin α-1B chain                                | TUBA1B     | 0.94723      |
| P10628     | Interferon-induced transmembrane protein 3       | IFITM3     | 0.950665     |
| P00299     | Chloride intracellular channel protein 1          | CLIC1      | 0.952683     |
| P30304     | Endoplasmic reticulum resident protein 29        | ERP29      | 0.954027     |
| Q8N8S7     | Protein enabled homolog                           | ENAH       | 0.954545     |
| P41252     | Isoleucine-tRNA ligase, cytoplasmic              | IARS       | 0.95526      |
| P61981     | 14-3-3 protein γ                                 | YWHA G     | 0.9565       |
| F8VPF3     | Myosin light polypeptide 6                        | MYL6       | 0.95902      |
| O00571     | ATP-dependent RNA helicase DDX3X                 | DDH3X; DDH3Y | 0.959895   |
| P45880     | Voltage-dependent anion-selective channel protein 2 | VDAC2 | 0.960875    |
| P19338     | Nucleolin                                        | NCL        | 0.963977     |
| P14625     | Endoplasm                                        | HSP90B1    | 0.96355      |
| O43707     | α-Actinin-4                                      | ACTN4      | 0.968487     |
| Q5J53      | Tubulin β chain                                  | TUBB       | 0.971493     |
| Q13409     | Cytoplasmatic dynein 1 intermediate chain 2      | DYNC1H2    | 0.976747     |
| P55060     | Exportin-2                                       | CSE1L      | 0.978383     |
| Q13838     | Spliceosome RNA helicase DDX39B                  | DDX39B     | 0.979103     |
| P02786     | Transferrin receptor protein 1                   | TFRC       | 0.982483     |
| P00387     | NADH-cytochrome b5 reductase 3                   | CYB5R3     | 0.98267      |
| Q79497     | ATP synthase subunit d, mitochondrial             | ATP5H      | 0.985415     |
| G8LJ5     | Dynamin-1-like protein                           | DNM1L      | 0.98906      |
| P04808     | Cystatin-B                                       | CSTB       | 0.98954      |
| P05198     | Eukaryotic translation initiation factor 2 subunit 1 | EIF2S1 | 0.98961      |
| Q9UL46     | Proteasome activator complex subunit 2           | PSME2      | 0.990545     |
| P55884     | Eukaryotic translation initiation factor 3 subunit B | EIF3B  | 0.991517     |
| P46783     | 40S ribosomal protein S10                        | RPS10; RPS10P5 | 0.99156     |
| Protein ID | Protein Name | Gene Names | Average(H/L) |
|-----------|--------------|------------|--------------|
| F2Z2Y4    | Pyridoxal kinase | PDXK       | 0.99206      |
| P09211    | Glutathione S-transferase P | GSTP1 | 0.992743    |
| P38646    | Stress-70 protein, mitochondrial | HSPA9 | 0.995527    |
| P80723    | Brain acid soluble protein 1 | BASP1 | 0.998527    |
| Q15143    | Actin-related protein 2/3 complex subunit 1B | ARPC1B | 1.003 |
| Q8NC51    | Plasminogen activator inhibitor 1 RNA-binding protein | SERBP1 | 1.003403   |
| P54727    | UV excision repair protein RAD23 homolog B | RAD23B | 1.005245   |
| P51991    | Heterogeneous nuclear ribonucleoprotein A3 | HNRNPA3 | 1.006415   |
| P07355    | Annexin A2 | ANXA2; ANXA2P2 | 1.007367   |
| P23246    | Splicing factor, proline- and glutamine-rich | SFPQ | 1.009463    |
| P08107    | Heat shock 70 kDa protein 1A/1B | HSPA1A | 1.01165     |
| P67775    | Serine/threonine-protein phosphatase 2A catalytic subunit α isoform | PPP2CA; PPP2CB | 1.011925   |
| P21291    | Cysteine and glycine-rich protein 1 | CSR1 | 1.01607     |
| P28066    | Proteasome subunit α type-5 | PSMA5 | 1.01847     |
| P68036    | Ubiquitin-conjugating enzyme E2 L3 | UBE2L3 | 1.02085     |
| Q9BUF5    | Tubulin β-6 chain | TUBB6 | 1.021827    |
| Q15459    | Splicing factor 3A subunit 1 | SF3A1 | 1.02408     |
| Q9P0L0    | Vesicle-associated membrane protein-associated protein A | VAPA | 1.026153   |
| C9JD32    | 60S ribosomal protein L23 | RPL23 | 1.026225   |
| P15293    | Reticulocalbin-1 | RCN1 | 1.02665     |
| P55735    | Protein SEC13 homolog | SEC13 | 1.02911     |
| Q99880    | Histone H2B type 1-L. | HIST1H2BL; HIST1H2BM; HIST1H2BN; HIST1H2BH; HIST2H2BF; HIST1H2BC; HIST1H2BD; H2BFS; HIST1H2BK | 1.02927   |
| D6RFM5    | Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial | SDHA | 1.034553   |
| P46821    | Microtubule-associated protein 1B | MAP1B | 1.03558     |
| Q5W0X3    | Peptidyl-prolyl cis-trans isomerase | FKBP1A | 1.03589   |
| K7EKO7    | Histone H3 | H3F3B; H3F3A | 1.037015   |
| P52272    | Heterogeneous nuclear ribonucleoprotein M | HNRNPM | 1.03914   |
| P50523    | Sodium/potassium-transporting ATPase subunit α-1 | ATP1A1; ATP1A3 | 1.043157   |
| P36578    | 60S ribosomal protein L4 | RPL4 | 1.044293   |
| P08238    | Heat shock protein HSF 90-β | HSP90AB1 | 1.044997   |
| P68371    | Tubulin β-4B chain | TUBB4B | 1.045547   |
| Q01081    | Splicing factor U2AF 35 kDa subunit | U2AF1; U2AF1L4 | 1.0472   |
| P35637    | RNA-binding protein FUS | FUS | 1.049003   |
| P56192    | Methionine-tRNA ligase, cytoplasmic | MARS | 1.0493   |
| P06576    | ATP synthase subunit β, mitochondrial | ATP5B | 1.049537   |
| P04083    | Annexin A1 | ANXA1 | 1.0517   |
Table 1. Cont.

| Protein ID | Protein Name | Gene Names | Average(H/L) |
|------------|--------------|------------|--------------|
| P41250     | Glycine-tRNA ligase | GARS       | 1.05216      |
| Q13813     | Spectrin α chain, non-erythrocytic 1 | SPTAN1     | 1.0563       |
| Q9Y678     | Coatomer subunit γ-1 | COPG1      | 1.0569       |
| M1Q256     | SUMO-activating enzyme subunit 1 | SAE1       | 1.0578       |
| Q9UHD8     | Septin-9 |           | 1.063053     |
| P31946     | 14-3-3 protein β/α | 42236      | 1.063833     |
| P63261     | Actin, cytoplasmic 2 | ACTG1      | 1.063967     |
| P13489     | Ribonuclease inhibitor | RNIH1      | 1.064393     |
| P47897     | Glutamine-tRNA ligase | QARS       | 1.0658       |
| B4DJV2     | Citrate synthase | CS         | 1.0662       |
| P04843     | Dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit 1 | RPN1      | 1.066757     |
| Q14974     | Importin subunit β-1 | KPNB1      | 1.072667     |
| Q15121     | Astrocytic phosphoprotein PEA-15 | PEA15      | 1.072933     |
| Q9NYL19    | Tropomodulin-3 |           | 1.0755       |
| O00410     | Importin-5 |           | 1.0767       |
| P26038     | Moesin |           | 1.07813      |
| Q9P2E9     | Ribosome-binding protein 1 | RRPB1      | 1.081993     |
| P68402     | Platelet-activating factor acetylhydrolase IB subunit β | PAFAH1B2   | 1.0887       |
| H0YEN5     | 40S ribosomal protein S2 | RPS2       | 1.091785     |
| Q5VU59     |          |           | 1.0933       |
| P02545     | Prelamin-A/C | LMNA       | 1.095077     |
| P35221     | Catenin α-1 | CTNNA1     | 1.09635      |
| Q08211     | ATP-dependent RNA helicase A | DHX9      | 1.096937     |
| P50991     | T-complex protein 1 subunit δ | CCT4      | 1.103        |
| O60493     | Sorting nexin-3 | SNX3       | 1.1169       |
| P61160     | Actin-related protein 2 | ACTR2      | 1.1175       |
| O95433     | Activator of 90 kDa heat shock protein ATPase homolog 1 | AHSA1      | 1.1199       |
| P62805     | Histone H4 |           | 1.1241       |
| P18465     | HLA class I histocompatibility antigen, B-57 α chain | HLA-B      | 1.12765      |
| Q8TAT6     | Nuclear protein localization protein 4 homolog | NPLC4      | 1.135        |
| P46940     | Ras GTPase-activating-like protein IQGAP1 | IQGAP1     | 1.135853     |
| P09972     | Fructose-bisphosphate aldolase C | ALDOC      | 1.1406       |
| P62424     | 60S ribosomal protein L7a | RPL7A      | 1.14125      |
| Q00610     | Clathrin heavy chain 1 | CLTC       | 1.14213     |
| Q15355     | Protein phosphatase 1G | PPM1G      | 1.1437       |
| Q16222     | UDP-N-acetylhexosamine pyrophosphorylase | UAP1       | 1.145295     |
| P25705     | ATP synthase subunit α, mitochondrial | ATP5A1     | 1.14579      |
| E7ETU9     | Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 | PLOD2      | 1.150217     |
| K7E7J8     | 40S ribosomal protein S15 | RPS15      | 1.1525       |
Table 1. Cont.

| Protein ID   | Protein Name                                      | Gene Names          | Average(H/L) |
|--------------|---------------------------------------------------|---------------------|--------------|
| P52292       | Importin subunit α-1                             | KPNAA2              | 1.153933     |
| Q15417       | Calponin-3                                        | CNN3                | 1.154837     |
| E7ETK0       | 4OS ribosomal protein S24                         | RPS24               | 1.1574       |
| F51149       | Ras-related protein Rab-7a                       | RAB7A               | 1.158243     |
| Q9NTK5       | OBG-like ATPase 1                                 | OLA1                | 1.1594       |
| Q5UBX0       | β-Hexosaminidase subunit β                        | HEXB                | 1.159533     |
| P12814       | α-Actinin-1                                       | ACTN1               | 1.165233     |
| F8VVM2       | Phosphate carrier protein, mitochondrial          | SLC25A3             | 1.165257     |
| Q9Y224       | UPF0568 protein C14orf166                         | C14orf166           | 1.1655       |
| P06748       | Nucleophosmin                                     | NPM1                | 1.1659       |
| P30101       | Protein disulfide-isomerase A3                    | PDIA3               | 1.167067     |
| P26641       | Elongation factor 1-γ                             | EEF1G               | 1.1681       |
| P78371       | T-complex protein 1 subunit β                     | CCT2                | 1.169767     |
| F8VY35       | Nucleosome assembly protein 1-like 1              | NAP1L1              | 1.17258      |
| P56537       | Eukaryotic translation initiation factor 6        | EIF6                | 1.172633     |
| E7EV56       | Pericentriolar material 1 protein                 | PCM1                | 1.1749       |
| P26599       | Polypyrimidine tract-binding protein 1             | PTBP1               | 1.1785       |
| P27348       | 14-3-3 protein δ                                  | YWHAQ               | 1.180407     |
| P22314       | Ubiquitin-like modifier-activating enzyme 1       | UBA1                | 1.182133     |
| D6RG13       | 40S ribosomal protein S3a                         | RPS3A               | 1.184367     |
| P00567       | Glutamate dehydrogenase 1, mitochondrial          | GLUD1; GLUD2        | 1.1844       |
| E8PNW4       | CD59 glycoprotein                                 | CD59                | 1.1867       |
| P11717       | Cation-independent mannose-6-phosphate receptor   | IGF2R               | 1.1869       |
| P17987       | T-complex protein 1 subunit α                     | TCP1                | 1.1904       |
| P60842       | Eukaryotic initiation factor 4A-1                 | EIF4A1              | 1.191733     |
| P04632       | Calpain small subunit 1                          | CAPNS1              | 1.19265      |
| P07900       | Heat shock protein HSP 90-α                       | HSP90A1             | 1.195633     |
| P20618       | Proteasome subunit β type-1                      | PSMB1               | 1.2078       |
| J3KPE3       | Guanine nucleotide-binding protein subunit β-2-like 1 | GNB2L1             | 1.209467     |
| P35613       | Basigin                                           | BSG                 | 1.21668      |
| P31930       | Cytochrome b-c1 complex subunit 1, mitochondrial  | UQRC1               | 1.217533     |
| P31942       | Heterogeneous nuclear ribonucleoprotein H3       | HNRNPH3             | 1.223433     |
| E9PCY7       | Heterogeneous nuclear ribonucleoprotein H         | HNRNPH1             | 1.2236       |
| F8W7C6       | Complement component 1 Q subcomponent-binding protein, mitochondrial | RPL10             | 1.225633     |
| Q07021       | Leucine-rich repeat-containing protein 59         | C1QBP               | 1.2273       |
| Q96AG4       | Leucine-rich repeat-containing protein 59         | LRRCS9              | 1.227793     |
| Q14315       | Filamin-C                                         | FLNC                | 1.2332       |
| P48643       | T-complex protein 1 subunit ε                     | CCT5                | 1.234767     |
| E7EQV3       | Polyadenylate-binding protein 1                   | PABPC1; PABPC4      | 1.235133     |
Table 1. Cont.

| Protein ID | Protein Name | Gene Names                              | Average(H/L) |
|------------|--------------|-----------------------------------------|--------------|
| P62701     | 40S ribosomal protein S4, X isoform | RPS4X        | 1.2362       |
| P29692     | Elongation factor 1-δ              | EEF1D        | 1.239133     |
| P33396     | ATP-citrate synthase               | ACLY         | 1.241963     |
| Q12906     | Interleukin enhancer-binding factor 3 | ILF3    | 1.245833     |
| P23396     | 40S ribosomal protein S3           | RPS3         | 1.2509       |
| P50990     | T-complex protein 1 subunit 0      | CCT8         | 1.257        |
| P11142     | Heat shock cognate 71 kDa protein  | HSPA8        | 1.258433     |
| Q12905     | Interleukin enhancer-binding factor 2 | ILF2    | 1.2642       |
| H0Y3Y4     | Septin-7                          | 42254        | 1.2656       |
| F8VZX2     | Poly(rC)-binding protein 2         | PCBP2        | 1.265963     |
| C9JK3      | 40S ribosomal protein SA           | RPSA; RPSAP58 | 1.2668       |
| P55550     | Myosin-10                          | MYH10        | 1.275133     |
| P23326     | Adenosylhomocysteinase             | AHCY         | 1.276        |
| P30050     | 60S ribosomal protein L12          | RPL12        | 1.287833     |
| H3BT13     | Small nuclear ribonucleoprotein Sm D3| SNRPD3    | 1.288        |
| I7HJ10     | ADP/ATP translocase 3              | SLC25A6; SLC25A4 | 1.30365     |
| E7EMC7     | Sequestosome-1                     | SQSTM1       | 1.3099       |
| P52907     | F-actin-capping protein subunit α-1 | CAPZA1 | 1.3127       |
| Q01813     | 6-Phosphofructokinase type C       | PFKP         | 1.312933     |
| Q02878     | 60S ribosomal protein L6           | RPL6         | 1.3141       |
| P19105     | Myosin regulatory light chain 12A  | MYL12A; MYL12B; MYL9 | 1.315967 |
| Q14019     | Coactosin-like protein              | COL1         | 1.318367     |
| Q57C18     | Transcription factor BTF3           | LMNA         | 1.318467     |
| P20290     |                                      | BTF3         | 1.324333     |
| Q9UZI1     | Stomatin-like protein 2, mitochondrial | STOML2 | 1.3251       |
| Q15149     | Plectin                            | PLEC         | 1.325767     |
| Q57U65     | Surfeit locus protein 4             | SURF4        | 1.3268       |
| F8W67T     | Heterogeneous nuclear ribonucleoprotein A1 | HNRNPA1; HNRNPA1L2 | 1.329333 |
| J3QX4X     | Miotic checkpoint protein BUB3      | BUB3         | 1.3315       |
| P33176     | Kinesin-1 heavy chain               | KIF5B        | 1.3317       |
| P62280     | 40S ribosomal protein S11           | RPS11        | 1.33505      |
| P17812     | CTP synthase 1                      | CTPS1        | 1.3383       |
| P35268     | 60S ribosomal protein L22           | RPL22        | 1.338767     |
| Q13200     | 26S proteasome non-ATPase regulatory subunit 2 | PSMD2 | 1.33905     |
| P18124     | 60S ribosomal protein L7            | RPL7         | 1.340267     |
| Q13162     | Peroxiredoxin-4                    | PRDX4        | 1.3457       |
| O95373     | Importin-7                         | IPO7         | 1.351167     |
| O75533     | Splicing factor 3B subunit 1        | SF3B1        | 1.35925      |
| O00622     | Protein CYR61                       | CYR61        | 1.36705      |
Table 1. Cont.

| Protein ID   | Protein Name                                                  | Gene Names               | Average (H/L) |
|--------------|---------------------------------------------------------------|--------------------------|---------------|
| P61353       | 60S ribosomal protein L27                                     | RPL27                    | 1.373033      |
| Q15233       | Non-POU domain-containing octamer-binding protein             | NONO                     | 1.3738        |
| Q99613       | Eukaryotic translation initiation factor 3 subunit C          | EIF3C; EIF3CL            | 1.37415       |
| P08574       | Cytochrome c1, heme protein, mitochondrial                    | CYC1                     | 1.37425       |
| P98179       | Putative RNA-binding protein 3                                | RBM3                     | 1.37635       |
| P17655       | Calpain-2 catalytic subunit                                   | CAPN2                    | 1.386833      |
| Q86UY0       | Thioredoxin domain-containing protein 5                       | TXNDC5                   | 1.390233      |
| P62979       | Ubiquitin-40S ribosomal protein S27a                          | RPS27A; UBB; UBC; UBA52; UBBP4 | 1.399267     |
| Q86VP6       | Cullin-associated NEDD8-dissociated protein 1                 | CAND1                    | 1.4086        |
| Q15691       | Microtubule-associated protein RP/EB family member 1         | MAPRE1                   | 1.4179        |
| Q7L2H7       | Eukaryotic translation initiation factor 3 subunit M          | EIF3M                    | 1.45085       |
| E7EX73       | Eukaryotic translation initiation factor 4 γ 1                 | EIF4G1                   | 1.4581        |
| X1I28        | 60S ribosomal protein L10                                     | RPL10                    | 1.4608        |
| P17844       | Probable ATP-dependent RNA helicase DDX5                     | DDX5                     | 1.470067      |
| P04899       | Guanine nucleotide-binding protein G4 subunit α-2             | GNAI2                    | 1.5439        |
| Q16891       | Mitochondrial inner membrane protein                          | IMMT                     | 1.5646        |
| P08670       | Vimentin                                                      | VIM                      | 1.578767      |
| P62241       | 40S ribosomal protein S8                                      | RPS8                     | 1.5809        |
| Q14764       | Major vault protein                                           | MVP                      | 1.63639       |
| P31689       | DNAJ homolog subfamily A member 1                             | DNAJA1                   | 1.6699        |
| Q9H299       | SH3 domain-binding glutamic acid-rich-like protein 3          | SH3BGR3L                 | 1.68785       |
| Q07065       | Cytoskeleton-associated protein 4                              | CKAP4                    | 1.728867      |
| Q86V81       | THO complex subunit 4                                         | AYREF                    | 1.7965        |
| QSTCU3       | Tropomyosin β chain                                           | TPM2                     | 1.8451        |
| O00505       | Importin subunit α-4                                          | KPN4A3                   | 2.1267        |
| Q6NZ2Z       | Polymerase I and transcript release factor                    | PTRF                     | 2.1653        |
| H0YD13       | CD44 antigen                                                  | CD44                     | 2.2206        |
| Q9BJ8J       | Extended synaptotagmin-1                                     | ESYT1                    | 2.36957       |
| P10619       | Lysosomal protective protein                                  | CTSA                     | 3.0967        |
Table 2. 486 mapped molecular proteins by IPA.

| ID   | Symbol | Entrez Gene Name                      | Location       | Type(s)            | Fold Change |
|------|--------|--------------------------------------|----------------|--------------------|-------------|
| P49588 | AARS  | Alanyl-tRNA synthetase               | Cytoplasm      | Enzyme             | −1.209      |
| P24752 | ACAT1 | Acetyl-CoA acetyltransferase 1       | Cytoplasm      | Enzyme             | −1.360      |
| Q9BWD1 | ACAT2 | Acetyl-CoA acetyltransferase 2       | Cytoplasm      | Enzyme             | −1.274      |
| P53396 | ACLY  | ATP citrate lyase                    | Cytoplasm      | Enzyme             | 1.242       |
| P81333 | ACTA1 | Actin, α 1, skeletal muscle          | Cytoplasm      | Other              | −1.131      |
| P63261 | ACTG1 | Actin, γ 1                           | Cytoplasm      | Other              | 1.064       |
| P12814 | ACTN1 | Actinin, α 1                         | Cytoplasm      | Other              | 1.165       |
| O43707 | ACTN4 | Actinin, α 4                         | Cytoplasm      | Other              | −1.033      |
| P61160 | ACTR2 | ARP2 actin-related protein 2 homolog (yeast) | Plasma Membrane | Other              | 1.118       |
| P61158 | ACTR3 | ARP3 actin-related protein 3 homolog (yeast) | Plasma Membrane | Other              | −1.090      |
| P23526 | AHCY  | Adenosinehomocysteinase              | Cytoplasm      | Enzyme             | 1.276       |
| Q96666 | AHNK  | AHNK nucleoprotein                   | Nucleus        | Other              | −1.233      |
| O95433 | AHS A1| AHA1, activator of heat shock 90 kDa protein ATPase homolog 1 (yeast) | Cytoplasm      | Other              | 1.120       |
| E9PMH2 | AIP   | Aryl hydrocarbon receptor interacting protein | Nucleus        | Transcription regulator | −1.330     |
| E9PCX2 | AKR1B1| Aldo-keto reductase family 1, member B1 (aldo reductase) | Cytoplasm      | Enzyme             | −3.673      |
| P30475 | ALDOA | Aldolase A, fructose-bisphosphate    | Cytoplasm      | Enzyme             | −1.090      |
| P09972 | ALDOC | Aldolase C, fructose-bisphosphate    | Cytoplasm      | Enzyme             | 1.141       |
| Q86811 | APEX1 | APEX nuclease (multifunctional DNA repair enzyme) 1 | Nucleus        | Enzyme             | −1.321      |
| P04083 | ANXA1 | Annexin A1                          | Plasma Membrane| Enzyme             | 1.052       |
| P07355 | ANXA2 | Annexin A2                          | Plasma Membrane| Other              | 1.007       |
| P06785 | ANXA5 | Annexin A5                          | Plasma Membrane| Other              | −1.294      |
| P08133 | ANXA6 | Annexin A6                          | Plasma Membrane| Ion channel        | −1.080      |
| Q10567 | AP1B1 | Adaptor-related protein complex 1, β 1 subunit | Cytoplasm      | Transporter        | −1.336      |
| P63010 | AP2B1 | Adaptor-related protein complex 2, β 1 subunit | Plasma Membrane| Transporter        | −1.400      |
| P27695 | APEX1 | APEX nuclease (multifunctional DNA repair enzyme) 1 | Nucleus        | Enzyme             | −1.321      |
| P84077 | ARF1  | ARF1 GTPase activating protein       | Cytoplasm      | Enzyme             | −1.231      |
| E3KTF6 | ARFGDIA| Rho GDP dissociation inhibitor (GDI) α | Cytoplasm      | Other              | −1.768      |
| O15143 | ARPC1B| Actin related protein 2/3 complex, subunit 1B, 41 kDa | Cytoplasm      | Other              | 1.003       |
| O15144 | ARPC2 | Actin related protein 2/3 complex, subunit 2, 34 kDa | Cytoplasm      | Other              | −1.072      |
| P31393 | ATIC  | 5-Aminomidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase | Cytoplasm      | Enzyme             | −1.304      |
| P50203 | ATP1A1| ATPase, Na+/K+ transporting, α1 polypeptide | Plasma Membrane| Transporter        | 1.043       |
| P25705 | ATP5A1| ATP synthase, H+ transporting, mitochondrial F1 complex, α subunit 1, cardiac muscle | Cytoplasm      | Transporter        | 1.146       |
| P06576 | ATP5B | ATP synthase, H+ transporting, mitochondrial F1 complex, β polypeptide | Cytoplasm      | Transporter        | 1.050       |
| O75947 | ATP5H | ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d | Cytoplasm      | Enzyme             | −1.015      |
| P61769 | B2M   | β2-Microglobulin                    | Plasma Membrane| Transmembrane receptor | −1.177     |
| P80723 | BASP1 | Brain abundant, membrane attached signal protein 1 | Nucleus        | Transcription regulator | −1.001     |
| P35613 | BSG   | Basigin (Ok blood group)             | Plasma Membrane| Transporter        | 1.217       |
| ID     | Symbol | Entrez Gene Name                                      | Location | Type(s)                  | Fold Change |
|--------|--------|-------------------------------------------------------|----------|--------------------------|-------------|
| P20290 | BTF3   | Basic transcription factor 3                          | Nucleus  | Transcription regulator  | 1.324       |
| J3QSX4 | BUB3   | BUB3 mitotic checkpoint protein                        | Nucleus  | Other                     | 1.332       |
| Q9Y224 | Cl4orf166 | Complement component 1, α subcomponent binding protein | Nucleus  | Other                     | 1.166       |
| Q9H871 | CACYBP | Calcyclin binding protein                              | Cytoplasm| Transcription regulator  | 1.227       |
| P27979 | CALR   | Calreticulin                                          | Cytoplasm| Transcription regulator  | −2.006      |
| O43852 | CALU   | Calumenin                                              | Cytoplasm| Other                     | −1.270      |
| Q86VP6 | CAND1  | Cullin-associated and neddylation-dissociated 1        | Cytoplasm| Transcription regulator  | 1.409       |
| P27824 | CANX   | Calnexin                                               | Cytoplasm| Other                     | −1.140      |
| Q01518 | CAP1   | CAP, adenylate cyclase-associated protein 1 (yeast)    | Plasma Membrane | Other         | −1.222      |
| P40121 | CAPG   | Capping protein (actin filament), gelsolin-like        | Nucleus  | Other                     | −1.145      |
| P07384 | CAPN1  | Calpain 1, (mu/1) large subunit                        | Cytoplasm| Peptidase                | −2.141      |
| P17655 | CAPN2  | Calpain 2, (m/II) large subunit                        | Cytoplasm| Peptidase                | 1.387       |
| P04632 | CAPNS1 | Calpain, small subunit 1                               | Cytoplasm| Peptidase                | 1.979       |
| Q44444 | CAPRIN1 | Cell cycle associated protein 1                        | Plasma Membrane | Other         | −1.230      |
| P52907 | CAPZA1 | Capping protein (actin filament) muscle Z-line, α 1    | Cytoplasm| Other                     | 1.313       |
| B1AK85 | CAPZB  | Capping protein (actin filament) muscle Z-line, β      | Cytoplasm| Other                     | −1.134      |
| Q9YV2V2 | CARHSP1| Calcium regulated heat stable protein 1, 24 kDa        | Cytoplasm| Other                     | −2.419      |
| E7ES10 | CAST   | Calpastatin                                            | Cytoplasm| Peptidase                | −2.137      |
| Q03135 | CAV1   | Caveolin 1, caveolae protein, 22 kDa                   | Plasma Membrane | Transmembrane receptor | −1.143      |
| Q13185 | CBX3   | Chromobox homolog 3                                    | Nucleus  | Transcription regulator  | −2.913      |
| P79371 | CCT2   | Chaperonin containing TCP1, subunit 2 (β)              | Cytoplasm| Other                     | 1.170       |
| B4DUR8 | CCT3   | Chaperonin containing TCP1, subunit 3 (γ)              | Cytoplasm| Other                     | −1.116      |
| P50991 | CCT4   | Chaperonin containing TCP1, subunit 4 (δ)              | Cytoplasm| Other                     | 1.103       |
| P48643 | CCT5   | Chaperonin containing TCP1, subunit 5 (ε)              | Cytoplasm| Other                     | 1.235       |
| P40227 | CCT6A  | Chaperonin containing TCP1, subunit 6A (ζ)             | Cytoplasm| Other                     | −1.202      |
| Q99832 | CCT7   | Chaperonin containing TCP1, subunit 7 (θ)              | Cytoplasm| Other                     | −1.226      |
| P50990 | CCT8   | Chaperonin containing TCP1, subunit 8 (θ)              | Cytoplasm| Enzyme                    | 1.257       |
| H0YD13 | CD44   | CD44 molecule (Indian blood group)                     | Plasma Membrane | Enzyme               | 2.221       |
| E9PNW4 | CD59   | CD59 molecule, complement regulatory protein            | Plasma Membrane | Other               | 1.187       |
| P06493 | CDK1   | Cyclin-dependent kinase 1                              | Nucleus  | Kinase                    | −1.130      |
| Q9UKY7 | CDV3   | CDV3 homolog (mouse)                                   | Cytoplasm| Other                     | −1.718      |
| P23828 | CFL1   | Cofilin 1 (non-muscle)                                 | Nucleus  | Other                     | −1.408      |
| Q07065 | CKA4   | Cytoskeleton-associated protein 4                       | Cytoplasm| Other                     | 1.729       |
| O00399 | CLIC1  | Chloride intracellular channel 1                       | Nucleus  | Ion channel               | −1.050      |
| Q9Y696 | CLIC4  | Chloride intracellular channel 4                       | Plasma Membrane | Ion channel           | −1.816      |
| Q00610 | CLTC   | Clathrin, heavy chain (Hc)                             | Plasma Membrane | Other               | 1.142       |
| ID     | Symbol  | Entrez Gene Name                          | Location     | Type(s)               | Fold Change |
|--------|---------|-------------------------------------------|--------------|-----------------------|-------------|
| Q15417 | CNN3    | Calponin 3, acidic                        | Cytoplasm    | Other                 | 1.155       |
| P53621 | COPA    | Coatomer protein complex, subunit α       | Cytoplasm    | Transporter           | −1.537      |
| P53618 | COPB1   | Coatomer protein complex, subunit β 1      | Cytoplasm    | Transporter           | −1.350      |
| P35606 | COPR2   | Coatomer protein complex, subunit β 2 (β prime) | Cytoplasm | Transporter | −1.323 |
| O14579 | COPE    | Coatomer protein complex, subunit ε        | Cytoplasm    | Transporter           | −1.375      |
| Q9Y678 | COPG1   | Coatomer protein complex, subunit γ 1      | Cytoplasm    | Transporter           | 1.057       |
| Q9ULV4 | CORO1C  | Coronin, actin binding protein, 1C         | Cytoplasm    | Other                 | −1.438      |
| Q14019 | COTL1   | Coactosin-like F-actin binding protein 1   | Cytoplasm    | Other                 | 1.318       |
| A6PVH9 | CPNE1   | Copine 1                                  | Nucleus      | Transporter           | −1.093      |
| H0YFA4 | CRIP2   | Cysteine-rich protein 2                   | Other        | Other                 | −1.947      |
| B4D7V2 | CS      | Citrate synthase                          | Cytoplasm    | Enzyme                | 1.066       |
| P55060 | CSE1L   | CSE1 chromosome segregation 1-like (yeast) | Nucleus      | Transporter           | −1.022      |
| P21291 | CSRP1   | Cysteine and glycine-rich protein 1        | Nucleus      | Other                 | 1.016       |
| P04080 | CSTB    | Cystatin B (stefin B)                      | Cytoplasm    | Peptidase             | −1.011      |
| P35221 | CTNNA1  | Catenin (cadherin-associated protein), α 1, 102 kDa | Plasma Membrane | Other       | 1.096       |
| P17812 | CTPS1   | CTP synthase 1                            | Nucleus      | Enzyme                | 1.338       |
| P10619 | CTSA    | Cathepsin A                               | Cytoplasm    | Peptidase             | 3.097       |
| P07858 | CTSB    | Cathepsin B                               | Cytoplasm    | Peptidase             | −1.125      |
| Q14247 | CTTN    | Cortactin                                 | Plasma Membrane | Other       | −1.161      |
| O60888 | CUTA    | CutA divalent cation tolerance homolog (E. coli) | Cytoplasm | Other                 | −1.324      |
| P00367 | CYB5R3  | Cytochrome b5 reductase 3                 | Cytoplasm    | Enzyme                | −1.018      |
| P08574 | CYC1    | Cytochrome c-1                            | Cytoplasm    | Enzyme                | 1.374       |
| O00622 | CYR61   | Cysteine-rich, angiogenic inducer, 61      | Extracellular Space | Other       | 1.367       |
| P07108 | DBI     | Diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein) | Cytoplasm | Other                 | −1.099      |
| Q16643 | DBN1    | Drebrin 1                                 | Cytoplasm    | Other                 | −1.109      |
| Q92499 | DDX1    | DEAD (Asp-Glu-Ala-Asp) box helicase 1      | Nucleus      | Enzyme                | −1.229      |
| Q13838 | DDX3W8B | DEAD (Asp-Glu-Ala-Asp) box polypeptide 39B | Nucleus      | Enzyme                | −1.021      |
| O00571 | DDX3X   | DEAD (Asp-Glu-Ala-Asp) box helicase 3, X-linked | Cytoplasm | Enzyme                | −1.042      |
| P17844 | DDX5    | DEAD (Asp-Glu-Ala-Asp) box helicase 5      | Nucleus      | Enzyme                | 1.470       |
| P26196 | DDX6    | DEAD (Asp-Glu-Ala-Asp) box helicase 6      | Nucleus      | Enzyme                | −1.499      |
| Q08211 | DHX9    | DEAH (Asp-Glu-Ala-His) box helicase 9      | Nucleus      | Enzyme                | 1.097       |
| E9PEJ4 | DLAT    | Dihydrolipoamide S-acetyltransferase       | Cytoplasm    | Enzyme                | −2.153      |
| P31689 | DNAJA1  | DnaJ (Hsp40) homolog, subfamily A, member 1 | Nucleus      | Other                 | 1.670       |
| O60884 | DNAJA2  | DnaJ (Hsp40) homolog, subfamily A, member 2 | Nucleus      | Enzyme                | −1.534      |
| Q75937 | DNAJC8  | DnaJ (Hsp40) homolog, subfamily C, member 8 | Nucleus      | Other                 | −1.971      |
| G8JLD5 | DNAJL1  | Dynamin 1-like                            | Cytoplasm    | Enzyme                | −1.011      |
| Q9C005 | DPV30   | Dpy-30 homolog (C. elegans)               | Nucleus      | Other                 | −1.737      |
| ID     | Symbol   | Entrez Gene Name                                           | Location     | Type(s)                             | Fold Change |
|--------|----------|-----------------------------------------------------------|--------------|-------------------------------------|-------------|
| Q16555 | DPYSL2   | Dihydropyrimidinase-like 2                                | Cytoplasm    | Enzyme                             | −1.124      |
| Q14204 | DYNCH1   | Dynemin, cytoplasmic 1, heavy chain 1                     | Cytoplasm    | Peptidase                          | −1.084      |
| Q13409 | DYNC1I2  | Dynemin, cytoplasmic 1, intermediate chain 2              | Cytoplasm    | Other                              | −1.024      |
| P30884 | ECHS1    | Enoyl-CoA hydratase, short chain, 1, mitochondrial         | Cytoplasm    | Enzyme                             | −1.351      |
| P68104 | EEF1A1   | Eukaryotic translation elongation factor 1 α 1             | Cytoplasm    | Transcription regulator             | −1.207      |
| P24534 | EEF1B2   | Eukaryotic translation elongation factor 1 β 2             | Cytoplasm    | Transcription regulator             | −1.208      |
| P29692 | EEF1D    | Eukaryotic translation elongation factor 1 delta (guanine nucleotide exchange protein) | Cytoplasm    | Transcription regulator             | 1.239       |
| P26641 | EEF1G    | Eukaryotic translation elongation factor 1 γ               | Cytoplasm    | Transcription regulator             | 1.168       |
| P13639 | EEF2     | Eukaryotic translation elongation factor 2                 | Cytoplasm    | Transcription regulator             | −1.089      |
| Q9H4M9 | EHD1     | EH-domain containing 1                                    | Cytoplasm    | Other                              | −1.647      |
| P05198 | EIF2S1   | Eukaryotic translation initiation factor 2, subunit 1 α, 35 kDa | Cytoplasm    | Transcription regulator             | −1.010      |
| P20842 | EIF2S2   | Eukaryotic translation initiation factor 2, subunit 2 β, 38 kDa | Cytoplasm    | Transcription regulator             | −1.660      |
| P58884 | EIF3B    | Eukaryotic translation initiation factor 3, subunit B      | Cytoplasm    | Transcription regulator             | −1.009      |
| Q99613 | EIF3C    | Eukaryotic translation initiation factor 3, subunit C      | Other        | Transcription regulator             | 1.374       |
| Q13347 | EIF3I    | Eukaryotic translation initiation factor 3, subunit I      | Cytoplasm    | Transcription regulator             | −1.163      |
| Q7L2H7 | EIF3M    | Eukaryotic translation initiation factor 3, subunit M      | Other        | Other                              | 1.451       |
| P60842 | EIF4A1   | Eukaryotic translation initiation factor 4A1               | Cytoplasm    | Transcription regulator             | 1.192       |
| E7EX73 | EIF4G1   | Eukaryotic translation initiation factor 4 γ, 1            | Cytoplasm    | Transcription regulator             | 1.458       |
| Q15056 | EIF4H    | Eukaryotic translation initiation factor 4H                | Cytoplasm    | Transcription regulator             | −1.387      |
| P63241 | EIF5A    | Eukaryotic translation initiation factor 5A                | Cytoplasm    | Transcription regulator             | −1.210      |
| P56537 | EIF6     | Eukaryotic translation initiation factor 6                 | Cytoplasm    | Transcription regulator             | 1.173       |
| Q8N887 | ENAH     | Enabled homolog (Drosophila)                               | Plasma Membrane | Other                              | −1.048      |
| P06733 | ENO1     | Enolase 1, (α)                                            | Cytoplasm    | Enzyme                             | −1.199      |
| P09104 | ENO2     | Enolase 2 (γ, neuronal)                                    | Cytoplasm    | Enzyme                             | −1.698      |
| P02814 | EPRS     | Glutamyl-prolyl-tRNA synthetase                            | Cytoplasm    | Enzyme                             | −1.568      |
| P30040 | ERP29    | Endoplasmic reticulum protein 29                           | Cytoplasm    | Transporter                        | −1.048      |
| P16768 | ESD      | Esterase D                                                | Cytoplasm    | Enzyme                             | −1.323      |
| Q9BSJ8 | ESYT1    | Extended synaptotagmin-like protein 1                      | Cytoplasm    | Other                              | 2.370       |
| H0YK49 | EFTA     | Electron-transfer-flavoprotein, α polypeptide              | Cytoplasm    | Transporter                        | −2.144      |
| E7EQ4  | EZR      | Ezrin                                                     | Plasma Membrane | Other                              | −1.066      |
| P49327 | FASN     | Fatty acid synthase                                        | Cytoplasm    | Enzyme                             | −1.453      |
| P14324 | FDFS     | Farnesyl dipiclate synthase                                | Cytoplasm    | Enzyme                             | −1.366      |
| Q5W0X3 | FKBPA    | FK506 binding protein 1A, 12 kDa                         | Cytoplasm    | Enzyme                             | 1.036       |
| Q02970 | FKBP4    | FK506 binding protein 4, 59 kDa                           | Nucleus      | Enzyme                             | −1.266      |
| P21333 | FLNA     | Filamin A, α                                              | Cytoplasm    | Other                              | −1.157      |
| Q7S569 | FLNB     | Filamin B, β                                              | Cytoplasm    | Other                              | −1.360      |
| Q14315 | FLNC     | Filamin C, γ                                              | Cytoplasm    | Other                              | 1.233       |
| ID      | Symbol | Entrez Gene Name                          | Location              | Type(s)                                | Fold Change |
|---------|--------|-------------------------------------------|-----------------------|----------------------------------------|-------------|
| P02751  | FN1    | Fibronectin 1                             | Extracellular Space   | Enzyme                                 | −3.472      |
| Q9624   | FUBP3  | Far upstream element (FUSE) binding protein 3 | Nucleus               | Transcription regulator                | −1.274      |
| P3867   | FUS    | FUS RNA binding protein                    | Nucleus               | Transcription regulator                | 1.049       |
| Q33283  | G3BP1  | GTPase activating protein (SH3 domain) binding protein 1 | Nucleus               | Enzyme                                 | −1.497      |
| P1413   | G6PD   | Glucose-6-phosphate dehydrogenase          | Cytoplasm             | Enzyme                                 | −1.504      |
| Q14697  | GANAB  | Glucosidase, α; neutral AB                 | Cytoplasm             | Enzyme                                 | −1.122      |
| P4046   | GAPDH  | Glucose-6-phosphate dehydrogenase          | Cytoplasm             | Enzyme                                 | −1.070      |
| P11413  | G6PD   | Glucose-6-phosphate dehydrogenase          | Cytoplasm             | Enzyme                                 | 1.052       |
| Q25616  | GCN1L1 | GCN1 general control of amino-acid synthesis 1-like 1 (yeast) | Cytoplasm             | Transcription regulator                | −1.604      |
| P31150  | GDH1   | GDP dissociation inhibitor 1               | Cytoplasm             | Other                                   | −1.630      |
| P29359  | GD2    | GDP dissociation inhibitor 2               | Cytoplasm             | Other                                   | −1.169      |
| Q04760  | GLO1   | Flyoxalase I                              | Cytoplasm             | Enzyme                                 | −1.349      |
| P03637  | GLUD1  | Glutamate dehydrogenase 1                 | Cytoplasm             | Enzyme                                 | 1.184       |
| E9917   | GML    | Glycosylphosphatidylinositol anchored molecule like | Plasma Membrane       | Other                                   | −1.146      |
| P49915  | GMP5   | Farnesylmonophosphate synthase             | Nucleus               | Enzyme                                 | −1.948      |
| P04899  | GNA2   | Farnesyl nucleotide binding protein (G protein), a inhibiting activity polypeptide 2 | Plasma Membrane       | Other                                   | 1.544       |
| J3KPE3  | GNBP1  | Farnesyl nucleotide binding protein (G protein), β polypeptide 2-like 1 | Cytoplasm             | Enzyme                                 | 1.209       |
| P06474  | GIP    | Farnesyl-6-phosphate isomerase             | Extracellular Space   | Enzyme                                 | −1.324      |
| P09211  | GSTP1  | Glutathione S-transferase pi 1             | Cytoplasm             | Enzyme                                 | −1.007      |
| Q5367   | H2AFY  | H2A histone family, member Y              | Nucleus               | Other                                   | −1.571      |
| K7EK07  | HIF3A/H3F3B | H3 histone, family 3A                   | Nucleus               | Other                                   | 1.037       |
| Q16636  | HADH   | Hydroxacyl-CoA dehydrogenase              | Cytoplasm             | Enzyme                                 | −1.626      |
| P40939  | HADHA  | Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), β subunit | Cytoplasm             | Enzyme                                 | −1.342      |
| B4DDD8  | HARS   | Histidyl-tRNA synthetase                   | Cytoplasm             | Enzyme                                 | −1.358      |
| F51658  | HDGF   | Hepatoma-derived growth factor             | Extracellular Space   | Growth factor                           | −2.205      |
| Q08341  | HDLPB  | High density lipoprotein binding protein   | Nucleus               | Transporter                             | −1.572      |
| Q5URX0  | HEXB   | Hexosaminidase B (β polypeptide)           | Cytoplasm             | Enzyme                                 | 1.160       |
| P14607  | HINT1  | Histidine triad nucleotide binding protein 1 | Nucleus               | Enzyme                                 | −1.864      |
| P16403  | HIST1H1C | Histone cluster 1, H1c                     | Nucleus               | Other                                   | −1.808      |
| Q99880  | HIST1H2BL | Histone cluster 1, H2bl                    | Nucleus               | Other                                   | 1.029       |
| Q16777  | HIST2H2AC | Histone cluster 2, H2ac                   | Nucleus               | Other                                   | −1.380      |
| P30445  | HLA-A  | Major histocompatibility complex, class I, A | Plasma Membrane       | Transmembrane receptor                  | 1.128       |
| P19169  | HLA-B  | Major histocompatibility complex, class I, B | Plasma Membrane       | Transmembrane receptor                  | −1.172      |
| Q577C4  | HMGDB  | High mobility group box 1                  | Nucleus               | Transcription regulator                | −1.199      |
| Q9UK76  | HN1    | Hematological and neurological expressed 1 | Nucleus               | Other                                   | −1.239      |
| F8Wf7   | HNRNPA1| Heterogeneous nuclear ribonucleoprotein A1 | Nucleus               | Other                                   | 1.329       |
| ID     | Symbol       | Entrez Gene Name                                      | Location | Type(s)          | Fold Change |
|--------|--------------|-------------------------------------------------------|----------|------------------|-------------|
| P22626 | HNRNPA2B1    | Heterogeneous nuclear ribonucleoprotein A2/B1         | Nucleus  | Other            | −1.102      |
| P51991 | HNRNPA3      | Heterogeneous nuclear ribonucleoprotein A3            | Nucleus  | Other            | 1.006       |
| E9PCY7 | HNRNPH1      | Heterogeneous nuclear ribonucleoprotein H1 (H)        | Nucleus  | Other            | 1.224       |
| P31942 | HNRNPH3      | Heterogeneous nuclear ribonucleoprotein H3 (2H9)      | Nucleus  | Other            | 1.223       |
| P61978 | HNRNPK       | Heterogeneous nuclear ribonucleoprotein K             | Nucleus  | Other            | −1.191      |
| P14866 | HNRNPL       | Heterogeneous nuclear ribonucleoprotein L             | Nucleus  | Other            | −1.360      |
| P52272 | HNRNPM       | Heterogeneous nuclear ribonucleoprotein M             | Nucleus  | Other            | 1.039       |
| O43390 | HNRNPR       | Heterogeneous nuclear ribonucleoprotein R             | Nucleus  | Other            | −1.090      |
| Q66859 | HNRNPU       | Heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor A) | Nucleus  | Transporter      | −1.169      |
| Q99714 | HSD1B10      | Hydroxysteroid (17-β) dehydrogenase 10                | Cytoplasm Enzyme | 1.196      |
| P07900 | HSP90AA1     | Heat shock protein 90 kDa α (cytosolic), class A member 1 | Cytoplasm Enzyme | 1.045      |
| P08238 | HSP90AB1     | Heat shock protein 90 kDa α (cytosolic), class B member 1 | Cytoplasm Enzyme | 1.045      |
| P14625 | HSP90B1      | Heat shock protein 90 kDa β (GRP94), member 1          | Cytoplasm Other | −1.036      |
| P34932 | HSPA4        | Heat shock 70 kDa protein 4                            | Cytoplasm Other | −1.068      |
| P11021 | HSPA5        | Heat shock 70 kDa protein 5 (glucose-regulated protein, 78 kDa) | Cytoplasm Enzyme | −1.178      |
| P11142 | HSPA8        | Heat shock 70 kDa protein 8                            | Cytoplasm Enzyme | 1.258      |
| P38646 | HSPA9        | Heat shock 70 kDa protein 9 (mortalin)                | Cytoplasm Other | −1.004      |
| P04792 | HSPB1        | Heat shock 27 kDa protein 1                            | Cytoplasm Other | −1.941      |
| P10809 | HSPD1        | Heat shock 60 kDa protein 1 (chaperonin)              | Cytoplasm Enzyme | −1.182      |
| Q9Y4L1 | HYOU1        | Hypoxia up-regulated 1                                 | Cytoplasm Other | −1.437      |
| P41252 | IARS         | Isoeucyl-tRNA synthetase                               | Cytoplasm Enzyme | −1.047      |
| Q13907 | IDI1         | Isopentenyl-diphosphate delta isomerase 1              | Cytoplasm Enzyme | −1.544      |
| Q31628 | IFITM3       | Interferon induced transmembrane protein 3             | Plasma Membrane Other | −1.052      |
| P11717 | IGF2R        | Insulin-like growth factor 2 receptor                  | Plasma Membrane Transmembrane receptor | 1.187      |
| Q12905 | ILF2         | Interleukin enhancer binding factor 2                  | Nucleus   Transcription regulator | 1.264      |
| Q12906 | ILF3         | Interleukin enhancer binding factor 3, 90 kDa         | Nucleus   Transcription regulator | 1.246      |
| Q16891 | IIMT         | Inner membrane protein, mitochondrial                   | Cytoplasm Other | 1.565      |
| H0Y4R1 | IMPDH2       | IMP (inosine 5'-monophosphate) dehydrogenase 2         | Cytoplasm Enzyme | −1.171      |
| C00410 | I0P5         | Importin 5                                             | Nucleus   Transporter | 1.077      |
| Q95373 | I0P7         | Importin 7                                             | Nucleus   Transporter | 1.355      |
| Q96970 | I0P9         | Importin 9                                             | Nucleus   Transporter | −1.113      |
| F46940 | IQGAP1       | IQ motif containing GTPase activating protein 1        | Cytoplasm Other | 1.136      |
| P35556 | ITGB1        | Integrin, β 1 (fibronectin receptor, β polyptide, antigen CD29 includes MDF2, MSK12) | Plasma Membrane Transmembrane receptor | −1.145      |
| Q07666 | KHDRBS1      | KH domain containing, RNA binding, signal transduction associated 1 | Nucleus   Transcription regulator | −1.175      |
| Q92945 | KHSRP        | KH-type splicing regulatory protein                     | Nucleus   Enzyme | −1.284      |
Table 2. Cont.

| ID       | Symbol      | Entrez Gene Name                      | Location       | Type(s)   | Fold Change |
|----------|-------------|---------------------------------------|----------------|-----------|-------------|
| P33176   | KIF5B       | Kinesin family member 5B              | Cytoplasm      | Other     | 1.332       |
| P52292   | KPNA2       | Karyopherin α 2 (RAG cohort 1, importin α 1) | Nucleus       | Transporter | 1.154       |
| C06505   | KPNA3       | Karyopherin α 3 (importin α 4)        | Nucleus       | Transporter | 2.127       |
| Q14974   | KPNB1       | Karyopherin (importin) β 1            | Nucleus       | Transporter | 1.073       |
| P04264   | KRT1        | Keratin 1                             | Cytoplasm      | Other     | −5.784      |
| P05783   | KRT18       | Keratin 18                            | Cytoplasm      | Other     | −1.122      |
| P05787   | KRT8        | Keratin 8                             | Cytoplasm      | Other     | −1.469      |
| P35527   | KRT9        | Keratin 9                             | Other          | Other     | −4.460      |
| P07942   | LAMB1       | Laminin, β 1                          | Extracellular Space | Other  | −1.088      |
| C09942   | LASP1       | LIM and SH3 protein 1                 | Cytoplasm      | Other     | −1.654      |
| P00338   | LDHA        | Lactate dehydrogenase A               | Cytoplasm      | Enzyme    | −1.361      |
| P07195   | LDHB        | Lactate dehydrogenase B               | Cytoplasm      | Enzyme    | −1.428      |
| P09352   | LGALS1      | Lectin, galactoside-binding, soluble, 1 | Extracellular Space | Other  | −1.161      |
| P02545   | LMNA        | Lamin A/C                             | Nucleus        | Other     | 1.095       |
| P20700   | LMB1        | Lamin B                               | Nucleus        | Other     | −1.253      |
| Q01081   | LOC102724594/ | U2 small nuclear RNA auxiliary factor 1 | Nucleus    | Other     | 1.047       |
| K7EJE8   | U2AF1       | Lon peptidase 1, mitochondrial        | Cytoplasm      | Peptidase | −1.410      |
| P42704   | LRPRRC      | Leucine-rich pentatricopeptide repeat containing | Cytoplasm | Other     | −1.059      |
| Q96AG4   | LLRC59      | Leucine rich repeat containing 59     | Cytoplasm      | Other     | 1.228       |
| P46821   | MAP1B       | Microtubule-associated protein 1B     | Cytoplasm      | Other     | 1.036       |
| P27816   | MAP4        | Microtubule-associated protein 4      | Cytoplasm      | Other     | −1.561      |
| P28482   | MAPK1       | Mitogen-activated protein kinase 1    | Cytoplasm      | Kinase    | −1.739      |
| Q15691   | MAPRE1      | Microtubule-associated protein, RP/EB family, member 1 | Cytoplasm | Other     | 1.418       |
| P29966   | MARCKS      | Myristoylated alanine-rich protein kinase C substrate | Plasma Membrane | Other     | −2.498      |
| P56192   | MARS        | Methionyl-RNA synthetase              | Cytoplasm      | Enzyme    | 1.049       |
| P42704   | MTRX3       | Matrin 3                              | Nucleus        | Other     | −1.307      |
| P25205   | MCM3        | Minichromosome maintenance complex component 3 | Nucleus   | Enzyme    | −1.411      |
| P33991   | MCM4        | Minichromosome maintenance complex component 4 | Nucleus   | Enzyme    | −1.472      |
| Q14566   | MCM6        | Minichromosome maintenance complex component 6 | Nucleus   | Enzyme    | −1.238      |
| P33993   | MCM7        | Minichromosome maintenance complex component 7 | Nucleus   | Enzyme    | −1.223      |
| P40925   | MDH1        | Malate dehydrogenase 1, NAD (soluble) | Cytoplasm      | Enzyme    | −1.659      |
| P40926   | MDH2        | Malate dehydrogenase 2, NAD (mitochondrial) | Cytoplasm | Enzyme    | −1.298      |
| P26038   | MSN         | Moesin                                | Plasma Membrane | Other     | 1.079       |
| Q14764   | MVP         | Major vault protein                   | Nucleus        | Other     | 1.636       |
| P35580   | MYH10       | Myosin, heavy chain 10, non-muscle    | Cytoplasm      | Other     | 1.275       |
| P35789   | MYH9        | Myosin, heavy chain 9, non-muscle     | Cytoplasm      | Enzyme    | −1.104      |
| P19105   | MYL12A      | Myosin, light chain 12A, regulatory, non-sarcomeric | Cytoplasm | Other     | 1.316       |
| ID     | Symbol | Entrez Gene Name                                      | Location           | Type(s)                  | Fold Change |
|--------|--------|------------------------------------------------------|--------------------|--------------------------|-------------|
| F8W1N5 | NACA   | Nascent polypeptide-associated complex α subunit     | Cytoplasm          | Transcription regulator   | -1.282      |
| F8VY35 | NAP1L1 | Nucleosome assembly protein 1-like 1                 | Nucleus            | Other                     | 1.173       |
| Q99733 | NAP1L4 | Nucleosome assembly protein 1-like 4                 | Cytoplasm          | Other                     | -1.300      |
| P49321 | NASP   | Nuclear autoantigenic sperm protein (histone-binding)| Nucleus            | Other                     | -1.640      |
| P19338 | NCL    | Nucleolin                                            | Nucleus            | Other                     | -1.037      |
| Q32Q12 | NME1-NME2 | NME1-NME2 readthrough                            | Cytoplasm          | Other                     | -1.298      |
| P40261 | NNMT   | Nicotinamide N-methyltransferase                    | Cytoplasm          | Enzyme                    | -2.513      |
| Q15233 | NONO   | Non-POU domain containing, octamer-binding          | Nucleus            | Other                     | 1.374       |
| E9PLK3 | NPEPS  | Aminopeptidase parvulin sensitive                    | Cytoplasm          | Peptidase                 | -1.868      |
| Q8EY6T | NPLC4  | Nuclear protein localization 4 homolog (S. cerevisiae)| Nucleus            | Other                     | 1.135       |
| P06748 | NPM1   | Nucleophosmin (nucleolar phosphoprotein B23, numatin)| Nucleus            | Transcription regulator    | 1.166       |
| Q6UNZ2 | NSELI  | NSFL1 (p97) cofactor (p47)                          | Cytoplasm          | Other                     | -1.139      |
| Q14098 | NUMA1  | Nuclear mitotic apparatus protein 1                 | Nucleus            | Other                     | -1.202      |
| Q9NTK5 | OLA1   | Obg-like ATPase 1                                   | Cytoplasm          | Other                     | 1.159       |
| Q66FW1 | OTUB1  | OTU deubiquitination, ubiquitin aldehyde binding 1  | Cytoplasm          | Enzyme                    | -1.304      |
| P07237 | P4HB   | Prolyl 4-hydroxylase, β polypeptide                 | Cytoplasm          | Enzyme                    | -1.341      |
| Q9UQ80 | PA2G4  | Proliferation-associated G4, 38kDa                  | Nucleus            | Transcription regulator    | -1.316      |
| E7EQV3 | PABPC1 | Poly(A) binding protein, cytoplasmic 1              | Cytoplasm          | Transcription regulator    | 1.235       |
| P68402 | PAFAH1B2 | Platelet-activating factor acetylhydrolase 1b,     | Cytoplasm          | Enzyme                    | 1.089       |
| E9PBS1 | PAICS  | Phosphoribosylaminomimidazole carboxylase,           | Cytoplasm          | Enzyme                    | -1.354      |
| Q9497  | PARK7  | Parkinson protein 7                                 | Nucleus            | Enzyme                    | -1.711      |
| Q15365 | PCBP1  | Poly(rC) binding protein 1                          | Nucleus            | Transcription regulator    | -1.493      |
| F8VZ2  | PCBP2  | Poly(rC) binding protein 2                          | Nucleus            | Other                     | 1.266       |
| P59746 | PCM1   | Pericentriolar material 1                           | Cytoplasm          | Other                     | 1.175       |
| B7Z597 | PCM1   | Protein-1-isoaaspartate (0-aspartate) O-methyltransferase | Cytoplasm          | Enzyme                    | -1.351      |
| P12004 | PCNA   | Proliferating cell nuclear antigen                  | Nucleus            | Enzyme                    | -1.321      |
| E7EPW6 | PDCD6  | Programmed cell death 6                             | Cytoplasm          | Other                     | -1.147      |
| F8VF3  | PDE6H  | Phosphodiesterase 6H, cGMP-specific, cone, γ      | Cytoplasm          | Enzyme                    | -1.043      |
| P30101 | PDA3   | Protein disulide isomerase family A, member 3       | Cytoplasm          | Peptidase                 | 1.167       |
| P13667 | PDA4   | Protein disulide isomerase family A, member 4       | Cytoplasm          | Enzyme                    | -1.155      |
| Q15084 | PDA6   | Protein disulide isomerase family A, member 6       | Cytoplasm          | Enzyme                    | -1.161      |
| O00151 | PDLBM1 | PDX and LIM domain 1                                | Cytoplasm          | Transcription regulator    | -1.397      |
| FZ2Y4  | PDXK   | Pyridoxal (pyridoxine, vitamin B6) kinase           | Cytoplasm          | Kinase                    | -1.008      |
| Q15121 | PEAS1  | Phosphoprotein enriched in astrocytes 15            | Cytoplasm          | Transporter               | 1.073       |
| P30086 | PEBP1  | Phosphatidylethanolamine binding protein 1          | Cytoplasm          | Other                     | -1.552      |
| Q91813 | PFKP   | Phosphofructokinase, platelet                        | Cytoplasm          | Kinase                    | 1.313       |
| P07377 | PFK1   | Proline 1                                            | Cytoplasm          | Other                     | -1.405      |
| P18669 | PGAM1  | Phosphoglycerate mutase 1 (brain)                   | Cytoplasm          | Phosphatase               | -1.701      |
| P52209 | PGD    | Phosphogluconate dehydrogenase                      | Cytoplasm          | Enzyme                    | -1.398      |
| ID     | Symbol | Entrez Gene Name                                      | Location          | Type(s)                          | Fold Change |
|--------|--------|-------------------------------------------------------|-------------------|----------------------------------|-------------|
| P00558 | PGK1   | Phosphoglycerate kinase 1                             | Cytoplasm         | Kinase                           | −1.287      |
| P36871 | PGM1   | Phosphoglucomutase 1                                  | Cytoplasm         | Enzyme                           | −1.393      |
| F5C3Y7 | PHB2   | Prohibitin 2                                          | Cytoplasm         | Transcription regulator           | −1.175      |
| O43175 | PHGDH  | Phosphoglycerate dehydrogenase                        | Cytoplasm         | Enzyme                           | −1.552      |
| Q13492 | PICALM | Phosphatidylinositol binding clathrin assembly protein| Cytoplasm         | Other                            | −1.195      |
| P14618 | PKM    | Pyruvate kinase, muscle                               | Cytoplasm         | Kinase                           | −1.341      |
| Q15149 | PLEC   | Plectin                                               | Cytoplasm         | Other                            | 1.326       |
| Q68664 | PLIN3  | Perilipin 3                                           | Cytoplasm         | Other                            | −1.084      |
| E7ETU9 | PLOD2  | Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2    | Cytoplasm         | Enzyme                           | 1.150       |
| P13797 | PL3    | Plasmin 3                                             | Cytoplasm         | Other                            | −1.143      |
| Q15181 | PPA1   | Pyrophosphatase (inorganic) 1                         | Cytoplasm         | Enzyme                           | −1.263      |
| P62937 | PPIA   | Peptidylprolyl isomerase A (cyclophilin A)            | Cytoplasm         | Enzyme                           | −1.057      |
| O13355 | PPM1G  | Protein phosphatase, Mg2+/Mn2+ dependent, 1G          | Nucleus           | Phosphatase                      | 1.144       |
| P62136 | PPP1CA | Protein phosphatase 1, catalytic subunit, α isozyme   | Cytoplasm         | Phosphatase                      | −1.250      |
| F67779 | PPP2CA | Protein phosphatase 2, catalytic subunit, α isozyme   | Cytoplasm         | Phosphatase                      | 1.012       |
| P30153 | PPR1A  | Protein phosphatase 2, regulatory subunit, α          | Cytoplasm         | Phosphatase                      | −1.191      |
| Q06380 | PRDX1  | Peroxiredoxin 1                                      | Cytoplasm         | Enzyme                           | −2.056      |
| P32119 | PRDX2  | Peroxiredoxin 2                                      | Cytoplasm         | Enzyme                           | −1.479      |
| Q13162 | PRDX4  | Peroxiredoxin 4                                      | Cytoplasm         | Enzyme                           | 1.346       |
| P30844 | PRDX5  | Peroxiredoxin 5                                      | Cytoplasm         | Enzyme                           | −1.297      |
| K7ELL7 | PRKCSH | Protein kinase C substrate 80K-H                      | Cytoplasm         | Enzyme                           | −1.483      |
| E7EU0  | PRKDC  | Protein kinase, DNA-activated, catalytic polypeptide  | Nucleus           | Kinase                           | −1.313      |
| H8YJX6 | PRMT5  | Protein arginine methyltransferase 5                  | Cytoplasm         | Enzyme                           | −1.975      |
| Q9U5M4 | PRP19  | Pre-mRNA processing factor 19                         | Nucleus           | Enzyme                           | −1.155      |
| P25786 | PSMA1  | Proteasome (prosome, macropain) subunit, α type, 1    | Cytoplasm         | Peptidase                        | −1.070      |
| P25787 | PSMA2  | Proteasome (prosome, macropain) subunit, α type, 2    | Cytoplasm         | Peptidase                        | −1.069      |
| H8YLC2 | PSMA4  | Proteasome (prosome, macropain) subunit, α type, 4    | Cytoplasm         | Peptidase                        | −1.204      |
| P20606 | PSMA5  | Proteasome (prosome, macropain) subunit, α type, 5    | Cytoplasm         | Peptidase                        | 1.018       |
| O14818 | PSMA7  | Proteasome (prosome, macropain) subunit, α type, 7    | Cytoplasm         | Peptidase                        | −1.157      |
| P2618  | PSMB1  | Proteasome (prosome, macropain) subunit, β type, 1    | Cytoplasm         | Peptidase                        | 1.208       |
| P62191 | PSMC1  | Proteasome (prosome, macropain) 26S subunit, ATPase, 1| Nucleus           | Peptidase                        | −1.298      |
| P43666 | PSMC4  | Proteasome (prosome, macropain) 26S subunit, ATPase, 4| Nucleus           | Peptidase                        | −1.249      |
| Q13200 | PSMD2  | Proteasome (prosome, macropain) 26S subunit, non−ATPase, 2| Cytoplasm         | Other                            | 1.339       |
| Q06323 | PSME1  | Proteasome (prosome, macropain) activator subunit 1 (PA28 α) | Cytoplasm         | Peptidase                        | −1.845      |
| Q9UL46 | PSME2  | Proteasome (prosome, macropain) activator subunit 2 (PA28 β) | Cytoplasm         | Peptidase                        | −1.010      |
| P26599 | PTBP1  | Polyuridyminic tract binding protein 1                | Nucleus           | Enzyme                           | 1.178       |
| Q13185 | PTGES3 | Prostaglandin E synthase 3 (cytosolic)                | Cytoplasm         | Enzyme                           | −1.312      |
| B8ZZQ6 | PTMA   | Prothymosin, α                                       | Nucleus           | Other                            | −1.826      |
| Q9UHX1 | PUF60  | Poly-U binding splicing factor 60 kDa                | Nucleus           | Transcription regulator           | 2.165       |
| ID     | Symbol | Entrez Gene Name                                             | Location   | Type(s)       | Fold Change |
|--------|--------|--------------------------------------------------------------|------------|---------------|-------------|
| P11216 | PYGB   | Phosphorylase, glycogen; brain                               | Cytoplasm  | Enzyme        | -1.093      |
| E9PK47 | PYGL   | Phosphorylase, glycogen, liver                               | Cytoplasm  | Enzyme        | -1.252      |
| F47897 | QARS   | Glutaminyl-tRNA synthetase                                   | Cytoplasm  | Enzyme        | 1.066       |
| B4DQU5 | RAB1A  | RAB1A, member RAS oncogene family                            | Cytoplasm  | Enzyme        | -1.365      |
| E9PLD0 | RAB1B  | RAB1B, member RAS oncogene family                            | Cytoplasm  | Other         | -1.182      |
| F51149 | RAB7A  | RAB7A, member RAS oncogene family                            | Cytoplasm  | Enzyme        | 1.158       |
| F54727 | RAD23B | RAD23 homolog B (S. cerevisiae)                              | Nucleus    | Other         | 1.005       |
| F5H018 | RAN    | RAN, member RAS oncogene family                              | Nucleus    | Enzyme        | -1.229      |
| C9JJS4 | RANBF1 | RAN binding protein 1                                        | Nucleus    | Other         | -1.461      |
| P54136 | RARS   | Arginyl-tRNA synthetase                                      | Cytoplasm  | Enzyme        | -1.180      |
| P86179 | RBM3   | RNA binding motif (RNP1, RRM) protein 3                      | Cytoplasm  | Other         | 1.376       |
| Q15293 | RCN1   | Reticulocalbin 1, EF-hand calcium binding domain             | Cytoplasm  | Other         | 1.027       |
| C9JNR4 | RHOA   | Ras homolog family member A                                  | Cytoplasm  | Enzyme        | -1.521      |
| P13489 | RNH1   | Ribonuclease/angiogenin inhibitor 1                          | Cytoplasm  | Other         | 1.064       |
| X1W28  | RPL10  | Ribosomal protein L10                                        | Nucleus    | Other         | -1.075      |
| P62906 | RPL10A | Ribosomal protein L10a                                       | Nucleus    | Other         | 1.288       |
| P30050 | RPL12  | Ribosomal protein L12                                        | Nucleus    | Other         | -1.330      |
| F8VUA6 | RPL18  | Ribosomal protein L18                                        | Cytoplasm  | Other         | -1.204      |
| P46778 | RPL21  | Ribosomal protein L21                                        | Cytoplasm  | Other         | 1.339       |
| P38268 | RPL22  | Ribosomal protein L22                                        | Nucleus    | Other         | 1.026       |
| C9JDD2 | RPL23  | Ribosomal protein L23                                        | Cytoplasm  | Other         | 1.373       |
| P61353 | RPL27  | Ribosomal protein L27                                        | Cytoplasm  | Other         | -1.206      |
| P39023 | RPL3   | Ribosomal protein L3                                         | Cytoplasm  | Enzyme        | 1.044       |
| P36578 | RPL4   | Ribosomal protein L4                                         | Cytoplasm  | Other         | -1.065      |
| P46777 | RPL5   | Ribosomal protein L5                                         | Cytoplasm  | Other         | 1.314       |
| Q02878 | RPL6   | Ribosomal protein L6                                        | Cytoplasm  | Other         | 1.340       |
| P18124 | RPL7   | Ribosomal protein L7                                         | Nucleus    | Transcription regulator | 1.141   |
| P62424 | RPL7A  | Ribosomal protein L7a                                       | Cytoplasm  | Other         | -1.191      |
| G3V1A1 | RPL8   | Ribosomal protein L8                                         | Other      | Other         | 1.421       |
| F8VWS0 | RPL10  | Ribosomal protein, large, P0                                 | Cytoplasm  | Other         | -1.274      |
| P05386 | RPL1P  | Ribosomal protein, large, P1                                 | Cytoplasm  | Other         | -1.062      |
| P05387 | RPL2P  | Ribosomal protein, large, P2                                 | Cytoplasm  | Enzyme        | 1.067       |
| P04843 | RPN1   | Ribophorin I                                                | Cytoplasm  | Enzyme        | -1.171      |
| P04844 | RPN2   | Ribophorin II                                               | Cytoplasm  | Other         | -1.009      |
| P46783 | RPS10  | Ribosomal protein S10                                        | Cytoplasm  | Other         | 1.335       |
| P62280 | RPS11  | Ribosomal protein S11                                        | Cytoplasm  | Other         | -1.062      |
| P25398 | RPS12  | Ribosomal protein S12                                        | Cytoplasm  | Other         | 1.152       |
| K7ETJ8 | RPS15  | Ribosomal protein S15                                        | Cytoplasm  | Other         | 1.092       |
| H0YEN5 | RPS2   | Ribosomal protein S2                                        | Cytoplasm  | Other         | 1.157       |
### Table 2. Cont.

| ID     | Symbol | Entrez Gene Name                                      | Location | Type(s)                  | Fold Change |
|--------|--------|-------------------------------------------------------|----------|--------------------------|-------------|
| P62979 | RPS27A | Ribosomal protein S27a                                 | Cytoplasm| Other                    | 1.399       |
| P23396 | RPS3   | Ribosomal protein S3                                   | Cytoplasm| Enzyme                   | 1.251       |
| D69RG8 | RPS3A  | Ribosomal protein S3A                                  | Nucleus  | Other                    | 1.184       |
| P62701 | RPS4X  | Ribosomal protein S4, X-linked                         | Cytoplasm| Other                    | 1.236       |
| M0R0F0 | RPS5   | Ribosomal protein S5                                   | Cytoplasm| Other                    | -1.080      |
| P62081 | RPS7   | Ribosomal protein S7                                   | Cytoplasm| Other                    | -1.189      |
| P62241 | RPS8   | Ribosomal protein S8                                   | Cytoplasm| Other                    | 1.581       |
| C9J9K3 | RPSA   | Ribosomal protein SA                                   | Cytoplasm| Transcription regulator  | 1.267       |
| Q9F2E9 | RBBP1  | Ribosome binding protein 1                             | Cytoplasm| Other                    | 1.082       |
| Q9NQC3 | RTN4   | Reticulin 4                                            | Cytoplasm| Other                    | -1.099      |
| R4GN98 | S100A6 | S100 calcium binding protein A6                        | Cytoplasm| Enzyme                   | 1.080       |
| M0QZ56 | SA1    | SUMO1 activating enzyme subunit 1                      | Cytoplasm| Transmitter              | 1.190       |
| D69FM5 | SDHA   | Succinate dehydrogenase complex, subunit A, flavoprotein (Fp) | Cytoplasm| Enzyme                   | 1.035       |
| P59735 | SEC13  | SEC13 homolog (S. cerevisiae)                          | Cytoplasm| Transporter              | 1.029       |
| Q15019 | SEPT2  | Septin 2                                               | Cytoplasm| Enzyme                   | -1.140      |
| H4OY3Y4 | SEPT7 | Septin 7                                               | Cytoplasm| Other                    | 1.266       |
| Q9UHD8 | SEPT9  | Septin 9                                               | Cytoplasm| Enzyme                   | 1.063       |
| Q8NC51 | SERBP1 | SERPINE1 mRNA binding protein 1                        | Cytoplasm| Other                    | 1.003       |
| P50454 | SERPINH1| Serpin peptidase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1) | Extracellular Space| Other                   | -1.178      |
| Q01105 | SET    | SET nuclear proto-oncogene                             | Nucleus  | Phosphatase               | -1.282      |
| Q15459 | SF3A1  | Splicing factor 3a, subunit 1, 120 kDa                 | Nucleus  | Other                    | 1.024       |
| Q75333 | SF3B1  | Splicing factor 3b, subunit 1, 155 kDa                 | Nucleus  | Other                    | 1.359       |
| P31947 | SFN    | Stratifin                                              | Cytoplasm| Other                    | -1.586      |
| P22246 | SFPO   | Splicing factor proline/glutamine-rich                 | Nucleus  | Other                    | 1.009       |
| Q9H299 | SH3BGR3| SH3 domain binding glutamate-rich protein like 3       | Nucleus  | Other                    | 1.688       |
| P34897 | SHMT2  | Serine hydroxymethyltransferase 2 (mitochondrial)      | Cytoplasm| Enzyme                   | -1.297      |
| F8VMV | SLC25A3| Solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3 | Cytoplasm| Transporter              | 1.165       |
| F05141 | SLC25A5| Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5 | Cytoplasm| Transporter              | -1.599      |
| I7HJJO | SLC25A6| Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 6 | Cytoplasm| Transporter              | 1.304       |
| Q96QD8 | SLC38A2| Solute carrier family 38, member 2                     | Plasma Membrane| Transporter             | -1.082      |
| Q7KZF4 | SND1   | Staphylococcal nuclease and tudor domain containing 1  | Nucleus  | Enzyme                   | -1.112      |
| P62314 | SNRPD1 | Small nuclear ribonucleoprotein D1 polypeptide 16 kDa   | Nucleus  | Other                    | -1.174      |
| H3BT13 | SNRPD3 | Small nuclear ribonucleoprotein D3 polypeptide 18 kDa   | Nucleus  | Other                    | 1.288       |
| C60493 | SNX3   | Sorting nexin 3                                        | Cytoplasm| Transporter              | 1.117       |
| P00441 | SOD1   | Superoxide dismutase 1, soluble                        | Cytoplasm| Enzyme                   | -1.264      |
| Q13813 | SPTAN1 | Septin, α, non-erythrocytic 1                           | Plasma Membrane| Other                  | 1.056       |
| Q0182 | SPTBN1 | Septin, β, non-erythrocytic 1                           | Plasma Membrane| Other                  | -1.545      |
| E7EMC7 | SQSTM1 | Sequestosome 1                                         | Cytoplasm| Transcription regulator  | 1.310       |
| Q8945 | SSRP1  | Structure specific recognition protein 1                | Nucleus  | Other                    | -1.498      |
Table 2. Cont.

| ID     | Symbol | Entrez Gene Name                                                                 | Location                  | Type(s)                        | Fold Change |
|--------|--------|----------------------------------------------------------------------------------|---------------------------|--------------------------------|-------------|
| P42224 | STAT1  | Signal transducer and activator of transcription 1, 91 kDa                      | Nucleus                   | Transcription regulator        | -1.353      |
| P31948 | STIP1  | Stress-induced phosphoprotein 1                                                 | Cytoplasm                 | Other                          | -1.086      |
| A2A2D0 | STMN1  | Stathmin                                                                         | Cytoplasm                 | Other                          | -1.445      |
| Q9UJZ1 | STML2  | Stomatin (EPB72)-like 2                                                        | Plasma Membrane           | Other                          | 1.325       |
| Q9YS9  | SUP716H| Suppressor of Ty 16 homolog (S. cerevisiae)                                     | Nucleus                   | Transcription regulator        | -1.137      |
| Q58U5  | SURF4  | Surf 4                                                                           | Cytoplasm                 | Other                          | 1.327       |
| O65056 | SYNC1P | Synaptotagmin binding, cytoplasmatic RNA interacting protein                    | Nucleus                   | Other                          | -1.378      |
| Q01995 | TAGLN2 | Transgelin                                                                       | Cytoplasm                 | Other                          | -1.657      |
| P37802 | TAPL2  | Transgelin 2                                                                     | Cytoplasm                 | Other                          | -1.382      |
| Q9UJZ1 | STOM1  | Stomatin (EPB72)-like 2                                                        | Plasma Membrane           | Other                          | 1.325       |
| Q9Y490 | STOM1  | Stomatin (EPB72)-like 2                                                        | Plasma Membrane           | Other                          | 1.072       |
| Q9NL9  | TMOD3  | Tropomodulin 3 (ubiquitous)                                                     | Cytoplasm                 | Other                          | 1.076       |
| P41266 | TMPO   | Thymopoietin                                                                     | Nucleus                   | Other                          | -1.488      |
| F5H7V9 | TNC    | Tenascin C                                                                       | Extracellular Space       | Other                          | -2.480      |
| Q92973 | TNPO1  | Transportin 1                                                                     | Nucleus                   | Transporter                    | -1.378      |
| P60174 | TP1    | Triosephosphate isomerase 1                                                      | Cytoplasm                 | Enzyme                         | -1.620      |
| Q510C3 | TMD2   | Tropomyosin 2 (β)                                                               | Other                     | Other                          | 1.845       |
| J3KN67 | TMD3   | Tropomyosin 3                                                                    | Cytoplasm                 | Other                          | -1.265      |
| P67936 | TMD4   | Tropomyosin 4                                                                    | Cytoplasm                 | Other                          | -1.185      |
| Q14773 | TMD1   | Tripeptidyl peptidase 1                                                         | Cytoplasm                 | Peptidase                      | -1.239      |
| Q13263 | TRIM28 | Tripartite motif containing 28                                                  | Nucleus                   | Transcription regulator        | -1.201      |
| F8VQE1 | TRMT1  | tRNA methyltransferase 1 homolog (S. cerevisiae)                                 | Extracellular Space       | Enzyme                         | -1.271      |
| P68363 | TUBA1B | Tubulin, α 1b                                                                     | Cytoplasm                 | Other                          | -1.056      |
| Q5J55  | TUBB   | Tubulin, β class I                                                              | Cytoplasm                 | Other                          | -1.029      |
| P68371 | TUBB4B | Tubulin, β 4B class IVb                                                         | Cytoplasm                 | Other                          | 1.046       |
| Q6BUF5 | TUBB6  | Tubulin, β 6 class V                                                             | Cytoplasm                 | Other                          | 1.022       |
| Q9ZCM7 | TUBB8  | Tubulin, β 8 class VIII                                                          | Cytoplasm                 | Other                          | -1.128      |
| P49441 | TUFM   | Tu translation elongation factor, mitochondrial                                  | Cytoplasm                 | Transcription regulator        | -1.173      |
| Q1292  | TWF1   | Twi11ulin act-binding protein 1                                                 | Cytoplasm                 | Kinase                         | -1.798      |
| D68G5  | TWF2   | Twi11ulin act-binding protein 2                                                 | Cytoplasm                 | Kinase                         | -1.347      |
| P42222 | TXLNA  | Taxillin α                                                                       | Extracellular Space       | Cytokine                       | -1.162      |
| Q666Y0 | TXNDC3 | Thioredoxin domain containing 5 (endoplasmic reticulum)                          | Cytoplasm                 | Enzyme                         | 1.390       |
| P25658 | UAA2F2 | U2 small nuclear RNA auxiliary factor 2                                          | Nucleus                   | Other                          | -1.209      |
| Q16222 | UAP1   | UDP-N-acetylglucosamine pyrophosphorylase 1                                     | Cytoplasm                 | Enzyme                         | 1.145       |
| P23314 | UBA1   | Ubiquitin-like modifier activating enzyme 1                                      | Cytoplasm                 | Enzyme                         | 1.182       |
### Table 2. Cont.

| ID      | Symbol | Entrez Gene Name                                                                 | Location               | Type(s)       | Fold Change |
|---------|--------|---------------------------------------------------------------------------------|------------------------|---------------|-------------|
| P68036  | UBE2L3 | Ubiquitin-conjugating enzyme E2L 3                                             | Nucleus                | Enzyme        | 1.021       |
| F8V2Z9  | UBE2N  | Ubiquitin-conjugating enzyme E2N                                                 | Cytoplasm              | Enzyme        | −1.650      |
| Q92575  | UBXN4  | Ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)                | Extracellular Space    | Other         | −1.082      |
| P99396  | UCHL1  |                                                                                   | Cytoplasm              | Peptidase     | −1.453      |
| P31930  | UQCRIC | Ubiquinol-cytochrome c reductase core protein I                                  | Cytoplasm              | Enzyme        | 1.218       |
| Q9POL0  | VAPA   | VAMP (vesicle-associated membrane protein)-associated protein A, 33 kDa         | Plasma Membrane        | Other         | 1.026       |
| P26640  | VARS   | Valyl-tRNA synthetase                                                            | Cytoplasm              | Enzyme        | −1.120      |
| K7ERT7  | VAT1   | Vesicle amine transport 1                                                        | Plasma Membrane        | Transporter   | −2.302      |
| P19206  | VCL    | Vinculin                                                                        | Plasma Membrane        | Enzyme        | −1.175      |
| P53072  | VCP    | Valosin containing protein                                                      | Cytoplasm              | Enzyme        | −1.058      |
| P21796  | VDAC1  | Voltage-dependent anion channel 1                                               | Cytoplasm              | Ion channel   | −1.335      |
| P45880  | VDAC2  | Voltage-dependent anion channel 2                                               | Cytoplasm              | Ion channel   | −1.041      |
| P06760  | VIM    | Vimentin                                                                         | Cytoplasm              | Other         | 1.579       |
| Q96QK1  | VPS35  | Vacular protein sorting 35 homolog (S. cerevisiae)                               | Cytoplasm              | Transporter   | −1.641      |
| P23381  | WARS   | Tryptophanyl-tRNA synthetase                                                     | Cytoplasm              | Enzyme        | −1.477      |
| Q75883  | WDR1   | WD repeat domain 1                                                               | Extracellular Space    | Other         | −1.206      |
| O14980  | XP1O   | exportin 1                                                                       | Nucleus                | Transporter   | −1.091      |
| P13010  | XRCC3  | X-ray repair complementing defective repair in Chinese hamster cells 5         | (double-strand-break joining) | Nucleus | Enzyme | −1.197 | |
| P12956  | XRCC6  | X-ray repair complementing defective repair in Chinese hamster cells 6         | Nucleus                | Enzyme        | −1.575      |
| P67809  | YBX1   | Y box binding protein 1                                                           | Nucleus                | Transcription regulator | −1.196 |
| P16989  | YBX3   | Y box binding protein 3                                                           | Nucleus                | Transcription regulator | −1.186 |
| P31946  | YWHA8  | Tyrosine 3-monoxygenase/trypophan 5-monoxygenase activation protein, β          | Cytoplasm              | Transcription regulator | 1.064 |
| P62258  | YWHA9  | Tyrosine 3-monoxygenase/trypophan 5-monoxygenase activation protein, epsilon    | Cytoplasm              | Other         | −1.216      |
| P61981  | YWHA6  | Tyrosine 3-monoxygenase/trypophan 5-monoxygenase activation protein, γ          | Cytoplasm              | Other         | −1.045      |
| Q04197  | YWHAH  | Tyrosine 3-monoxygenase/trypophan 5-monoxygenase activation protein, η          | Cytoplasm              | Transcription regulator | −1.559 |
| P27348  | YWHAQ  | Tyrosine 3-monoxygenase/trypophan 5-monoxygenase activation protein, θ          | Cytoplasm              | Other         | 1.180       |
| P63104  | YWHAZ  | Tyrosine 3-monoxygenase/trypophan 5-monoxygenase activation protein, ζ          | Cytoplasm              | Enzyme        | −1.123      |
| Q15942  | ZXY    | Zyxin                                                                            | Plasma Membrane        | Other         | −1.100      |
Table 3. 290 canonical signaling pathways regulated by vancomycin in HK-2 cells.

| INGENUITY Canonical Pathways | \(-\log(p\text{-Value})\) | Ratio | z-Score | Molecules |
|-----------------------------|-------------------------|-------|---------|-----------|
| eIF2 signaling              | 29.5                    | 2.32 \times 10^{-1} | -0.229 | RPL2, EIF3C, RPL1, MAPK1, RPS3A, RPL2, RPS8, EIF2S1, EIF4G1, RPL7, RPS11, RPS4X, RPS7, RPL6, RPL7A, EIF3B, PPPCA, RPS5, RPS5, RPL8, RPS24, PABPC1, RPL4, RPL3, RPS2, RPL27, RPL11, RPL21, RPL23, RPL12, RPL7, RPL16a, EIF3M, RPS12, EIF2S2, EIF8, EIF14, EIF3I, RPS13, RPL10, RPS27a, RPL5, RPSA |
| Remodeling of epithelial adherent junctions | 16.2                    | 2.94 \times 10^{-1} | 0.000  | TUBA1B, ACTR2, ARPC1B, TUBB4B, MAPRE1, RAB7A, CTNNB1, IQGAP1, TUBB, ACTR3, TUB86, TUB88, ARPC2, ZYX, VCL, ACTN4, DNM1L, ACTG1, ACTN1, ACTA1 |
| Regulation of eIF4 and p70S6K signaling | 16.0                    | 1.85 \times 10^{-1} | -1.000 | EIF3C, RPS3A, MAPK1, PPP2CA, RPS8, EIF4G1, EIF2S1, RPS4X, RPS11, RPS7, EIF3B, RPS5, RPS24, ITGB1, PABPC1, RPS2, RPS10, RPS12, EIF3M, EIF2S2, PPP2R1A, EIF4A1, EIF3I, RPS15, RPS15a, RPS5a |
| mTOR signaling              | 11.4                    | 1.33 \times 10^{-1} | -0.447 | EIF3C, RPS3A, MAPK1, PPP2CA, RPS8, FKBP1A, EIF4G1, RPS4X, RPS11, RPS7, EIF3B, RPS3, RPS5, RPS24, RPS2, RPS10, RPS12, EIF3M, PPP2R1A, RHOA, EIF4A1, RPS15, EIF3I, RPS27a, RPSA |
| Protein ubiquitination pathway | 11.4                    | 1.14 \times 10^{-1} |       | B2M, PSMA7, HLA-A, UBE2N, HLA-B, HSPA5, DNAJ1, UCHL1, HSPA4, HSP90B1, HSP90AB1, DNAJC8, PSMA2, HSPA9, PSM2, PSM4, PSMA1, HSDP1, HSPA4, PSM1, PSMC1, UBE2L3, PSMD2, PSMA5, PSMA4, PSMB1, HSP90AA1, UB1, HSPB1 |
| Glycolysis I                | 11.4                    | 4.40 \times 10^{-1} |       | PGK1, ENO1, GPD1, PGAM1, PKM, ENO2, ALDOA, GAPDH, PKP, ALDOC |
| Caveolar-mediated endocytosis signaling | 11.0                    | 2.22 \times 10^{-1} |       | ITGB1, B2M, FLNB, HLA-A, HLA-B, COPA, COPE, COPB2, COPB1, COPG1, FLNA, FLNC, CAV1, PTRF, ACTG1, ACTA1 |
| Ran signaling               | 10.3                    | 5.29 \times 10^{-1} |       | KPNB1, KPN3, CSE1L, KPN2A, TNPO1, RAN, XPO1, RANBP5, IPO5 |
| Gluconeogenesis I           | 9.88                    | 4.00 \times 10^{-1} |       | PKG1, ENO1, GPD1, PGAM1, ENO2, ALDOA, GAPDH, MDH1, MHD2, ALDOC |
| Epithelial adherent junction signaling | 9.51                    | 1.37 \times 10^{-1} |       | TUBA1B, MYH10, ACTR2, MYH9, ARPC1B, TUBB4B, CTNNB1, IQGAP1, TUBB, ACTR3, TUB66, TUB86, ARPC2, RHOA, ZYX, VCL, ACTN4, ACTG1, ACTN1, ACTA1 |
| tRNA charging               | 8.93                    | 2.82 \times 10^{-1} |       | WARS, RARS, GARS, HARS, TARS, AARS, VARS, IARS, IARS, EPRS, QARS |
| Actin cytoskeleton signaling | 8.59                    | 1.06 \times 10^{-1} |       | ITGB1, ACTR2, MYH10, MYH9, FN1, FN1, CFL1, MAPK1, ARPC1B, TUBB4B, CTNNB1, IQGAP1, TUBB, ACTR3, FLNA, EZR, ARPC2, RHOA, VCL, ACTN4, ACTG1, ACTA1, ACTN1, MSN, MYL12A |
| Regulation of cellular mechanics by calpain protease | 8.10                    | 2.11 \times 10^{-1} | 0.378  | ITGB1, CAPN5I, MAPK1, EZR, CAPN1, TLN1, CAPN2, VCL, CAST, ACTN4, CDK1, ACTN1 |
| Integrin signaling          | 7.74                    | 1.04 \times 10^{-1} | -0.894 | ITGB1, ACTR2, ARPC1B, MAPK1, ARF1, TLN1, ACTR3, CAPN5I, CAPN1, RHOA, ARPC2, CAV1, ZYX, CAPN2, VCL, ACTN4, CTN, ACTG1, ACTN1, MYL12A |
| Virus entry via endocytic pathways | 7.62                    | 1.57 \times 10^{-1} |       | B2M, ITGB1, FLNB, FLNC, FLNA, HLA-A, AP2B1, HLA-B, CLTC, CAV1, RVRC, AP1B1, ACTG1, ACTA1 |
| Unfolded protein response    | 7.31                    | 2.04 \times 10^{-1} |       | HSPA8, HSPA4, CALR, P4HB, HSP90B1, UBxN4, HSPA9, VCL, CANX, DNAJ1, HSPA5 |
| ILK signaling               | 6.94                    | 1.02 \times 10^{-1} | -1.414 | ITGB1, FLNB, MYH10, MYH9, FN1, CFL1, MAPK1, PPP2CA, VIM, PPP2RIA, FLNA, FLNC, RHOA, KRT18, ACTN4, ACTG1, ACTN1, ACTA1, NACA |
Table 3. Cont.

| INGENUITY Canonical Pathways                                 | $-\log(p\text{-Value})^a$ | Ratio $^b$ | z-Score $^c$ | Molecules                                                                 |
|--------------------------------------------------------------|---------------------------|------------|-------------|---------------------------------------------------------------------------|
| 14-3-3-mediated signaling                                   | 6.89                      | 1.28 $\times 10^{-1}$ |            | TUBA1B, YWHAQ, YWHAH, YWHAE, MAPK1, TUBB4B, PDIA3, YWHAB, YWHAZ, VIM, TUBB, YWHAQ, TUBB6, TUBB8, SFN |
| Rhogdi signaling                                            | 6.73                      | 1.04 $\times 10^{-1}$ | $-1.000$   | ITGB1, GD1, ACTR2, CFL1, ARPC1B, GNB2L1, GD2, GNA12, ACTR3, RHOA, ARPC2, EZR, CD44, ARHGDI1, ACTG1, ACTA1, MSN, MYL12A |
| RhoA signaling                                              | 6.65                      | 1.23 $\times 10^{-1}$ | $-0.258$   | ACTR2, PN1, SEPT9, ARPC1B, CFL1, SEPT7, ACTR3, ARPC2, EZR, RHOA, ACTG1, ACTA1, SEPT2, MSN, MYL12A |
| Signaling by Rho family GTPases                             | 6.64                      | 8.97 $\times 10^{-2}$ | 0.471      | ITGB1, ACTR2, CFL1, MAPK1, SEPT9, ARPC1B, SEPT7, GNB2L1, VIM, IQGAP1, GNA12, STMN1, ACTR3, EZR, ARPC2, RHOA, ACTG1, ACTA1, SEPT2, MSN, MYL12A |
| PI3K/Akt signaling                                          | 5.84                      | 1.14 $\times 10^{-1}$ | $-0.535$   | YWHAQ, ITGB1, PPP2R1A, HSP90B1, YWHAQ, HSP90A1, YWHAH, MAPK1, YWHAE, YWHAH, YWHAZ, PPP2CA, YWHAZ, HSP90AA1, SFN |
| Germ cell-sertoli cell junction signaling                   | 5.82                      | 1.00 $\times 10^{-1}$ |            | ITGB1, TUBA1B, MAPK1, CFL1, TUBB4B, CTNNA1, TUBB, IQGAP1, TUBB6, TUBB8, RHOA, ZYX, ACTN4, ACTG1, ACTN1, ACTA1 |
| Cell cycle: G$_2$/M DNA damage checkpoint regulation        | 5.69                      | 1.84 $\times 10^{-1}$ | $-0.447$   | YWHAQ, PRKDC, YWHAQ, YWHAH, YWHAH, YWHAZ, SFN, CDK1 |
| Clathrin-mediated endocytosis signaling                     | 5.63                      | 9.19 $\times 10^{-2}$ |            | ITGB1, ACTR2, ARPC1B, PICALM, AP2B1, CLTC, RAB7A, APB1, HSP8, ACTR3, ARPC2, RAB11A, TFR, DNM1L, CTN, ACTG1, ACTA1 |
| Glutaryl-CoA degradation                                     | 5.51                      | 4.55 $\times 10^{-1}$ |            | HSD17B10, ACAT2, ACAT1, HADHA, HADH |
| p70S6K signaling                                            | 5.26                      | 1.09 $\times 10^{-1}$ | 0.000      | GNA12, YWHAQ, PPP2R1A, YWHAQ, YWHAH, MAPK1, YWHAE, EEF2, YWHAH, PDIA3, PPP2CA, YWHAZ, SFN |
| Hippo signaling                                             | 5.20                      | 1.28 $\times 10^{-1}$ | 0.632      | YWHAQ, PPP2R1A, YWHAQ, YWHAH, YWHAH, PPP2CA, YWHAH, CD44, YWHAZ, SFN, PPP1CA |
| Regulation of actin-based motility by rho                   | 4.96                      | 1.21 $\times 10^{-1}$ | $-1.265$   | ITGB1, ACTR2, PN1, ACTR3, ARPC1B, CFL1, ARPC2, RHOA, ARHGDI1, ACTA1, MYL12A |
| Isoleucine degradation I                                     | 4.89                      | 3.57 $\times 10^{-1}$ |            | HSD17B10, ECHS1, ACAT2, ACAT1, HADHA |
| Aldosterone signaling in epithelial cells                   | 4.76                      | 9.21 $\times 10^{-2}$ |            | MAPK1, PDIA3, HSP9, HSPD1, DNAJA1, HSP5, HSPA8, HSPA4, HSP90B1, HSP90AB1, DNAJC8, HSP90AA1, AHCY, HSPB1 |
| Protein kinase a signaling                                  | 4.67                      | 6.22 $\times 10^{-2}$ |            | FLNB, HIST1H1C, MYH10, YWHAQ, YWHAH, MAPK1, YWHAE, YWHAH, YWHAZ, PDIA3, GNB2L1, YWHAZ, PYGL, PYGB, PDHE6H1, CTNNA2, IQGAP1, HSP90A1, HSP90B1, HSP90B2, FLNA, FLNC, RHOA, SFN, PPP1CA, APEX1, MYL12A |
| Sertoli cell-sertoli cell junction signaling                | 4.59                      | 8.43 $\times 10^{-2}$ |            | ITGB1, SPTBN1, TUBA1B, MAPK1, TUBB4B, CTNNA1, YBX3, TUBB, TUBB6, TUBB8, ACTN4, SPTAN1, ACTG1, ACTN1, ACTA1 |
| Lipid antigen presentation by CD1                          | 4.56                      | 2.31 $\times 10^{-1}$ |            | B2M, CALR, PDIA3, AP2B1, CANX, AP1B1 |
| Superpathway of geranylgeranyldiphosphate biosynthesis I (via mevalonate) | 4.43                      | 2.94 $\times 10^{-1}$ |            | FDPS, ACAT2, IDI1, ACAT1, HADHA |
| INGENUITY Canonical Pathways | −log(p-Value) a | Ratio b | z-Score c | Molecules |
|-----------------------------|----------------|---------|-----------|-----------|
| VEGF signaling              | 4.20           | 1.10 × 10⁻¹ | 0.000 | EIF2S2, YWHAE, MAPK1, VCL, ACTN4, EIF2S1, SFN, ACTG1, ACTA1, ACTN1 |
| Fcγ receptor-mediated phagocytosis in macrophages and monocytes | 4.12 | 1.08 × 10⁻¹ | −1.265 | ACTR2, ACTR3, ARPC1B, MAPK1, ARPC2, EZR, RAB11A, TLN1, ACTG1, ACTA1 |
| Tryptophan degradation III (eukaryotic) | 4.06 | 2.50 × 10⁻¹ | | HSD17B10, ACAT2, ACTA1, HADHA, HADH |
| Pentose phosphate pathway | 4.03 | 3.64 × 10⁻¹ | | PGD, TKT, TALDO1, G6PD |
| Nrf2-mediated oxidative stress response | 3.95 | 7.78 × 10⁻² | −1.890 | SOD1, MAPK1, PRDX1, DNAJA1, EP2P9, DNAJC8, STIP1, VCP, CCT7, DNAJA2, SQSTM1, ACTG1, ACTA1, GSTP1 |
| Purine nucleotides de novo biosynthesis II | 3.86 | 3.33 × 10⁻¹ | | GMPS, IMPDH2, PAICS, ATIC |
| Huntington’s disease signaling | 3.86 | 6.96 × 10⁻² | | SDHA, MAPK1, GNB2L1, HSPA9, CLTC, PSME2, HSPA5, HSPA8, HSPA4, DYNCI12, PSME1, CAPNS1, ATP5B, CAPN1, CAPN2, DNM1L |
| Erk/MAPK signaling | 3.77 | 7.49 × 10⁻² | −1.000 | ITGB1, YWHAQ, YWHAH, MAPK1, PPP2CA, YWHAB, YWHAZ, TLN1, YWHAQ, PPP2R1A, HIF3A/HIF3B, PPP1CA, STAT1, HSPB1 |
| Rac signaling | 3.71 | 9.62 × 10⁻² | −0.333 | ITGB1, ACTR2, ACTR3, ARPC1B, MAPK1, CFL1, ARPC2, RHOA, CD44, IQGAP1 |
| Mevalonate pathway I | 3.71 | 3.08 × 10⁻¹ | | ACAT2, ID1, ACAT1, HADHA |
| Breast cancer regulation by stathmin1 | 3.68 | 7.33 × 10⁻² | | TUBA1B, MAPK1, PPP2CA, TUBB4B, GNB2L1, TUBB, CDK1, GNA12, STMN1, PPP2R1A, TUBB6, TUBB8, RHOA, PPP1CA |
| Antigen presentation pathway | 3.65 | 1.62 × 10⁻¹ | | B2M, CALR, HLA-A, PDIA3, HLA-B, CANX |
| FAK signaling | 3.64 | 1.03 × 10⁻¹ | | ITGB1, CAPNS1, MAPK1, CAPN1, TLN1, CAPN2, VCL, ACTG1, ACTA1 |
| Leukocyte extravasation signaling | 3.52 | 7.07 × 10⁻² | 0.000 | ITGB1, MAPK1, CTNNA1, GNA12, EZR, RHOA, CD44, ACTN4, VCL, CTN, ACTG1, ACTN1, ACTA1, MSN |
| Telomere extension by telomerase | 3.45 | 2.67 × 10⁻¹ | | HNRNPA1, XRC6, HNRNPA2B1, XRC5 |
| Gap junction signaling | 3.45 | 7.74 × 10⁻² | | GNA12, DRN1, TUBA1B, TUBB6, MAPK1, TUBB8, TUBB4B, PDIA3, CAV1, TUBB, ACTG1, ACTA1 |
| Myc mediated apoptosis signaling | 3.35 | 1.21 × 10⁻¹ | | YWHAQ, YWHAH, YWHAE, YWHAB, YWHAZ, SFN |
| Superpathway of cholesterol biosynthesis | 3.32 | 1.79 × 10⁻¹ | | FDPS, ACAT2, ID1, ACAT1, HADHA |
| IGF-1 signaling | 3.28 | 9.28 × 10⁻² | | YWHAQ, YWHAH, YWHAE, MAPK1, YWHAI, YWHAB, YWHAZ, SFN, CYR61 |
| Spliceosomal cycle | 3.24 | 1.00 | | LOC10272494/U2AF1, U2AF2 |
| Tight junction signaling | 3.16 | 7.19 × 10⁻² | | MYH10, PPP2R1A, MYH9, PPP2CA, RHOA, VAPA, CTNNA1, YBX3, SPTAN1, VCL, ACTG1, ACTA1 |
| Cdc42 signaling | 3.16 | 7.19 × 10⁻² | −0.707 | ITGB1, B2M, ACTR2, ACTR3, ARPC1B, MAPK1, CFL1, HLA-A, ARPC2, HLA-B, IQGAP1, MYL12A |
| Erk5 signaling | 3.13 | 1.11 × 10⁻¹ | | YWHAQ, YWHAH, YWHAE, YWHAB, YWHAZ, SFN |
| Paxillin signaling | 3.12 | 8.82 × 10⁻² | −1.667 | ITGB1, MAPK1, ARF1, TLN1, VCL, ACTN4, ACTG1, ACTA1, ACTN1 |
### Table 3. Cont.

| INGENUITY Canonical Pathways | \(-\log(p\text{-Value})^a\) | Ratio \(b\) | z-Score \(c\) | Molecules |
|-----------------------------|-----------------|-----------|----------------|-----------|
| Mitochondrial dysfunction   | 3.07            | 7.02 \(\times 10^{-2}\) |               | HSD17B10, SDHA, ATP5H, ATP5B, PARK7, PRDX5, ATP5A1, CYC1, VDAC1, UQCRC1, CYB5R3, VDAC2 |
| Hypoxia signaling in the cardiovascular system | 3.05 | 1.08 \(\times 10^{-1}\) |               | PARK7, PRDX5, ATP5A1, CYC1, VDAC1, UQCRC1, CYB5R3, VDAC2 |
| Mitotic roles of polo-like kinase | 3.01 | 1.06 \(\times 10^{-1}\) |               | HSP90B1, PPP2RIA, HSP90AB1, PPP2CA, CAPN1, HSP90AA1, CDK1 |
| Sucrose degradation V (mammalian) | 2.99 | 3.33 \(\times 10^{-1}\) |               | TP1, ALDOA, ALDOC |
| Ketolysis                   | 2.99            | 3.33 \(\times 10^{-1}\) |               | ACAT2, ACAT1, HADHA |
| CTLA4 signaling in cytotoxic T lymphocytes | 2.92 | 9.09 \(\times 10^{-2}\) |               | B2M, PPP2RIA, PPP2CA, HLA-A, AP2B1, CLTC, HLA-B, AP1B1 |
| Endoplasmic reticulum stress pathway | 2.86 | 1.90 \(\times 10^{-1}\) |               | CALR, HSP90B1, EIP2S1, HSP70 |
| Ketogenesis                 | 2.84            | 3.00 \(\times 10^{-1}\) |               | ACAT2, ACAT1, HADHA |
| Glycogen degradation II     | 2.84            | 3.00 \(\times 10^{-1}\) |               | PGM1, PYGB, PYGL |
| Inosine-5'-phosphate biosynthesis II | 2.77 | 6.67 \(\times 10^{-1}\) |               | PAICS, ATIC |
| Ephrin b signaling          | 2.75            | 9.59 \(\times 10^{-2}\) | -0.447 | GNAI2, MAPK1, CFL1, RHOA, GNR2L1, CAP1, HNRNPK |
| TCA cycle II (eukaryotic)   | 2.70            | 1.74 \(\times 10^{-1}\) |               | SDHA, CS, MDH1, MDH2 |
| Actin nucleation by ARP-WASP complex | 2.67 | 1.07 \(\times 10^{-1}\) | -0.816 | ITGB1, ACTR2, ACTR3, ARPC1B, ARPC2, RHOA |
| Glycogen degradation III    | 2.60            | 2.50 \(\times 10^{-1}\) |               | PGM1, PYGB, PYGL |
| Telomerase signaling        | 2.59            | 8.08 \(\times 10^{-2}\) | 0.000 | HSP90B1, PPP2RIA, MAPK1, HSP90AB1, PPP2CA, HSP90AA1, TP1, PTGES3 |
| Cell cycle control of chromosomal replication | 2.44 | 1.48 \(\times 10^{-1}\) |               | MCM3, MCM6, MCM4, MCM7 |
| Axonal guidance signaling   | 2.40            | 4.62 \(\times 10^{-2}\) |               | DPYS12, ITGB1, TUBA1B, ACTR2, PNN1, CFL1, MAPK1, ARPC1B, TUBB4B, PDIA3, GNB2L1, TUBB, GNAI2, ACTR3, TUBB6, TUBB8, ARPC2, RHOA, RTN4, MYL12A |
| DNA double-strand break repair by non-homologous end joining | 2.39 | 2.14 \(\times 10^{-1}\) |               | PRKDC, XRCC6, XRCC5 |
| Glucocorticoid receptor signaling | 2.37 | 5.36 \(\times 10^{-2}\) |               | MAPK1, YWHAH, HSPA9, HSPA5, PTGES3, HSPA8, HMG2B1, HSPA4, HSP90B1, HSP90AB1, ANXA1, FKBP4, HSP90AA1, STAT1 |
| Fatty acid \(\beta\)-oxidation I | 2.27 | 1.33 \(\times 10^{-1}\) |               | HSD17B10, ECHS1, HADHA, HADH |
| Pentose phosphate pathway (oxidative branch) | 2.27 | 4.00 \(\times 10^{-1}\) |               | PGD, G6PD |
| Trans, trans-farnesyl diphosphate biosynthesis | 2.27 | 4.00 \(\times 10^{-1}\) |               | FDPS, IDH1 |
| Apoptosis signaling         | 2.26            | 7.87 \(\times 10^{-2}\) | 1.134 | CAPN51, MAPK1, CAPN1, LMNA, CAPN2, SPTAN1, CDK1 |
| Granulocyte B signaling     | 2.22            | 1.88 \(\times 10^{-1}\) |               | PRKDC, NUMA1, LMNB1 |
| Parkinson’s signaling       | 2.22            | 1.88 \(\times 10^{-1}\) |               | UCHL1, MAPK1, PARK7 |
| Agrin interactions at neuromuscular junction | 2.22 | 8.70 \(\times 10^{-2}\) | -1.342 | ITGB1, MAPK1, LAMB1, CTTN, ACTG1, ACTA1 |
| Aryl hydrocarbon receptor signaling | 2.18 | 6.43 \(\times 10^{-2}\) | -0.378 | HSP90B1, MAPK1, HSP90AB1, HSP90AA1, GSTP1, PTGES3, HSPB1, MCM7, AIP |
| Pyruvate fermentation to lactate | 2.10 | 3.33 \(\times 10^{-1}\) |               | LDHA, LDHB |
Table 3. Cont.

| INGENUITY Canonical Pathways | −log(p-Value) b | Ratio b | z-Score c | Molecules |
|-----------------------------|-----------------|---------|-----------|-----------|
| Pentose phosphate pathway (non-oxidative branch) | 2.10 | 3.33 × 10⁻¹ | TKT, TALDO1 |
| Semaphorin signaling in neurons | 2.07 | 9.43 × 10⁻² | ITGB1, DPYSL2, MAPK1, CFL1, RHOA |
| Ephrin receptor signaling | 2.04 | 5.75 × 10⁻² | ITGB1, GNAI2, ACTR2, ACTR3, ARPC1B, MAPK1, CFL1, ARPC2, RHOA, GNB2L1 |
| CDK5 signaling | 2.02 | 7.07 × 10⁻² | 0.000 | ITGB1, PPP2R1A, MAPK1, PPP2CA, CAPN1, LAMB1, PPP1CA |
| Superpathway of serine and glycine biosynthesis I | 1.96 | 2.86 × 10⁻¹ | PHGDH, SHMT2 |
| Aspartate degradation II | 1.96 | 2.86 × 10⁻¹ | MDH1, MDH2 |
| Granzyme A signaling | 1.94 | 1.50 × 10⁻¹ | HIST1H1C, SET, APEX1 |
| Prostate cancer signaling | 1.86 | 7.32 × 10⁻² | HSP90B1, MAPK1, PA2G4, HSP90AB1, HSP90AA1, GSTP1 |
| fMLP signaling in neutrophils | 1.82 | 6.48 × 10⁻² | 0.000 | GNAI2, ACTR2, ACTR3, ARPC1B, MAPK1, ARPC2, GNB2L1 |
| Mechanisms of viral exit from host cells | 1.79 | 9.76 × 10⁻² | 0.000 | XPO1, LMNB1, ACTG1, ACTA1 |
| UDP-N-acetyl-D-galactosamine biosynthesis II | 1.74 | 2.22 × 10⁻¹ | GPI, UAP1 |
| eNOS signaling | 1.70 | 5.67 × 10⁻² | 0.000 | HSPA8, HSPA4, HSP90B1, HSP90AB1, HSPA9, CAV1, HSP90AA1, HSPA5 |
| Acetyl-CoA biosynthesis III (from citrate) | 1.62 | 1.00 | ACLY |
| Ber pathway | 1.49 | 1.67 × 10⁻¹ | PCNA, APEX1 |
| Amyloid processing | 1.48 | 7.84 × 10⁻² | 0.000 | CAPNS1, MAPK1, CAPN1, CAPN2 |
| Agranulocyte adhesion and diapedesis | 1.42 | 4.76 × 10⁻² | ITGB1, GNAI2, MYH10, FN1, MYH9, EZR, ACTG1, ACTA1, MSN |
| Cytotoxic T lymphocyte-mediated apoptosis of target cells | 1.40 | 9.38 × 10⁻² | 0.000 | B2M, HLA-A, HLA-B |
| Role of CHK proteins in cell cycle checkpoint control | 1.37 | 7.27 × 10⁻² | 0.000 | PCNA, PPP2R1A, PPP2CA, CDK1 |
| Oxidative phosphorylation | 1.33 | 5.50 × 10⁻² | SDHA, ATP5H, ATP5B, ATP5A1, CYC1, UQCRC1 |
| Palmitate biosynthesis I (animals) | 1.33 | 5.00 × 10⁻¹ | FASN |
| Fatty acid biosynthesis initiation II | 1.33 | 5.00 × 10⁻¹ | FASN |
| Formaldehyde oxidation II (glutathione-dependent) | 1.33 | 5.00 × 10⁻¹ | ESD |
| Glycine biosynthesis I | 1.33 | 5.00 × 10⁻¹ | SHMT2 |
| Glutamate biosynthesis II | 1.33 | 5.00 × 10⁻¹ | GLUD1 |
| Glutamate degradation X | 1.33 | 5.00 × 10⁻¹ | GLUD1 |
| Chondroitin sulfate degradation (metazoa) | 1.31 | 1.33 × 10⁻¹ | CD44, HEXB |
| Androgen signaling | 1.30 | 5.41 × 10⁻² | GNAI2, HSPA4, CALR, MAPK1, GNB2L1, HSP90AA1 |
| Dermatan sulfate degradation (metazoa) | 1.26 | 1.25 × 10⁻¹ | CD44, HEXB |
| INGENUITY Canonical Pathways                                           | $-\log(p\text{-Value})$ a | Ratio b | z-Score c | Molecules                                                                 |
|-------------------------------------------------------------|---------------------------|---------|-----------|---------------------------------------------------------------------------|
| α-Adrenergic signaling                                      | 1.24                      | 5.75 $\times 10^{-2}$ | ~1.00    | GNAI2, MAPK1, GNB2L1, PYGB, PYGL                                        |
| Neuregulin signaling                                        | 1.22                      | 5.68 $\times 10^{-2}$ | ~1.00    | ITGB1, HSP90B1, MAPK1, HSP90AB1, HSP90AA1                               |
| Methionine degradation I (to homocysteine)                  | 1.21                      | 1.18 $\times 10^{-1}$ | ~1.00    | PRMT5, AHCY                                                              |
| Crosstalk between dendritic cells and natural killer cells  | 1.21                      | 5.62 $\times 10^{-2}$ | ~1.00    | HLA-A, HLA-B, TLN1, ACTG1, ACTA1                                       |
| Calcium signaling                                           | 1.19                      | 4.49 $\times 10^{-2}$ | ~1.00    | MYH10, CALR, MYH9, MAPK1, TPM3, TPM4, TPM2, ACTA1                       |
| PPARα/RXRα activation                                       | 1.18                      | 4.47 $\times 10^{-2}$ | 0.378    | CAND1, HSP90B1, MAPK1, HSP90AB1, PDI3, FASN, HSP90AA1, AIP              |
| Valine degradation I                                        | 1.17                      | 1.11 $\times 10^{-1}$ | ~1.00    | ECHS1, HADHA                                                             |
| Death receptor signaling                                    | 1.16                      | 5.43 $\times 10^{-3}$ | 1.342    | LMNA, SPTAN1, ACTG1, ACTA1, HSPB1                                       |
| Neuroprotective role of THOP1 in Alzheimer’s disease        | 1.16                      | 7.50 $\times 10^{-2}$ | ~1.00    | YWHAE, HLA-A, HLA-B                                                      |
| Diphthamide biosynthesis                                    | 1.16                      | 3.33 $\times 10^{-1}$ | ~1.00    | EEF2                                                                     |
| NADH repair                                                 | 1.16                      | 3.33 $\times 10^{-1}$ | ~1.00    | GAPDH                                                                    |
| Methylglyoxal degradation I                                 | 1.16                      | 3.33 $\times 10^{-1}$ | ~1.00    | GLO1                                                                     |
| Hypusine biosynthesis                                       | 1.16                      | 3.33 $\times 10^{-1}$ | ~1.00    | EF5A                                                                     |
| Oxidized GTP and DGTP detoxification                       | 1.16                      | 3.33 $\times 10^{-1}$ | ~1.00    | DDX6                                                                     |
| Gadd45 signaling                                            | 1.13                      | 1.05 $\times 10^{-1}$ | ~1.00    | PCNA, CDK1                                                               |
| DNA damage-induced 14-3-3σ signaling                       | 1.13                      | 1.05 $\times 10^{-1}$ | ~1.00    | SFN, CDK1                                                                |
| Cysteine biosynthesis III (mammalia)                       | 1.13                      | 1.05 $\times 10^{-1}$ | ~1.00    | PRMT5, AHCY                                                              |
| PPAR signaling                                              | 1.13                      | 5.32 $\times 10^{-2}$ | 0.447    | HSP90B1, MAPK1, HSP90AB1, HSP90AA1, AIP                                 |
| Tec kinase signaling                                        | 1.07                      | 4.43 $\times 10^{-2}$ | ~1.342   | ITGB1, GNAI2, RHOA, GNB2L1, STAT1, ACTG1, ACTA1                         |
| Nitric oxide signaling in the cardiovascular system         | 1.05                      | 5.05 $\times 10^{-2}$ | 0.447    | HSP90B1, MAPK1, HSP90AB1, CAV1, HSP90AA1                               |
| Cellular effects of sildenafil (viagra)                     | 1.05                      | 4.65 $\times 10^{-2}$ | ~1.00    | MYH10, MYH9, PDI3, ACTG1, ACTA1, MYL12A                                  |
| Chemosignaling                                              | 1.05                      | 5.63 $\times 10^{-2}$ | ~1.00    | GNAI2, MAPK1, CFL1, RHOA                                               |
| Uracil degradation II (reductive)                          | 1.04                      | 2.50 $\times 10^{-1}$ | ~1.00    | DPYSL2                                                                   |
| Thymine degradation                                         | 1.04                      | 2.50 $\times 10^{-1}$ | ~1.00    | DPYSL2                                                                   |
| Geranylgeranyldiphosphate biosynthesis                      | 1.04                      | 2.50 $\times 10^{-1}$ | ~1.00    | FDFS                                                                     |
| Rapoport-luebering glycolytic shunt                        | 1.04                      | 2.50 $\times 10^{-1}$ | ~1.00    | PGAM1                                                                    |
| Polyamine regulation in colon cancer                       | 1.02                      | 9.09 $\times 10^{-2}$ | ~1.00    | PSME1, PSME2                                                             |
| HIF1α signaling                                             | 1.01                      | 4.90 $\times 10^{-2}$ | ~1.00    | MAPK1, HSP90AA1, LDHA, APEX1, LDHB                                      |
| Cardiac β-adrenergic signaling                              | 1.00                      | 4.51 $\times 10^{-2}$ | ~0.447   | PPP2R1A, PPP2CA, GNB2L1, PPP1CA, APEX1, PDE6H                            |
### Table 3. Cont.

| INGenuity Canonical Pathways | $-\log(p\text{-Value})$ | Ratio | z-Score | Molecules |
|-----------------------------|--------------------------|-------|---------|-----------|
| nNOS signaling in neurons   | $9.92 \times 10^{-1}$    | 6.38 $\times 10^{-2}$ | $-0.447$ | CAPN1, CAPN2 |
| AMPK signaling              | $9.90 \times 10^{-1}$    | 4.48 $\times 10^{-2}$ |         | PP2R1A, MAPK1, PP2CA, FASN, PFKP, PPM1G |
| IL-22 signaling             | $9.53 \times 10^{-1}$    | 8.33 $\times 10^{-2}$ |         | MAPK1, STAT1 |
| Sertine biosynthesis        | $9.44 \times 10^{-1}$    | 2.00 $\times 10^{-1}$ |         | PFKD1 |
| DTMP de novo biosynthesis   | $9.44 \times 10^{-1}$    | 2.00 $\times 10^{-1}$ |         | SHMT2 |
| Folate polyglutamylation    | $9.44 \times 10^{-1}$    | 2.00 $\times 10^{-1}$ |         | SHMT2 |
| Xenobiotic metabolism signaling | $9.35 \times 10^{-1}$ | 3.69 $\times 10^{-2}$ |         | HSP90B1, PP2R1A, MAPK1, HSP90AB1, PP2CA, HSP90AA1, GSTP1, PTGES3, ESF, AIP |
| Cyclins and cell cycle regulation | $9.34 \times 10^{-1}$ | 5.13 $\times 10^{-2}$ |         | PP2R1A, PA2G4, PP2CA, CDK1 |
| Role of JAK family kinases in IL-6-type cytokine signaling | $9.24 \times 10^{-1}$ | 8.00 $\times 10^{-2}$ |         | MAPK1, STAT1 |
| Type I diabetes mellitus signaling | $9.08 \times 10^{-1}$ | 4.55 $\times 10^{-2}$ |         | MAPK1, HLA-A, HLA-B, HSF3, STAT1 |
| Role of tissue factor in cancer | $9.08 \times 10^{-1}$ | 4.55 $\times 10^{-2}$ |         | ITGB1, P4HB, MAPK1, CFL1, CYR61 |
| Antiproliferative role of Tob in T cell signaling | $8.95 \times 10^{-1}$ | 7.69 $\times 10^{-2}$ |         | PABPC1, MAPK1 |
| Arginine biosynthesis IV    | $8.70 \times 10^{-1}$    | 1.67 $\times 10^{-1}$ |         | GLUD1 |
| Superoxide radicals degradation | $8.70 \times 10^{-1}$ | 1.67 $\times 10^{-1}$ |         | SOD1 |
| UDP-N-acetyl-D-glucosamine biosynthesis II | $8.70 \times 10^{-1}$ | 1.67 $\times 10^{-1}$ |         | UAP1 |
| GDP-mannose biosynthesis    | $8.70 \times 10^{-1}$    | 1.67 $\times 10^{-1}$ |         | GPl |
| IL-15 production            | $8.69 \times 10^{-1}$    | 7.41 $\times 10^{-2}$ |         | TF1, STAT1 |
| CCR3 signaling in eosinophils | $8.28 \times 10^{-1}$ | 4.27 $\times 10^{-2}$ |         | GNAI2, MAPK1, CFL1, RHOA, GNBP21 |
| IL-8 signaling              | $8.25 \times 10^{-1}$    | 3.83 $\times 10^{-2}$ | $-0.816$ | GNAI2, MAPK1, RHOA, GNBP21, IQGAP1, LAPS1, CSTB |
| Glioma invasiveness signaling | $8.09 \times 10^{-1}$ | 5.26 $\times 10^{-2}$ |         | MAPK1, RHOA, CD44 |
| Acetyl-CoA biosynthesis I (pyruvate dehydrogenase complex) | $8.08 \times 10^{-1}$ | 1.43 $\times 10^{-1}$ |         | DLAT |
| GDP-glucose biosynthesis    | $8.08 \times 10^{-1}$    | 1.43 $\times 10^{-1}$ |         | PGCl |
| G β γ signaling             | $7.98 \times 10^{-1}$    | 4.55 $\times 10^{-2}$ |         | GNAI2, MAPK1, GNBP21, CAV1 |
| Role of p14/p19arf in tumor suppression | $7.95 \times 10^{-1}$ | 6.67 $\times 10^{-2}$ |         | NPM1, SF3A1 |
| PAK signaling               | $7.86 \times 10^{-1}$    | 4.49 $\times 10^{-2}$ |         | ITGB1, MAPK1, CFL1, MYL12A |
| Induction of apoptosis by HIV1 | $7.63 \times 10^{-1}$ | 5.00 $\times 10^{-2}$ |         | SLC25A6, SLC25A3, SLC25A5 |
| Glucose and glucose-1-phosphate degradation | $7.55 \times 10^{-1}$ | 1.25 $\times 10^{-1}$ |         | PGCl |
| Superpathway of methionine degradation | $7.51 \times 10^{-1}$ | 6.25 $\times 10^{-2}$ |         | PRMT5, AHCT |
| GM-CSF signaling            | $7.43 \times 10^{-1}$    | 4.84 $\times 10^{-2}$ |         | MAPK1, GNBP21, STAT1 |
| Estrogen receptor signaling | $7.26 \times 10^{-1}$    | 3.94 $\times 10^{-2}$ |         | PRKDC, DD5X, H3F3A/H3F3B, MAPK1, PHB2 |
| PTP pathway                 | $7.20 \times 10^{-1}$    | 4.76 $\times 10^{-2}$ |         | PTP1, RHOA, HSP81 |
Table 3. Cont.

| INGENUITY Canonical Pathways                        | −log(p-Value) | Ratio | z-Score | Molecules                          |
|-----------------------------------------------------|---------------|-------|---------|-----------------------------------|
| Oncostatin m signaling                              | 7.11 × 10⁻¹   | 5.88 × 10⁻² | MAPK1, STAT1 |
| Interferon signaling                                | 7.11 × 10⁻¹   | 5.88 × 10⁻² | IFITM3, STAT1 |
| Prostanoid biosynthesis                             | 7.09 × 10⁻¹   | 1.11 × 10⁻¹  | PTGES3 |
| Folate transformations I                            | 7.09 × 10⁻¹   | 1.11 × 10⁻¹  | SHMT2 |
| Pyridoxal 5'-phosphate salvage pathway             | 7.06 × 10⁻¹   | 4.69 × 10⁻²  | PDZK, MAPK1, CDK1 |
| Cell cycle regulation by bfg family proteins       | 6.92 × 10⁻¹   | 5.71 × 10⁻²  | PTP2R1A, PTP2CA |
| Intron splicing                                     | 6.92 × 10⁻¹   | 5.71 × 10⁻²  | APEX1, PD66H |
| Amyotrophic lateral sclerosis signaling             | 6.84 × 10⁻¹   | 4.08 × 10⁻²  | SOD1, CAPNS1, CAPN1, CAPN2 |
| p53 signaling                                       | 6.84 × 10⁻¹   | 4.08 × 10⁻²  | PRKDC, PCNA, SFN, GML |
| Role of PI3K/Akt signaling in the pathogenesis of influenza | 6.80 × 10⁻¹   | 4.55 × 10⁻²  | GNA12, KPN1, MAPK1 |
| Phospholipase c signaling                           | 6.70 × 10⁻¹   | 3.35 × 10⁻²  | −1.633 |
| Glycine ßine degradation                            | 6.68 × 10⁻¹   | 1.00 × 10⁻¹  | SHMT2 |
| Complement system                                   | 6.56 × 10⁻¹   | 5.41 × 10⁻²  | CD59, C1QB |
| Macropinocytosis signaling                          | 6.55 × 10⁻¹   | 4.41 × 10⁻²  | ITGB1, RHOA, ACTN4 |
| Relaxin signaling                                   | 6.54 × 10⁻¹   | 3.70 × 10⁻²  | GNA12, MAPK1, GNB2L1, APEX1, PD66H |
| CCR5 signaling in macrophages                       | 6.42 × 10⁻¹   | 4.35 × 10⁻²  | GNA12, MAPK1, GNB2L1 |
| Melatonin signaling                                 | 6.30 × 10⁻¹   | 4.29 × 10⁻²  | GNA12, MAPK1, PDIA3 |
| Role of PKR in interferon induction and antiviral response | 6.06 × 10⁻¹   | 5.00 × 10⁻²  | STAT1, EIF251 |
| Synaptic long term depression                       | 6.06 × 10⁻¹   | 3.55 × 10⁻²  | GNA12, PTP2R1A, MAPK1, PTP2CA, PDIA3 |
| Dendritic cell maturation                           | 5.90 × 10⁻¹   | 3.35 × 10⁻²  | B2M, MAPK1, HLA-A, PDIA3, HLA-B, STAT1 |
| Production of nitric oxide and reactive oxygen species in macrophages | 5.83 × 10⁻¹   | 3.33 × 10⁻²  | −0.816 |
| Sphingosine-1-phosphate signaling                   | 5.79 × 10⁻¹   | 3.67 × 10⁻²  | GNA12, MAPK1, PDIA3, RHOA |
| Assembly of rna polymerase III complex               | 5.69 × 10⁻¹   | 7.69 × 10⁻²  | SF3A1 |
| Systemic lupus erythematous signaling               | 5.62 × 10⁻¹   | 3.18 × 10⁻²  | PRPF19, MAPK1, HLA-A, HNRNPA2B1, HLA-B, SNRPD1, SNRPD3 |
| PDGF signaling                                      | 5.54 × 10⁻¹   | 3.90 × 10⁻²  | MAPK1, CAV1, STAT1 |
| iNOS signaling                                      | 5.48 × 10⁻¹   | 4.55 × 10⁻²  | MAPK1, STAT1 |
| Cardiac hypertrophy signaling                       | 5.45 × 10⁻¹   | 3.14 × 10⁻²  | GNA12, MAPK1, PDIA3, RHOA, GNB2L1, HSPB1, MYL12A |
| Dopamine receptor signaling                         | 5.44 × 10⁻¹   | 3.85 × 10⁻²  | PTP2R1A, PTP2CA, PDIA3 |
| INGENUITY Canonical Pathways                                      | $-\log(p\text{-Value})$ | Ratio | z-Score | Molecules                                      |
|-----------------------------------------------------------------|--------------------------|-------|---------|-----------------------------------------------|
| Urate biosynthesis/inosine                                      | $5.42 \times 10^{-1}$    | 1.74  | 1.71    | IMPDH2                                        |
| 5'-phosphate degradation                                        | $5.42 \times 10^{-1}$    | 1.74  | 1.71    |                                               |
| Colanic acid building blocks biosynthesis                       | $5.25 \times 10^{-1}$    | 3.29  | 0.000   | GNAI2, MAPK1, RH0A, GNB2L1, MYL12A            |
| CXCR4 signaling                                                | $5.21 \times 10^{-1}$    | 4.35  | 0.000   | ACTG1, ACTA1                                  |
| MSP-RON signaling pathway                                       | $5.17 \times 10^{-1}$    | 6.67  | 2.000   | AKR1B1                                        |
| Methyglyoxal degradation III                                    | $5.14 \times 10^{-1}$    | 3.14  | 0.447   | GNAI2, MAPK1, PDI3A, RH0A, GNB2L1, MYL12A     |
| Thrombin signaling                                             | $5.10 \times 10^{-1}$    | 3.39  | 0.000   | ACTR2, ACTR3, ARPC1B, ARPC2                   |
| Implicated in T-helper cells                                    | $5.06 \times 10^{-1}$    | 6.67  | 2.000   | PCNA                                          |
| MCP-1 signaling                                                 | $4.97 \times 10^{-1}$    | 4.17  | 2.000   |                                               |
| Methylglyoxal degradation II (animals)                          | $4.94 \times 10^{-1}$    | 6.25  | 2.000   |                                               |
| Gαi signaling                                                  | $4.92 \times 10^{-1}$    | 3.33  | 2.000   | GNAI2, MAPK1, GNB2L1, CAV1                    |
| Autoimmune thyroid disease signaling                            | $4.85 \times 10^{-1}$    | 4.08  | 2.000   | HLA-A, HLA-B                                  |
| TR/RXR activation                                              | $4.79 \times 10^{-1}$    | 3.53  | 2.000   | ENO1, FASN, PFKP                              |
| F-linolenate biosynthesis II (animals)                          | $4.72 \times 10^{-1}$    | 5.88  | 2.000   | CYB5R3                                        |
| Allograft rejection signaling                                   | $4.71 \times 10^{-1}$    | 3.49  | 2.000   | B2M, HLA-A, HLA-B                             |
| Dopamine-DARPP32 feedback in camp signaling                    | $4.68 \times 10^{-1}$    | 3.11  | 2.000   | GNAI2, PTP2R1A, PTP2CA, PDI3A, PPP1CA         |
| UVa-induced MAPK signaling                                      | $4.54 \times 10^{-1}$    | 3.41  | 2.000   | MAPK1, PDI3A, STAT1                           |
| CNTF signaling                                                 | $4.51 \times 10^{-1}$    | 3.85  | 2.000   | MAPK1, STAT1                                  |
| Endometrial cancer signaling                                    | $4.51 \times 10^{-1}$    | 3.85  | 2.000   | MAPK1, CTNNA1                                 |
| OX40 signaling pathway                                          | $4.46 \times 10^{-1}$    | 3.37  | 2.000   | B2M, HLA-A, HLA-B                             |
| UVB-induced MAPK signaling                                      | $4.41 \times 10^{-1}$    | 3.77  | 2.000   | H3F3A/H3F3B, MAPK1                            |
| Communication between innate and adaptive immune cells          | $4.31 \times 10^{-1}$    | 3.30  | 2.000   | B2M, HLA-A, HLA-B                             |
| IL-1 signaling                                                 | $4.31 \times 10^{-1}$    | 3.30  | 2.000   | GNAI2, MAPK1, GNB2L1                          |
| Thrombopoietin signaling                                       | $4.21 \times 10^{-1}$    | 3.64  | 2.000   | MAPK1, STAT1                                  |
| Purine nucleotides degradation II (aerobic)                     | $4.16 \times 10^{-1}$    | 5.00  | 2.000   | IMPDH2                                        |
| Wnt/Ca++ signaling                                             | $4.11 \times 10^{-1}$    | 3.57  | 2.000   | PDI3A, PDE6H                                  |
| EGF signaling                                                  | $4.11 \times 10^{-1}$    | 3.57  | 2.000   | MAPK1, STAT1                                  |
| Glioma signaling                                               | $4.01 \times 10^{-1}$    | 3.16  | 2.000   | MAPK1, PA2G4, IGF2R                           |
| INGENUITY Canonical Pathways                                      | -log(p-Value) * | Ratio  b | z-Score  c | Molecules                           |
|-----------------------------------------------------------------|-----------------|----------|------------|-------------------------------------|
| Maturity onset diabetes of young (mody) signaling               | 3.84 x 10^-1    | 4.55 x 10^-2 | GAPDH     |
| ATM signaling                                                   | 3.84 x 10^-1    | 3.39 x 10^-2 | TRIM28, CDK1 |
| Granulocyte adhesion and diapedesis                             | 3.81 x 10^-1    | 2.82 x 10^-2 | ITGB1, GNAI2, EZR, HSPB1, MSN |
| Estrogen-dependent breast cancer signaling                      | 3.59 x 10^-1    | 3.23 x 10^-2 | HSD17B10, MAPK1 |
| Role of JAK1, JAK2 and TYK2 in interferon signaling             | 3.56 x 10^-1    | 4.17 x 10^-2 | STAT1     |
| Estrogen-mediated s-phase entry                                 | 3.56 x 10^-1    | 4.17 x 10^-2 | CDK1      |
| Antiproliferative role of somatostatin receptor 2               | 3.51 x 10^-1    | 3.17 x 10^-2 | MAPK1, GNB2L1 |
| Role of JAK1 and JAK3 in γc cytokine signaling                  | 3.51 x 10^-1    | 3.17 x 10^-2 | MAPK1, STAT1 |
| Role of lipids/lipid rafts in the pathogenesis of influenza     | 3.43 x 10^-1    | 4.00 x 10^-2 | FDP5      |
| IL-17a signaling in gastric cells                               | 3.43 x 10^-1    | 4.00 x 10^-2 | MAPK1     |
| Cell cycle: G1/S checkpoint regulation                          | 3.43 x 10^-1    | 3.12 x 10^-2 | PA2G4, RPL5 |
| Non-small cell lung cancer signaling                            | 3.35 x 10^-1    | 3.08 x 10^-2 | MAPK1, PA2G4 |
| Pancreatic adenocarcinoma signaling                             | 3.31 x 10^-1    | 2.83 x 10^-2 | MAPK1, PA2G4, STAT1 |
| GABA receptor signaling                                         | 3.21 x 10^-1    | 2.99 x 10^-2 | AP2B1, AP1B1 |
| Pyrimidine ribonucleotides interconversion                      | 3.19 x 10^-1    | 3.70 x 10^-2 | CTPS1     |
| Growth hormone signaling                                        | 3.07 x 10^-1    | 2.90 x 10^-2 | MAPK1, STAT1 |
| Corticotropin releasing hormone signaling                        | 3.04 x 10^-1    | 2.70 x 10^-2 | GNAI2, MAPK1, KRT1 |
| Pyrimidine ribonucleotides de novo biosynthesis                 | 2.97 x 10^-1    | 3.45 x 10^-2 | CTPS1     |
| IL-3 signaling                                                  | 2.94 x 10^-1    | 2.82 x 10^-2 | MAPK1, STAT1 |
| PEDF signaling                                                  | 2.94 x 10^-1    | 2.82 x 10^-2 | MAPK1, RHOA |
| GPCR-mediated integration of enterocodocrine signaling exemplified by an I. cell | 2.94 x 10^-1    | 2.82 x 10^-2 | GNAI2, PDIA3 |
| JAK/STAT signaling                                             | 2.87 x 10^-1    | 2.78 x 10^-2 | MAPK1, STAT1 |
| Glutathione-mediated detoxification                             | 2.87 x 10^-1    | 3.33 x 10^-2 | GSTP1     |
| Sonic hedgehog signaling                                        | 2.87 x 10^-1    | 3.33 x 10^-2 | CDK1      |
| Hereditary breast cancer signaling                              | 2.84 x 10^-1    | 2.61 x 10^-2 | NPM1, SFN, CDK1 |
| NF-kb activation by viruses                                     | 2.81 x 10^-1    | 2.74 x 10^-2 | ITGB1, MAPK1 |
| Prolactin signaling                                             | 2.81 x 10^-1    | 2.74 x 10^-2 | MAPK1, STAT1 |
| STAT3 pathway                                                   | 2.81 x 10^-1    | 2.74 x 10^-2 | MAPK1, IGF2R |
| 4-1BB signaling in T lymphocytes                                | 2.78 x 10^-1    | 3.23 x 10^-2 | MAPK1     |
| INGENUITY Canonical Pathways                                      | $-\log(p$-Value) | Ratio $^b$ | $z$-Score $^c$ | Molecules                                                                 |
|------------------------------------------------------------------|-----------------|------------|----------------|---------------------------------------------------------------------------|
| Flt3 signaling in hematopoietic progenitor cells                  | $2.75 \times 10^{-1}$ | $2.70 \times 10^{-2}$ | MAPK1, STAT1 |
| Leptin signaling in obesity                                       | $2.75 \times 10^{-1}$ | $2.70 \times 10^{-2}$ | MAPK1, PDA3 |
| Ga12/13 signaling                                                | $2.74 \times 10^{-1}$ | $2.56 \times 10^{-2}$ | MAPK1, RHOA, MYL12A |
| p38 MAPK signaling                                               | $2.74 \times 10^{-1}$ | $2.56 \times 10^{-2}$ | H3F3A/H3F3B, STAT1, HSPB1 |
| TREM1 signaling                                                  | $2.69 \times 10^{-1}$ | $2.67 \times 10^{-2}$ | ITGB1, MAPK1 |
| Synaptic long term potentiation                                   | $2.65 \times 10^{-1}$ | $2.52 \times 10^{-2}$ | MAPK1, PDA3, PPP1CA |
| HMGB1 signaling                                                  | $2.60 \times 10^{-1}$ | $2.50 \times 10^{-2}$ | HMGB1, MAPK1, RHOA |
| G protein signaling mediated by tubby                            | $2.60 \times 10^{-1}$ | $3.03 \times 10^{-2}$ | GNRI2L1 |
| MIF-mediated glucocorticoid regulation                           | $2.60 \times 10^{-1}$ | $3.03 \times 10^{-2}$ | MAPK1 |
| Retinol biosynthesis                                             | $2.60 \times 10^{-1}$ | $3.03 \times 10^{-2}$ | ESD |
| Ethanol degradation ii                                           | $2.60 \times 10^{-1}$ | $3.03 \times 10^{-2}$ | HSD17B10 |
| LXR/RXR activation                                               | $2.56 \times 10^{-1}$ | $2.48 \times 10^{-2}$ | ECHS1, FASN, HADH |
| IL-9 signaling                                                   | $2.51 \times 10^{-1}$ | $2.94 \times 10^{-2}$ | STAT1 |
| Inhibition of angiogenesis by TSP1                               | $2.51 \times 10^{-1}$ | $2.94 \times 10^{-2}$ | MAPK1 |
| Reelin signaling in neurons                                      | $2.47 \times 10^{-1}$ | $2.53 \times 10^{-2}$ | ITGB1, PAFAH1B2 |
| IL-17a signaling in fibroblasts                                  | $2.43 \times 10^{-1}$ | $2.86 \times 10^{-2}$ | MAPK1 |
| Role of JAK2 in hormone-like cytokine signaling                  | $2.43 \times 10^{-1}$ | $2.86 \times 10^{-2}$ | STAT1 |
| Stearate biosynthesis I (animals)                                | $2.43 \times 10^{-1}$ | $2.86 \times 10^{-2}$ | FASN |
| Noradrenaline and adrenaline degradation                         | $2.43 \times 10^{-1}$ | $2.86 \times 10^{-2}$ | HSD17B10 |
| Nucleotide excision repair pathway                               | $2.43 \times 10^{-1}$ | $2.86 \times 10^{-2}$ | RAD23B |
| Ceramide signaling                                               | $2.42 \times 10^{-1}$ | $2.50 \times 10^{-2}$ | PPP2R1A, PPP2CA |
| Estrogen biosynthesis                                             | $2.28 \times 10^{-1}$ | $2.70 \times 10^{-2}$ | HSD17B10 |
| April mediated signaling                                         | $2.21 \times 10^{-1}$ | $2.63 \times 10^{-2}$ | MAPK1 |
| Netrin signaling                                                 | $2.14 \times 10^{-1}$ | $2.56 \times 10^{-2}$ | ENAH |
| B cell activating factor signaling                               | $2.07 \times 10^{-1}$ | $2.50 \times 10^{-2}$ | MAPK1 |
| Thyroid cancer signaling                                         | $2.07 \times 10^{-1}$ | $2.50 \times 10^{-2}$ | MAPK1 |
| Transcriptional regulatory network in embryonic stem cells        | $2.07 \times 10^{-1}$ | $2.50 \times 10^{-2}$ | SET |
| MIF regulation of innate immunity                                | $2.01 \times 10^{-1}$ | $2.44 \times 10^{-2}$ | MAPK1 |

$a$ The $p$ value of the protein is computed by the permutation test. $b$ The average ratio is for all peptides associated with the protein (i.e., $\log_2 L/H$). $c$ $z$-Score is the measure of how many standard deviation units that protein’s $\log_2 L/H$ ratio is away from its population mean.
| ID | Molecules in Network | Score | Molecules | Top Diseases and Functions |
|----|---------------------|-------|-----------|---------------------------|
| 1  | ALDO, ALDOA, ALDOC, ATP synthase, C1orf166, DXD1, ENO1, ENO2, enolase, FUS, HIST2H2AC, HNRNPU, NAP1L4, NCL, NONO, PA2G4, PK1, Ras, RPL5, RPL6, RPL7, RPL8, RPL12, RPL18, RPL22, RPL23, RPL10A, RPL7A, RPLP1, RPLP2, SF3Q, SQSTM1, SYNCRIP, T3-TR-RXR, TARS | 47    | 30         | RNA post-transcriptional modification, carbohydrate metabolism, small molecule biochemistry |
| 2  | 14-3-3, 14-3-3 (β, τ, Ω), 14-3-3(γ, ε, ζ, Ω), 14-3-3p(γ, ε, ζ) adenosine-triphosphatase, ATP5A1, ATP5B, C1QBP, CAPZB, CLTC, dishevelled, DYNC1H1, EPRS, ESYT1, GNA2, GN2L3, GSK3, HSP90AA1, HSPA9, KIF5B, MARS, PDCD6, RNH1, SFN, SLC2A5, SLC2A6, TPI1, TUFM, YWHAB, YWHAE, YWHAD, YWHAQ, YWHAZ | 42    | 28         | Protein trafficking, cell death and survival, nucleic acid metabolism |
| 3  | 60S ribosomal subunit, CAND1, CLIC1, EIF2, ERK, HNRNPH3, IPO9, Ku, LAMB1, laminin1, laminin2, NPM1, PXDK, PYGB, ribosomal 40s subunit, RNR, RPL3, RPL4, RPL10, RPL21, RPL27, RPLP0, RPS2, RPS3, RPS5, RPS7, RPS8, RPS10, RPS11, RPS12, RPS24, RPS2A7, RPS4X, RPSA | 40    | 27         | Hematological disease, organismal injury and abnormalities, RNA post-transcriptional modification |
| 4  | α-Tubulin, Ant, ATP5H, β-tubulin, CCT2, CCT3, CCT4, CCT5, CCT7, CCT8, CCT6A, DYSPL, dynemin, EHD1, ENA1, ERF29, GCN1L1, integrin α5 β1, MAP1B, MAPK1, NUMA1, PPP2CA, PPP2R1A, TCPI, TUBA1B, TUBB6, TUBB8, TUBB4B, tubulin (complex), tubulin (family), VAPA, VDAC, VDAC1, VDAC2, ZYX | 40    | 27         | Cellular assembly and organization, cell-to-cell signaling and interaction, reproductive system development and function |
| 5  | ACRY, actin, Cytoskeleton II receptor type 1, Arf, ARF1, CN3N, COP1, COP1B, COP2, COPE, COPG1, CS, EIF3, EIF6, EIF3C, EIF3M, HN1, LRRRC59, malate dehydrogenase, MAP4, MDH1, MDH2, N-cadherin, PARK7, RAB1B, SEPT2, SEPT7, Septin, SMHT2, TALDO1, TXNDC5, WARS | 38    | 26         | Infectious disease, small molecule biochemistry, reproductive system disease |
| 6  | 195 proteasome, 205 proteasome, 265 proteasome, RUB3, CPNE1, ECHS1, immunoproteasome Pa28/20s, KPN3, MHC CLASS I (family), NF-kβ (complex), NPLOC4, NSF1C, OTUB1, PDLIM1, PRDX2, Proteasome PA700/20s, PSMA, PSMA1, PSMA2, PSMA4, PSMA5, PSMA7, PSMB1, PSMC1, PSMC4, PSMD4, PSMD6, RPS14, RPN2, UBA1, UBE2, UBE2L3, UBEN2, ubiquitin | 36    | 25         | Infectious disease, organismal injury and abnormalities, immunological disease |
| 7  | AHC, calpain, CYR61, DXD6, DXDX, EIF8, EIF3B, EIF3I, EIF4A, EIF4M, HN1, LRRRC59, malate dehydrogenase, MAP4, MDH1, MDH2, N-cadherin, PARK7, RAB1B, SEPT2, SEPT7, Septin, SMHT2, TALDO1, TXNDC5, WARS | 36    | 25         | Protein synthesis, cellular movement, gene expression |
| 8  | CALU, CBX3, CD59, COK1, DDB1, DDX5, DNA-methyltransferase, DPC30, GML, GSTP1, H3F3A/H3F3B, histone H3, histone H4, HNRNPH3, HNRNPH4, HNRNP2, IFITM3, IgA, IGF1, MATR3, NAP1L1, NAP1L2, NAP1L3, PAM, PKM, PPM1G, PRMT5, secerase γ, SH3BP2L3, Sol, SOD1, SRC (family), TFCR, thymidine kinase, TRIM2, UBXN4, YBX1 | 36    | 25         | Cellular growth and proliferation, infectious disease, cellular development |
| 9  | APEX1, c-Src, CLIC4, CSE1L, H2AFY, HGF1, HIST1H1C, histone H1, HNRNPH1, HNRNP2, HNRNP3, importin α, importin β, integrin α5β1, IPO5, IPO7, karyopherin β, KPN2A, KPN2B, LOC102724594/U2AF1, PHGDH, PRPF9, PTMA, RAN, RANBP1, SAE1, SF3B1, snRNPA, snRNBP2, SNRPD2, SNRPD3, TNPO1, transportin, U2AF2, VEGF | 34    | 24         | Molecular transport, protein trafficking, RNA post-transcriptional modification |
| ID | Molecules in Network | Score | Molecules | Top Diseases and Functions |
|----|----------------------|-------|-----------|---------------------------|
| 10 | Adaptor protein 1, AIP, AP1y, AP1B1, CALR, CAP1, CD1, CD1D-CANX-CALR-ERp57, CFL1, CRIP2, cytoplasmic dynein, DNAJ, DNAJA1, DNAJA2, DNAJC8, FKBP4, G-actin, HSF, HSP90, HSP22/HSP90, HSP90B1, HYOU1, JNK, P4HB, PMCT1, PDLA3, PDLA4, PDLA6, PRDX4, PTGES3, PYGL, STIP1, TMSB4, TPM2, TPM3 | 32 | 23 | Post-translational modification, protein folding, drug metabolism |
| 11 | ACTG1, ADRB, AP2B1, ATPase, CAPZA1, casein, caspase, creatine kinase, DLAT, DYN11B2, EEF2, EEF1A1, HSP90AB1, HSPA4, HSPA5, HSPA8, HSPB1, HSPD1, IFN, LONP1, mediator, MHC Class II (complex), MMP, NACA, PHB2, PPAP2C, PRKDC, RPNI, RSK, STN1, TLR, TULN, VCP | 32 | 23 | Post-translational modification, protein folding, cell morphology |
| 12 | ACTN1, ACTN4, α-actinin, α-actinin, ARPA3/2, cadherin, CAPG, CAPN2, Cdc2, CSRPR1, CTNNNA1, cytochrome b, F actin, GPI, IMPDH2, integrin γ, KRT1, KRT8, KRT9, KRT18, lamin b, LMP2, PDE (complex), PLEC, spectrin, STP1, STP2, talin, TNF4, TPM4, TUBB, VCL, VIM | 30 | 22 | Cellular compromise, cellular assembly and organization, cellular function and maintenance |
| 13 | ACTR2, ACTR3, α-actin, ARHGDAIA, ARPC2, ARPC1B, BCR (complex), CD44, CTTN, ERTR, EZR, GD1, GD2, IQGAP1, MAPK, MIR124, MSN, PAHFC1B2, PAK, PLIN3, PL3S, RAB5, RAB11A, RAB7, Rac, Rac homolog, Rho GD, RTN4, SEC13, Sos, TMD3, TWF2, VAT1, VAV | 30 | 22 | Cellular assembly and organization, cellular function and maintenance, cell morphology |
| 14 | 3-Hydroxyacyl-CoA dehydrogenase, ACAT1, ACAT2, acetyl-CoA C-acyltransferase, AHNAT, AKRIB1, ANX1, ANXA2, calmodulin, CAPN1, CAPNs3, CAST, CAV1, cavelin, CKAP4, CYC1, cytochrome bc1, cytochrome c, cytochrome-c oxidase, DNM1L, dynamin, fibrinogen, GAPDH, GLUD1, HADH, HADHA, HADHB1, HMM1, integrin, MIP, MPF, Msda, tyrosine kinase, UQCRCl, VLDL-cholesterol | 28 | 21 | Endocrine system development and function, lipid metabolism, small molecule biochemistry |
| 15 | AARS, AHSA1, B2M, B2m-MHC1a, CACYBP, CANX, CAPRIN1, chymotrypsin, EEF1B2, EEF1D, EEF1G, E0A, ERK1/2, ESD, GARS, GC-GCR dimer, GMPs, HARS, HLA Class I, HLA-a, HLA-b, HLA-b27, KIR, MHC Class I (complex), MHC I-α, Na+/K+/ATPase, NPEP1, PEH, PGDF (family), PKI, RPS3A, TAP, TBCA, VARS | 26 | 20 | Post-translational modification, protein folding, dermatological diseases and conditions |
| 16 | BTF3, Cbfα3, CDKN1A, cyclin A, cyclin D, cyclin E, DHX9, E2F, Gap, HDLBP, Helo RNA polymerase II, HCM, HCM3, HCM4, HCM6, HCM7, PCMI, PCNA, PDE, Ras, Rs, RHOA, RPA, S100A6, SERBP1, SNIP1, STAP, SUPT16H, TAGLN, TIP60, TMPO, tropomyosin, XCC, YCC, YBX3 | 26 | 20 | DNA replication, recombination, and repair, cell morphology, cellular function and maintenance |
| 17 | ACTA1, BASP1, CaMKIb, cofilin, COROX1, COT1, CTP1, DBN1, FKBP12, GLO1, glyoxen, glyoxyen phosphatase, ITPR, LDH (complex), LDHA, LDHB, MARCKS, MEK2, Misc, MYH9, MYH10, MYL12A, myosin2, PFK1, PICALM, PKA, PIP1 protein complex group, PP2A, profitin, PRTF, RAPI, RBM3, RNA polymerase I, Rock, voltage-gated calcium channel, WDR1 | 24 | 19 | Cellular movement, connective tissue disorders, hematological disease |
| 18 | ALYREF, ATP1A1, BSG, calcineurin A, calcineurin protein(s), CK2, DDX39B, EIF2S1, EIF5A, EFTF, FCER1, focal adhesion kinase, HEXB, HINT1, IgE, IGF2R, lkb, JIN1K1/2, MAPK1/2, mitochondrial complex 1, Nfat (complex), Nfat (family), NF-κB (family), peptidylprolyl isomerase, phosphatase, PLCγ, PPI1-C, PPI1/PPI2A, PPIA, PPP1CA, RGN1, SET, STOM12, VLA-4, XPO1 | 19 | 16 | Molecular transport, RNA trafficking, cell death and survival |
### Table 4. Cont.

| ID | Molecules in Network | Score | Molecules | Top Diseases and Functions |
|----|----------------------|-------|-----------|---------------------------|
| 19 | CARHSP1, CDV3, CECR2, CLDN12, CTS4, CUTA, CYB5R3, DMXL2, FADS1, FAM57A, FBXO11, HEBP2, HM13, KHSRP, LRPPRC, NEU1, NME1-NME2, NNT, NRM, PARN, PFKP, PGM1, POLRMT, SDHA, SDHAF2, SDHC, SIRT5, SLC25A25, SURF4, TIPARP, TKT, TRMT1, UAP1, UBC, VPS37A, ZCCHC6 | 19 | 16 | Developmental disorder, hereditary disorder, metabolic disease |
| 20 | ANXA5, collagen, collagen α1, collagen type II, collagen type III, collagen type IV, collagen(s), complement component 3, C4A, C4B, CSTB, CTSB, eotaxin, FDPS, fibrin, FLT3L, G6PD, GPIH-BIII, Hsp27, IARS, laminin, P38 MAPK, PDGF (complex), PDGF-α, peroxidase (miscellaneous), PKG, PLOD2, PRDX1, PRDX5, QARS, RBBP1, SERPINH1, TNC, TTP1, trypsin | 17 | 15 | Cancer, endocrine system disorders, organismal injury and abnormalities |
| 21 | AMPK, caspase 3/7, CD3, CD8, cyclin B, FASN, HRNRPA2B1, HNRNPR, IFN, IFNγ, IFNAR, IL-2R, IL12 (complex), interferon-α, JAK, KHDH5B1, LGALS1, Mek, MHC, MTORC1, p70 S6K, p85 (PIK3R), PEBP1, PGAM1, PGD, PRKAA, PTBP1, PTK, RARS, SIRNA, STAT1, STAT5a/b, TCR, TWF1 | 14 | 13 | RNA post-transcriptional modification, dermatological diseases and conditions, cell death and survival |
| 22 | ARPIN/C15orf38-AP3S2, ATIC, EMD, FAM169A, γ-tubulin, GANAB, GBA3, GIP, HEATR5A, HTA1551, KLF18B, LMA, MAP2K1, MHC1L1, NAPC, PAICS, PRKCSH, RCD1, RNA polymerase II, SLC22A3, SLC33A1, SLC41A2, TAC1L2, TCE, THUMP2, TMEM16, TMEM164, TMEM210, TMEM185A, TRAF6, UBC, UCHL1, WDR70, ZNF397, ZNF280C | 8 | 9 | Carbohydrate metabolism, small molecule biochemistry, cell morphology |
| 23 | ALP, Ap1, C1q, Clec, FGF, FGFR, FN1, HDL, hemoglobin, HIST1H2BL, histon, HMGB1, IgG, IgG2, IgM, IL1, IL12 (family), immunoglobulin, insulin, ITGβ1, LASP1, LDL, LRP, NADPH oxidase, NR1H, PDGF BB, PEA15, PIK3 (family), P2K, pro-inflammatory cytokine, Shc, SLC38A2, TGFβ, TSH | 6 | 7 | Cell-to-cell signaling and interaction, tissue development, cardiovascular system development and function |
| 24 | Adaptor protein 2, ADCY, bARK, CAP2, CG, chemokine, clathrin, CRH, estrogen receptor, FPR, FSH, G protein, G protein α, G protein β, G protein γ, Gi-coupled receptor, growth hormone, HINT1, IKK (complex), IL8r, LH, LR2, metalloprotease, MMP19, myosin2, NMDA receptor, PDGF, PDN, PLC, PP1H, proinsulin, S1PR5, SFK, TNF (family), TRHR | 1 | 2 | Connective tissue development and function, tissue morphology, behavior |
Table 5. 500 categories of predicted diseases and functions regulated by vancomycin in HK-2 cells.

| Categories              | Diseases or Functions Annotation | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-------------------------|---------------------------------|------------------|-------------------|--------------------------------------------------------------------------|---------------------|
| Cell death and survival | Cell death                      | $2.14 \times 10^{-35}$ | 0.626             | AARS, ACAT1, ACLY, ACTN4, AHSA1, AKR1B1, ALDOA, ALDOC, ANXA1, ANXA2, ANXA5, AP2B1, APEX1, ARHGDI1, ATP1A1, ATP5A1, B2M, BASP1, BSG, BTF3, C1QB, CACYBP, CALR, CANX, CAPN1, CAPN2, CAPN5, CAPRIN1, CAST, CAV1, CCT2, CCT3, CCT4, CCT5, CCT6A, CCT7, CCT8, CD44, CD59, CDK1, CFI, CLIC4, CSE1L, CSTB, CTNNAL1, CTSE, CTTN, CYR61, DDX3X, DDX5, DDX9, DNAJ1A1, DNMLI, DYNClH1, EEF1A1, EEF1D, EHD1, EIF2B1, EIF3B, EIF3C, EIF3I, EIF4G1, EIF5A, EIF6, ENS1, ESR1, FASN, FDS, FKBP1A, FKBP4, FLNA, FLNB, FN1, FUS, G6PD, GAPDH, GLO1, GIUD1, GML, GNAI2, GNB2L1, GTP1, HADHA, HDGE, HEXB, HINT1, HIST1H1C, HLA-A, HLA-B, HMGB1, HNRNPA1, HNRNPK, HS178B10, HSP90AA1, HSP90AB1, HSP90B1, HSPA4, HSPA5, HSPA8, HSPA9, HSPB1, HSPDI1, HYO1, IGF2R, ILF2, ILF3, IMMT, IMPDH2, ITGB1, KHDRBS1, KGPNA2, KPNBI, KRT18, KRT8, LDHA, LGALS1, LMNA, LMNBI, LONP1, MAP1B, MAP4, MAPK1, MCM7, MDHI, MSN, MVP, MYB9, NCL, NPM1, NUMA1, OTUB1, P4HB, PAG4, PAFHA1B2, PARK7, PCBP2, PCMT1, PCNA, PDCX6, PDL13, PDXK, PEIA1, PEPB1, PHB2, PKM, PLEC, PLN3, PPLA, PPPCA, PPP2CA, PPP2R1A, PRDX1, PRDX2, PRDX4, PRDX5, PRKDC, PRMT5, PRPF19, PSMB1, PSMC1, PSMC4, PSMD2, PSME2, PTGES3, PTMA, QARS, RAD23B, RAN, RANBP1, RBM3, ROHA, RPL10, RPL70, RPS24, RPS3A, RPSA, RRBP1, RTN4, S10OA6, SDHA, SERPINH1, SET, SFA1, SERFQ, HSHGR1L3, SLC25A5, SLC25A6, SND1, SOD1, SPTBN1, SQSTM1, SSRP1, STAT1, STIP1, STPN1, STMN1, STOM1, TAGLN2, TCP1, TFR1, TNC, TPM3, TIP1, TRIM28, TUBB, TUBB6, TUFM, TXNDC5, UBA1, UBE2L3, UBE2N, UCHL1, VAPA, VCL, VCP, VDAC1, VDAC2, VIM, XPO1, XRCC5, XRCC6, YBX1, YBX3, YWHAB, YWHAE, YWHAG, YWHAI, YWHAO, YWHAZ, ZYX | 232 |
Table 5. Cont.

| Categories                               | Diseases or Functions Annotation | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------|----------------------------------|---------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cellular growth and proliferation        | Proliferation of cells           | $5.39 \times 10^{-34}$ | −1.530             | AARS, ACAT1, ACH1, ACR1, ACTN4, ALDH4A1, AKR1B1, ALDOA, ANXA1, ANXA2, ANXA5, | 242                 |
|                                          |                                  |               |                    | APEX1, ARHGDIA, ATPI1A, B2M, BASP1, BSG, BF3, C1QBP, CALR, CAPN1, CAPN2,   |                     |
|                                          |                                  |               |                    | CAPRN1, CAPZA1, CAST, CAV1, CCT2, CCT3, CCT5, CD44, CD59, CDK1, CFL1, CLC1, |                     |
|                                          |                                  |               |                    | CLTC, COPE, CSE1L, CSR1P1, CTNN1A1, CTST, CTTN, CYR61, DBL, DBC1, DD3X5,   |                     |
|                                          |                                  |               |                    | DNAJA1, DNAJA2, DNML1, DPY30, DPYSL2, DYNCH1H1, EEF1A1, EEF1D, EIF1B,     |                     |
|                                          |                                  |               |                    | EIF3C, EIF3E, EIF4A1, EIF4G1, EIF5A, EIF6, ENO1, ESR, FASN, FKBP1A, FKBP4, |                     |
|                                          |                                  |               |                    | FLNA, FN1, FUS, G3BP1, G6PD, GADPH, GML, GNAI2, GNB2L1, GPR1, H2AFY,       |                     |
|                                          |                                  |               |                    | H3F3A/H3F3B, HADHA, HDGF, HEXB, HINT1, HMGB1, HNRNP1, HNRNP2B, HNRNP4,      |                     |
|                                          |                                  |               |                    | HNRNP4, HNRNP5, HNRPNP, HSNP0A1, HSNP0B1, HSNP0B1, HSNP4, HSPA4, HSPA5,   |                     |
|                                          |                                  |               |                    | HSPB1, HSPD1, IFTM3, IGF2, IL2, ILF2, IMMT, IMPD2, IP07, IQGAP1, ITGB1,    |                     |
|                                          |                                  |               |                    | KHDRBS1, KPN2, KRT8, LAMB1, LAMPI, LDHA, LGALS5, LMNA, LMNB1, LONP1, MAP1B, |                     |
|                                          |                                  |               |                    | MAPK1, MAPRE1, MARCKS, MCM3, MCM4, MCM7, MVP, MYH10, MYH9, NACA, NAP1L1,  |                     |
|                                          |                                  |               |                    | NASP, NCL, NNM1, NPM1, NUMA1, PA2G4, PARK7, PCNA, PDCD6, PDI3A, PDXK,    |                     |
|                                          |                                  |               |                    | PEAK5, PEBFB1, PFKP, PFKI, PGK1, PICALM, PKM, PLEC, PLIN3, PL53, PP1A,    |                     |
|                                          |                                  |               |                    | PPM1G, PPICA, PP2CA, PP2R1A, PRDX1, PRDX2, PRDX4, PRKCSH, PRKDC, PRMT5,  |                     |
|                                          |                                  |               |                    | PRPF19, PSM4A, PSMC1, PSMC4, PSMD2, PSME2, PTBP1, PTGES3, PTMA, RAB11A,  |                     |
|                                          |                                  |               |                    | RAN, RANBP1, RBM3, RHOA, RH1, RPS3A, RPS4X, RPSA, RTA4, S100A6, SAE1,      |                     |
|                                          |                                  |               |                    | SERTP, SERPINH1, SET, SFP, SFQ, SHMT2, SLC25A5, SLC25A6, SN1D1, SNX3,     |                     |
|                                          |                                  |               |                    | SOD1, SPTAN1, SPTBN1, SQSTM1, STAT1, STIP1, STMIN1, SURF4, TAGL1, TAGLN2,  |                     |
|                                          |                                  |               |                    | TCF1, TLE1, TMPO, TNC, TPS, TRIM28, TUBB, TUBB4B, TXLNA, TXNDC5, UBA1,     |                     |
|                                          |                                  |               |                    | UBE2B3, UBE2B, UCHL1, VAPA, VCL, VCP, VDAC1, VIM, WARS, XRC5, XRC6, YB1X,  |                     |
|                                          |                                  |               |                    | YB5, YWHAG, YWHAI, YWHAQ, YWHAZ, YXZ |                     |
| Cell death and survival                 | Apoptosis                        | $8.59 \times 10^{-31}$ | 0.054              | AARS, ACAT1, ACH1, AHNAK, AKR1B1, ALDOA, ALDOC, ANXA1, ANXA2, ANXA5,      | 192                 |
|                                          |                                  |               |                    | APEX1, ARHGDIA, ATPI1A, B2M, BASP1, BSG, BF3, C1QBP, CALR, CAPN1, CAPN2,   |                     |
|                                          |                                  |               |                    | CAPRN1, CAPZA1, CAST, CAV1, CCT2, CCT3, CD44, CD59, CDK1, CFL1, CLC4,      |                     |
|                                          |                                  |               |                    | COPE, CSE1L, CTST, CTNN1A1, CTST, CTTN, CYR61, DD3X5, DDX5, DHX9, DNAJA1,   |                     |
|                                          |                                  |               |                    | DNML1, DYNCH1H1, EEF1A1, EEF1D, EHD1, EIF2A, EIF2B, EIF3C, EIF3E, EIF4G1,  |                     |
|                                          |                                  |               |                    | EIF5A, EIF6, ENO1, ESR, FASN, FKBP1A, FKBP4, FLNA, FLNB, FN1, FUS, G6PD,    |                     |
|                                          |                                  |               |                    | GAPDH, GLO1, GLO1D, GML, GNAI2, GNB2L1, GPR1, H2AFY, H3F3A/H3F3B, HADHA,  |                     |
|                                          |                                  |               |                    | HDGF, HEXB, HINT1, HIST1H1C, HLA-B, |                     |
Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value     | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------|----------------------------------|------------|-------------------|--------------------------------------------------------------------------|---------------------|
| Cell death and survival | Necrosis                         | $1.65 \times 10^{-30}$ | 1.232              | HMGB1, HNRPAP1, HNRPDK, HSD17B10, HSP90AA1, HSP90AB1, HSP90B1, HSPA4, HSPA5, HSPA8, HSPA9, HSPB1, HSPD1, HYOU1, IGF2R, ILF2, IMMT, ITGB1, KHDRBS1, KPN2, KRT18, KRT8, LDHA, LGALS1, LMAA, LMNB1, MAP1B, MAP4, MAPK, MDH1, MSN, MVP, NCL, NPM1, NUMA1, OTUB1, P4HB, PA2G4, PAFAH1B2, PARK7, PCK2, PCBP2, PCM7, PCNA, PDCD6, PDLA3, PDXX, PEA15, PEBP1, PHB2, PKM, PPIA, PPP1CA, PPR2CA, PPR2K1A, PRDX1, PRDX2, PRDX4, PRDX5, PRKDC, PRMT5, PRPF19, PSMB1, PTM, QARS, RAD23B, RANBP1, RBM3, RHOA, RPL10, RPL10, RPS24, RPS3, RPS3A, RRBP1, RTN4, S100A6, SERPINH1, SET, SFN, SFPQ, SHBGL3L, SLC25A5, SLC25A5, SND1, SOD1, SPTBN1, SQSTM1, SSRP1, STAT1, STIP1, STMN1, STOM2, TAGLN2, TCP1, TFRC, TNC, TRIM28, TXNDC5, UBA1, UCHL1, VCI, VCP, VDAC1, VDAC2, VIM, XPO1, XRCC5, XRCC6, XBY1, YWHAB, YWHAE, YWHAA, YWHAZ, YWHAZ | 188 |
| Categories                        | Diseases or Functions Annotation | p-Value  | Activation z-Score | Molecules                                                                 | Number of Molecules |
|----------------------------------|----------------------------------|----------|-------------------|---------------------------------------------------------------------------|---------------------|
| Infectious disease               | Viral infection                  | $2.33 \times 10^{-30}$ | $-1.968$          | ACTN1, ACTR2, ANXA1, ANXA2, ANXA5, ANXA6, APIB1, AP2B1, ARFI, ARPC1B, ATP5B, B2M, BSG, BTF3, C1orf166, CAV1, CCT2, CD44, CLI4, CLTC, COPA, COPB1, COPB2, CSE1L, CTSB, DDX3X, DDX5, DDX6, DHX9, DNAJ1, DNAJA1, DNAJA2, DNML1, EEF1A1, EIF2S1, EIF3C, EIF5, FASN, FDPS, FKBP1A, FLNA, FN1, G3BP1, GANAB, GAPDH, GML, GPl, HSF3A/HF3B, HIST1H1C, HLA-A, HLA-B, HMGB1, HRNRPH1, HRNRPK, HRNRPM, HRNRPN, HSP90AA1, HSP90AB1, HSP90B1, HSP9A5, HSP9A9, HSPDI, IFTM3, IgF2R, ILF3, IMPD12, ITGB1, KHDRBS1, KHSRP, KPNB1, KRT18, KRT8, LALAL1, LAMA1, LONPI, MAP4, MAPK1, MVE, NCL, NPM1, PCBP2, PDLA3, PDIA6, PDAX, PCGL, PICALM, PLIN3, PLOD2, PPIA, PRDX1, PRDX2, PSMA1, PSMA2, PSMA5, PSMA7, PSMC4, PSMD2, PSME2, PTGES3, PYGL, RAB11A, RAB18, RAB7A, RAN, RANBP1, RHAO, RNH1, RPL10A, RPL12, RPL18, RPL3, RPL5, RPS27A, RPS5, RPSA, SA1, SFA1, SFB3, SFQ, SNRPD3, SPTAN1, SPTBN1, SSRP1, STAT1, STIP1, SUPT16H, TALDN2, TALDO1, TFCR, TFK, TMPO, TUBB, TUBB4B, TWF1, UAPI, UBE2L3, UQRC1, XPO1, YBX1, ZYX | 142 |
| Cell death and survival          | Cell death of tumor cell lines   | $1.13 \times 10^{-27}$ | 0.949             | AHS1A1, AKR1B1, ANXA2, APEX1, ARHGDIA, ATP1A1, ATP5A1, B2M, CALR, CAPN1, CAPN2, CAPSN1, CAST, CAV1, CCT2, CCT3, CCT4, CCT5, CET6A, CET7, CCT8, CD44, CD39, CDK1, CSE1L, CTB, CTNN, CRY61, DDX3X, DDX11L, DYN1H1, EEF2S1, EON1, EHR, FASN, FKBP1A, FLNB, FN1, GEPD, GAPDH, GL01, GML, GNB1L1, GPl, GSTP1, HINT1, HRNRPA1, HRNRPK, HSP90A1B, HSPA4, HSPA5, HSPA6, HSAP, HSPDI, IGF2R, ILF2, IMMT, ITGB1, KHDRBS1, KPN2, KPNB1, KRT18, LALAL1, LAMA1, LMNB1, LONPI, MAPK1, MCM7, MSN, MVP, NCL, NPM1, OTUB1, P4HB, PAG24, PARK7, PCBP2, PCNA, PE15, PEB1, PKM, PPIA, PPIA1, PPIA2, PPIA3, PRDX1, PRDX2, PRKDC, PRMT5, PRPF9, PSMD2, PTMA, RAD23B, RHAO, RPLP1, RPS24, RPS3, RTN4, SFQ, SFQ, SLCS2A5, SLCS2A5, SFD1, SOD1, SQSTM1, SSRP1, STAT1, STIM1, STOM1, TALDN2, TCF1, TFRC, TRIM28, TUBB6, TUFM, UBE2L3, UCH1, VCP, VDAC1, VDAC2, XPO1, XRC3, XRC6, YBX1, YWHAE, YWHAH, YWHAH | 131 |
| Protein synthesis                | Translation                      | $6.09 \times 10^{-25}$ | 0.792             | APEX1, CALR, CAPRN1, DDX3X, DDX6, DDX9, EEF1A1, EEF1B2, EEF2, EIF2S1, EIF3B, EEF3C, EEF3E, EEF3F, EEF4A1, EEF4G1, EEF4H, EEF5A, EPR5, FN1, GANAB, GNB1L1, HRNRPK, HSP9A5, HSP9A1, ILF3, ITGB1, MARS, NACA, NCL, PABPC1, PCBP1, PPIC1A, PTBP1, RBM3, RPL23, RPS24, RPS3, RPS3A, RPS4X, RPS5, RPS7, RRP1, SNCRI, TUFM, WARS, YBX1 | 47 |
| Protein synthesis                | Translation of protein            | $2.00 \times 10^{-23}$ | 0.860             | APEX1, CALR, CAPRN1, DDX3X, DDX6, DDX9, EEF1A1, EEF1B2, EIF2S1, EIF3B, EEF3C, EEF3E, EEF3F, EEF4A1, EEF4G1, EEF4H, EIF5A, EPR5, FN1, GANAB, GNB1L1, HRNRPK, HSP9A5, HSP9A1, ILF3, ITGB1, MARS, NACA, NCL, PABPC1, PCBP1, PPIC1A, PTBP1, RBM3, RPL23, RPS24, RPS3, RPS3A, RPS4X, RPS5, RPS7, RRP1, SNCRI, TUFM, WARS, YBX1 | 45 |
| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|---------|-------------------|-----------|-------------------|
| **Protein synthesis** | Expression of protein | $2.95 \times 10^{-22}$ | 0.229 | ANXA1, APEX1, CALR, CAPRIN1, CAV1, DDX3X, DDX6, DHX9, EEF1A1, EEF1B2, EEF2, EEF3, EEF3C, EEF3E, EEF4A1, EEF4G1, EEF4H, EEF5A, EPRS, FN1, GAPDH, GNBP2L1, HNRNPK, HSIP5, HSIP8, ILF3, ITCB1, KHDBR81, MARS, NACA, NCL, PABPC1, PCBP1, PPM1G, PPM1CA, PTBP1, RBM3, RPL23, RPS24, RPS3, RPS3A, RPS4X, RPS5, RPS7, RRBP1, SOD1, SYNCRIP, WARS, YBX1 | 50 |
| **Protein synthesis** | Synthesis of protein | $3.25 \times 10^{-22}$ | $-0.265$ | ANXA1, APEX1, CALR, CAPRIN1, CAV1, DDX3X, DDX6, DHX9, EEF1A1, EEF1B2, EEF2, EEF3, EEF3C, EEF3E, EEF4A1, EEF4G1, EEF4H, EEF5A, EEIF6, EPRS, FN1, GAPDH, GNBP2L1, HNRNPK, HSIP5, HSIP8, ILF3, ITCB1, KHDBR81, MFK1, MARS, NACA, NCL, NPM1, PABPC1, PARK7, PCBP1, PPM1G, PPM1CA, PTBP1, RBM3, RPL23, RPS24, RPS3, RPS3A, RPS4X, RPS5, RPS7, RRBP1, SOD1, STIP1, SYNCRIP, TUFM, WARS, YBX1 | 58 |
| **Cell death and survival** | Apoptosis of tumor cell lines | $3.17 \times 10^{-21}$ | 0.816 | AHSA1, AKR1B1, ANXA2, ARHGDA1, B2M, CALR, CAPN1, CAPN2, CAPN51, CAST, CAV1, CCT2, CCT4, CD44, CD59, CDK1, CSE1L, CTSS, CTXN, CYR61, DNM2, DYN1H1, ENO1, EFR, ENSP, FLNB, FN1, G6PD, GAPDH, GLO1, GML, GNBP2L1, GSTP1, HNRPAD1, HNRNPK, HSIP80A1B1, HSIP4, HSIP5, HSIP8, HSIP9, HSPBI, HSPDI, IGF2R, IGLW, ITGA11, KHDRBS1, KPN2, KRT18, LAG3L1, LMNB1, MAP3K1, MSN, MVP, NCL, NPM1, OTUB1, P4HB, PA2G4, PARK7, PCBP2, PCNA, PEA15, PEP11, PP1A, PPM1CA, PPM2CA, PPM2R1A, PRDX1, PRKDC, PRMT5, PRPF19, PTMA, RAD23B, RHOA, RPL19, RPS24, RPS3, RTN4, S100A6, SFN, SFQ, SLC25A5, SMD1, SOD1, SSRP1, STAT1, STMN1, STOML2, TAGLN2, TCP1, TFR1, TRIM28, UCHL1, VCP, VDAC1, VDAC2, XPO1, XRCC5, YBX1, YWHAE, YWHAZ | 102 |
| **Cellular assembly and organization, cellular function and maintenance** | Organization of cytoplasm | $4.80 \times 10^{-20}$ | $-1.198$ | ACTG1, ACTN4, ACTR2, ACTR3, ALDOA, ANXA1, ARHGDA1, ARPC2, BASP1, BSG, C1QBP, CALR, CAMP, CAPG, CAPN2, CAPN51, CAPRIN1, CAPZB, CAST, CAV1, CD44, CDK1, CFL1, CKAP4, CLIC, COPB2, CTERC, CSR1, CTSS, CYR61, DBN1, DNM1L, DPYSL2, EEF1A1, EH1D, EIAH1, EZR, ENSP, FBKB4, FN1, FBLN, FBLN3, FDN1, GADD45B, GDI1, HDGF, HEXFA, HMGBI1, HNRNPK, HSIP80A1B1, HSIP4, HSPA, HSPB1, HSPD1, IGF2R, IGLW, ITGA11, KHDRBS1, KPN2, KRT18, LAG3L1, LMNB1, MAP3K1, MSN, MVP, NCL, NPM1, OTUB1, P4HB, PA2G4, PARK7, PCBP2, PCNA, PEA15, PEP11, PP1A, PPM1CA, PPM2CA, PPM2R1A, PRDX1, PRKDC, PRMT5, PRPF19, PTMA, RAD23B, RHOA, RPL19, RPS24, RPS3, RTN4, S100A6, SFN, SFQ, SLC25A5, SMD1, SOD1, SSRP1, STAT1, STMN1, STOML2, TAGLN2, TCP1, TFR1, TRIM28, UCHL1, VCP, VDAC1, VDAC2, XPO1, XRCC5, YBX1, YWHAE, YWHAZ | 116 |
| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|---------------------------------|---------|-------------------|-----------|--------------------|
| Protein synthesis | Metabolism of protein | 8.33 × 10^{-20} | 0.064 | ANXA1, APEX1, CALR, CANX, CAPN1, CAPN2, CAPNS1, CAPRIN1, CAST, CAV1, COPG1, CSTB, CT5B, DDX3X, DDX6, DHX9, EEF1A1, EEF1B2, EEF2, EIF2S1, EIF3B, EIF3C, EIF3I, EIF3M, EIF4A1, EIF4G1, EIF4H, EIF5A, EIF6, EPRS, FLNA, FN1, GAPDH, GNB2L1, HEXB, HNRNPK, HSP90B1, HSPA5, HSPB1, HSPD1, ILF3, IPO9, ITGB1, KHDRBS1, LONP1, MAPK1, MARS, MYH9, NACA, NCL, NPEPPS, NPM1, PABPC1, PARK7, PCBP1, PDI3, PMM1G, PPP1CA, PPP2CA, PSMC4, PSMD2, PTBP1, RBM3, RPL23, RPL5, RPS24, RPS3, RPS4X, RPS5, RPS7, RRBP1, SNX3, SOD1, SQSTM1, STIP1, SYNCRIP, TTP1, TUFM, UBE2L3, UBE2N, UBXN4, UCHL1, VCP, WARS, XPO1, YBX1 | 87 |
| Cancer, organismal injury and abnormalities, reproductive system disease | Mammary tumor | 1.12 × 10^{-19} | 1.847 | AKR1B1, ALDOA, ALDOLC, ALYREF, ANXA1, ARHGDI1, ATP5A1, BSG, CIQB, CAV1, CBX3, CCT3, CD44, CDK1, CSE1L, CTNN, CYB61, DDX5, DYNCKH1, EEF1A1, EIF3B, EIF3C, EIF4A1, ENAH, ENO1, ETFA, FASN, FDPS, FKBP1A, FLNA, FLNB, FN1, FUS, GCN1L1, GLO1, GSTP1, H2AFY, H3F3A/H3F3B, HDLBP, HLA-A, HLA-B, HNRNPA1, HSP90AA1, HSP90AB1, HSP90B1, HSPA5, HSPD1, ILF3, ITGB1, KHSRP, KPN2A, KRT18, KRT8, LAMB1, LASP1, LGALS1, LMNA, LONP1, MAPRE1, MARS, MCM4, MCM6, MYH10, MYH9, NAPIL4, NCL, NPEPPS, P4HB, PAFAH1B2, PCNA, PDCD6, PPI1, PKG1, PKM, PLEC, PRDX1, PRDX5, PRC2HS, PTBP1, PTF1, RANBP1, RHOA, RPL4, RPL6, RPLP0, RPS24, RPS3, RPS4X, S100A6, SF3B1, SFPQ, SHMT2, SLC25A5, SLC25A6, SOD1, STAT1, STIP1, TAGLN, TAGLN2, TCP1, TNL1, TNC, TPI1, TUBA1B, TUBB, TUBB4B, TUBB6, UBA1, UCHL1, VCL, VDAC2, WDR1, XPO1, XRC5, YWHAH, YWHAJ, YWHAI, YWHAZ, YZ | 119 |
| Dermatological diseases and conditions | Psoriasis | 2.52 × 10^{-19} | | ANXA1, ANXA2, ARHGDIA, ARPC1B, CIQB, CALR, CAV1, CBX3, CCT5, CFL1, COPB2, CSTB, CT5B, CYB5B3, DBN1, EEF1A1, EIF2A, EIF2S2, EIF5A, EIF6, EFSN, FKBP1A, FN1, GAPDH, GARS, GSTP1, H2AFY, H3F3A, H3F3B, HSPA5, HSPA8, KPN2A, KPNB1, KRT11, KRT18, LGALS1, MARCKS, OTUB1, P4HB, PCBP2, PCTM1, PCNA, PGAM1, PGD, PKM, PPI2CA, PSM2, PTP1, RANBP1, RHOA, RPL4, RPL6, RPLP0, RPS24, RPS3, RPS4X, S100A6, SF3B1, SFPQ, SHMT2, SLC25A5, SLC25A6, SOD1, STAT1, STIP1, TAGLN, TAGLN2, TCP1, TNL1, TNC, TPI1, TUBA1B, TUBB, TUBB4B, TUBB6, UBA1, UCHL1, VCL, VDAC2, WDR1, XPO1, XRC5, YWHAH, YWHAJ, YWHAI, YWHAZ, YZ | 63 |
| Infectious disease | Infection of cells | 2.88 × 10^{-19} | -2.041 | ACTR2, ANXA2, ARPC1B, ARF1, ARPC1B, ATP5B, BSG, CIQB, CAV1, CCT5, CLC1, COPB2, CSTB, CT5B, CYB5B3, DBN1, EEF1A1, EIF2A, EIF2S2, EIF5A, EIF6, EFSN, FKBP1A, FN1, GAPDH, GARS, GSTP1, H2AFY, H3F3A, H3F3B, HSPA5, HSPA8, KPN2A, KPNB1, KRT11, KRT18, LGALS1, MARCKS, OTUB1, P4HB, PCBP2, PCTM1, PCNA, PGAM1, PGD, PKM, PPI2CA, PSM2, PTP1, RANBP1, RHOA, RPL4, RPL6, RPLP0, RPS24, RPS3, RPS4X, S100A6, SF3B1, SFPQ, SHMT2, SLC25A5, SLC25A6, SOD1, STAT1, STIP1, TAGLN, TAGLN2, TCP1, TNL1, TNC, TPI1, TUBA1B, TUBB, TUBB4B, TUBB6, UBA1, UCHL1, VCL, VDAC2, WDR1, XPO1, XRC5, YWHAH, YWHAJ, YWHAI, YWHAZ, YZ | 78 |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions | Annotation | Activation z-Score | p-Value | Molecules                                                                                     | Number of Molecules |
|----------------------------------------------------------------------------|-----------------------|------------|-------------------|---------|-----------------------------------------------------------------------------------------------|---------------------|
| **Infectious disease**                                                     | Replication of virus  |            | -0.358            | 5.92 × 10⁻¹⁹ | ANXA5, ANXA6, ATP5B, B2M, BTF3, C14orf166, CA9, CLIC4, COPA, COPB1, COPB2, COPG1, CSE1L, DDX3X, DDX5, DDX6, DDX9, DNAJA1, EEF1A1, EIF2S1, EIF3C, FASN, FDP5, FKBP1A, G3BP1, HMGB1, HNRRNP1, HSP90AA1, HSP90AB1, HSPD1, IFITM3, IL3, KPNB1, KRT8, LONP1, MAPK1, MVP, NCL, NPM1, PCB2, PLIN3, PPIA, PRDX1, PRDX2, PSMA1, PSDM2, RAB11A, RPS10, RPS27A, RPS5, RPSA, SAE1, SF3A1, SF3B1, SFQ, SSRP1, STAT1, TMO, TUBB1, XP01, YBX1 | 62 |
| **Neurological disease**                                                  | Progressive motor neuropathy |            | 9.90 × 10⁻¹⁹ | 1.190 | ANXA1, ANXA2, ANXA5, CAPN2, CAPZB, C2CT, COPE, CSE1L, CYR61, DBI, EEF1A1, EIF4A1, EIF4G1, ENO2, EZR, FASN, FOS, GSTP1, H3F3A/H3F3B, HLA-B, HN, HNRRNP1, HSPA5, HSPB1, IMPDH2, LDH1, LDHB, MAP1B, MAPK1, MDH1, NNM, PARK7, PCNA, PDI3, PEP1, FKBP, FN1, PGK1, PRDX2, PSMA1, PSDM2, RAB11A, RPS10, RPS27A, RPS5, RPSA, SAE1, SF3A1, SF3B1, SFQ, SSRP1, STAT1, TMO, TUBB1, XP01, YBX1 | 58 |
| **Cellular assembly and organization, cellular function and maintenance**  | Organization of cytoskeleton |            | -1.190           | 1.01 × 10⁻¹⁸ | ACTG1, ACTN4, ACTR2, ACTR3, ALDOA, ANXA1, ARHGDL1A, ARPC2, BAP1, BSG, C1QBP, CALR, CANX, CAP1, CAPG, CAPN2, CAPNS1, CAPRI1, CAPZB, CAST, CAV1, CD44, CDK1, CFL1, CKAP4, COPB2, COROC1, CSRPI, CTNN, CYR61, DBN1, DNM1L, DPP5L2, EEF1A1, EHD1, ENAH, ESR, FASN, FKBP4, FLNA, FLNB, FLNC, FN1, GAPDH, GDI1, HEDGE, HMGB1, HNRRNP1, HSP90AA1, HSPB1, IQGAP1, ITG1, KIF5B, KPNB1, KRT8, KRT9, LAMBI, LASP1, MAP1B, MAP4, MAPK1, MAPRE1, MARCKS, MSN, MYH10, MYH9, NNM, NUMA1, PCMI, PDI3, PFN1, PHGDH, PICALM, PKK, PLEC, PL35, PPP2CA, PRKCSH, PRKDC, RAB11A, RAN, RANBP1, ROH1, ROB1P1, RTN4, SEPT2, SEPT7, SEPT9, SOD1, SPTAN1, SPTBN1, SSRP1, STIP1, STMIN1, TLN1, TMOD3, TNC, TTPM3, TUBB1, TWF2, UCHL1, VAPA, VCL, VIM, XPO1, YBX1, YWHAH | 107 |
| **Post-translational modification, protein folding**                       | Folding of protein    |            | 0.988            | 1.21 × 10⁻¹⁸ | AARS, AIP, B2M, CALR, CANX, CT4, DNAJA1, DNAJA2, ERPA2, FKBP1A, FKBP4, HSP90AA1, HSP90AB1, HSPA5, HSPB1, HSPD1, P4HB, PDI6, PRDX4, RAB7A, TCRA, TCP1 | 24 |
| **Neurological disease, psychological disorders**                         | Disorder of basal ganglia |            | 2.74 × 10⁻¹⁸ | 1.01 × 10⁻¹⁸ | ACTA1, AHC1, ANXA2, B2M, BAP1, CAPNS1, CAPZB, CA9, CD44, COPE, CSE1L, CYC1, DDX1, DNAJA1, EIF1A1, EIF4G1, ENO2, FKBP4, GAPDH, GPE, GSTP1, H3F3A/H3F3B, HADH, HINT1, HLA-B, HNRRNP1, HSP90AA1, HSPA5, HSPB1, LAMBI, LDHA, LDHB, MAP1B, MDH1, MYL12A, NPM1, PARK7, PCMT1, PCNA, PDE6H, PDLIM1, PEP1, PFN1, PKC1, PKM, PLOD2, PPIA, PRDX2, PSME1, PTGES3, RAB11A, RAN, RANBP1, RPL3, RPS3A, RPS4X, RPSA, RTN4, SDHA, SLC25A6, SOD1, STMIN1, TIP1, TIPM3, TUBA1B, TUBB4B, UCHL1, UQRC1, VIM, VPS35, XRCC6, YWHAZ | 74 |
| Categories                                                  | Diseases or Functions Annotation | Activation p-Value | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-------------------------------------------------------------|---------------------------------|-------------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cellular assembly and organization, cellular function and maintenance | Microtubule dynamics             | $4.81 \times 10^{-18}$ | $-0.705$         | ACTG1, ACTN4, ACTR2, ARPC2, BASP1, BSG, C1QBP, CANX, CAP1, CAPG, CAPN2, CAPN5, CAPR1N, CAPZB, CAST, CAV1, CD44, CDX1, CFL1, CKAPA, COPB2, CSR1P, CTNN, CYR61, DBN1, DNML, DPYSL2, EEFA1A, EHDI, ENAH, EZR, FASN, FKBP4, FLNA, FN1, GAPDH, GD11, HDFE, HMBG1, HNRNPK, HPSP90AA1, HPSP91, IQGAP1, ITGB1, KIF5B, KPNB1, KRT18, LAMB1, LSP1, MAP1B, MAP4, MAPK1, MAPREI, MARCKS, MSN, MYH10, MYH9, NNMT, NUMA1, PCM1, PDI1, PDI1A, PHGDH, PICALM, PKM, PLEC, PPP2CA, PRKCSH, RAB11A, RAN, RANBP1, RHOD, RRP1B, RTN4, SEP72, SEPT7, SEPT9, SOD1, SPTBN1, SSRP1, STIP1, STN1, TELN1, TNC, TPM3, TUBB, TWF2, UCHL1, VAPA, VCL, VIM, XPO1, YBX1, YWHAH | 95                  |
| Infectious disease                                          | Replication of RNA virus         | $4.87 \times 10^{-18}$ | $-0.506$         | ANXA5, ANXA6, B2M, BTST, C14orf166, CAV1, CLIC4, COPA, COPB1, COPB2, COPG1, CSE1L, DDX3X, DDX5, DDX6, DHX9, DNAJA1, EEFA1A, EIF2S1, EIF3C, FASN, FDPS, G3BP1, HMGB1, HNRNPM, HPSP90AA1, HPSP90AB1, HPSP91, INF1M1, IFL3, KPNB1, LONP1, MAPK1, MIP, NCL, NPM1, PCBP2, PLIN3, PFIA, PRDX1, PRDX2, PSMA1, PSMD2, RAB11A, RPS27A, RPS5, RPSA, SA1, SF3A1, SF3B1, SFQ, STAT1, TMPO, TUBB, XPO1, YBX1 | 57                  |
| Infectious disease                                          | Infection by RNA virus           | $7.40 \times 10^{-18}$ | $-2.209$         | ACTR2, ANXA1, ANXA2, AAP1B1, AP2B1, ARF1, ARPC1B, ATP5B, B2M, BSG, CCT2, CD44, CLTC, COPA, COPB1, COPB2, COPG1, CSE1L, DDX3X, DDX5, DDX6, DHX9, DNAJA1, EIF3, FDPS, FNS1, GPB1, GANAB, GML, GZI, H3F3A/H3F3B, HMBG1, HNRNPH1, HNRNPK, HNRNP, HSP90, HSP90AB1, HSP91, INF1M1, IFL3, KPNB1, LONP1, MAPK1, MIP, NCL, NPM1, PCBP2, PLIN3, PFIA, PRDX1, PRDX2, PSMA1, PSMD2, RAB11A, RPS27A, RPS5, RPSA, SA1, SF3A1, SF3B1, SFQ, STAT1, TMPO, TUBB, XPO1, YBX1 | 79                  |
| Neurological disease, skeletal and muscular disorders        | Neuromuscular disease             | $2.20 \times 10^{-17}$ |                   | ACAT1, ACAT5, ANXA1, ANXA2, B2M, BASP1, CAPN1, CAPZB, CD44, COPE, CSE1L, CYC1, DDX1, DNAJA1, EEFA1A, EIF4G1, ENO2, FKBP1A, FKBP4, GAPD, GNP, GSP1, H3F3A/H3F3B, HADH, HINT1, HLA-B, HNRNPA1, HNRNPU, HPSP90AA1, HPSP91, HPSP94, HSP95, HSP96, IMPDH2, LAMB1, LDHA, LDHB, MAP1B, MDH1, MYL1A2, NPM1, PARK7, PCMT1, FCNA, PDE6H, PDEA3, FDLIM1, PEP1B, PFP1, PKG1, PKM, PLOD2, PPFA, PRDX2, PSMA, PTM1, PP1A, RAB11A, RAN, RANBP1, RPL1, RPL5, RPS3A, RPS4X, RPSA, RTN4, SDHA, SLC25A6, SOD1, STN1, TPI1, TPM3, TUBAI1, UCHL1, UQCR1C1, UQCRG1, VIM, VPS35, XRCC6, YWHAZ | 78                  |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|----------------------------------|------------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cancer, organismal injury and abnormalities, reproductive system disease  | Breast cancer                    | 6.17 × 10^{-17}  |                    | AKR1B1, ALDOA, ALDOC, ANXA1, ARHGDA1, ATP5A1, BSG, C1QBP, CAV1, CBX3, CCT3, CD44, CDK1, CSE1L, CYB61, DD5X, DYNCH11, EEFA1, EIF3B, EIF3C, EIF4A1, ENAH, ENO1, ETF, FASN, FDP5, FKBP1A, FLNA, FLNB, FNI, FUS, GCN1L1, GLO1, GSTP1, H2AFY, HSF3A/HSF3B, HLA-A, HLA-B, HNRNPA1, HSP90A1, HSP90AB1, HSP90B1, HSPD1, ILF3, ITGB1, KHSRP, KPN2, KRT8, LAMB1, LASP1, LGLAS1, LMNA, LONP1, MAPRE1, MARS, MCM6, MYH10, MYH9, NAP1L4, NCL, NPEPPS, P4HB, PAFBIH2, PCNA, PDC6X, PFN1, PK2, PG1, PG2, PK, PLEC, PRDX1, PRDX5, PRKCSH, PTP1, PTF, RANBP1, RPL4, RPL6, RPL9, RPS24, RPS3, S100A6, SF3B1, SPQQ, SHMT2, SLC25A5, SLC25A6, SOD1, STAT1, TAGLN, TAGLN2, TCP1, TLN1, TNC, TPI1, TUBA1B, TUBB, TUBB4B, TUBB6, UBA1, VCL, VDAC2, WDR1, XPO1, YWHAH, YWHAQ, YWHAZ, ZYX | 108                 |
| Neurological disease                                                     | Movement disorders               | 1.91 × 10^{-16}  | 0.283              | ACAT1, AHCY, ANXA2, B2M, BAP51, CANX, CAPNS1, CAPZB, CAV1, CD44, COPE, CSE1L, CSTB, CTS8, CTB, CYC1, DDX1, DNAJ1, EEF1A1, EEF2, EIF4G1, ENO2, FDP5, FKBP1A, FKBP4, FUS, GAPDH, GPI, GSTP1, HSF3A/HSF3B, HADH, HEXB, HINT1, HLA-B, HNRNPU, HSP90A1, HSP9A5, HSP9A8, HSP91, IGF2R, LAMB1, LDHA, LDHB, LMNA, MAP1B, MDH1, MYL12A, NPM1, PARK7, PON1, PCNA, PDE6H, POM12L, PEBP1, PFN1, PGK1, PKM, PLO2, PPP3, PSM1, PSM1, PTGES, RAB11A, RAN, RANBP1, RPL3, RPS3A, RPS4X, RPSA, RTN4, SDHA, SLC25A6, SOD1, SQSTM1, STN1, TPI1, TPM3, TPI1, TUBA1B, TUBB4B, UCHL1, UQCRCC1, VIM, VPS53, XRC6, YWHAZ | 87                  |
| Cancer                                                                   | Breast or ovarian cancer         | 2.54 × 10^{-16}  |                    | AKR1B1, ALDOA, ALDOC, ANXA1, ARHGDA1, ATIC, ATP5A1, B2M, BSG, C1QBP, CAV1, CBX3, CCT3, CCT5, CD44, CDK1, CSE1L, CYB61, DD5X, DYNCH11, EEFA1, EIF3B, EIF3C, EIF4A1, ENAH, ENO1, ETF, FASN, FDP5, FKBP1A, FLNA, FLNB, FNI, FUS, GAPDH, GCN1L1, GLO1, GSTP1, H2AFY, HSF3A/HSF3B, HLA-A, HLA-B, HNF1, HNRNPA1, HSP90A1, HSP90AB1, HSP90B1, HSPD1, ILF3, ITGB1, KHSRP, KPN2, KRT8, LAMB1, LASP1, LGLAS1, LMNA, LONP1, MAPRE1, MARS, MCM6, MYH10, MYH9, NAP1L4, NCL, NPEPPS, P4HB, PAFBIH2, PCNA, PDC6X, PDDA3, PEA15, PFN1, PGK1, PG2, PK, PLEC, PRDX1, PRDX5, PRKCSH, PTP1, PTF, RANBP1, RPL4, RPL6, RPL9, RPS24, RPS3, S100A6, SF3B1, SPQQ, SHMT2, SLC25A5, SLC25A6, SOD1, SSRP1, STAT1, TAGLN, TAGLN2, TCP1, TLN1, TNC, TPI1, TUBA1B, TUBB, TUBB4B, TUBB6, UBA1, VCL, VDAC2, WDR1, XPO1, YWHAH, YWHAQ, YWHAZ, ZYX | 118                 |
### Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation | $p$-Value     | Activation z-Score | Molecules                                                                                                                                                                                                                                                                                                                                                     | Number of Molecules |
|---------------------------------------------------------------------------|----------------------------------|---------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------ian                                                                                                                                                                                                                                                                                          |                   |
| **Cellular movement**                                                     | Cell movement                    | $4.44 \times 10^{-15}$ | $-1.559$          | ACTN4, ACTR2, ACTR3, AHHCY, AKR1B1, ALDOA, ANXA1, ANXA2, ANXA5, ARF1, ARHCD1A, ARPC1B, ARPC2, BSG, CIQBP, CALR, CAP1, CAPG, CAPN1, CAPN2, CAPNS1, CAST, CAV1, CD44, CD59, CDK1, CFL1, CLIC4, CORO1C, CRIP2, CSE1L, CTNNAI1, CTSB, CTTN, CYR61, DBN1, DX3V, DNAJ1, DYS3L2, EHD1, ENAH, EFR, FASN, FKBP4, FNLA, FLNB, FLNC, FNI, GADD, GDI1, GNAI2, GNB2L1, GTP, HARS, HDGF, HLA-A, HMBG1, HNRNPA2B1, HNRNPK, HNRNP1, HSP90AA1, HSP90AB1, HSP90B1, HSP9A5, HSPB1, HSPD1, HYOU1, IGF2R, ILF3, IQGAP1, ITGB1, KHDRBS1, KPN2A, KRT8, LAMB1, LASP1, LAGLS1, LMNA, LMBNL1, MAP1B, MAPK1, MAPRE1, MARKCS, MCM3, MCM7, MSN, MYH10, MYF9, MMY1L2A, NACA, NCL, NPM1, PA2G4, PARK7, PDCD6, PEPB1, PFN1, PHB2, PKM, PLEC, PPI1, PRDX1, PRDX2, PRMT5, PTMA, RHOA, RNI1, RPSA, RTN4, S100A6, SEPT7, SEPT9, SERPINH1, SFN, SOD1, SQSTM1, STAT1, STN1, TAGLN2, TAR5, TLN1, TMOD3, TNC, TPD3, VLC, VCP, VIM, WARS, YBX1, YWHAE, YWHAZ, ZYX | 132               |
| **Dermatological diseases and conditions**                                | Chronic psoriasis                | $5.65 \times 10^{-15}$ |                   | C1QBP, CCT5, COPB2, CTSB, CT5, EIF2S1, EIF2S2, EIF5A, GARS, GSTP1, HSP8, KPA2, KPN2B, MARCKS, PCMT1, PGAM1, PGD, PKM, PPP2CA, PSME2, RABPN1, SLC25A5, STAT1, TAGLN, Tf1F1, UBE2N                                                                 | 26                |
| **Nucleic acid metabolism, small molecule biochemistry**                 | Metabolism of nucleoside triphosphate | $1.02 \times 10^{-14}$ | $-2.160$          | ACLY, ALDOA, ANXA1, ATP1A1, ATP5A1, ATP5B4, CAV1, CCT8, CDK3, CTPS1, DD5X, DX5X9, DX5X, DHX9, DNM1L, G3BP1, HMBG1, HSP90AA1, HSP9A5, HSPD1, LONP1, MCM7, MYH10, MYH9, NNNMT, OLA1, PKM, PSMC1, PSMC4, SLC25A5, SOD1, VCP, VDAC1 | 35                |
| **Neurological disease, psychological disorders, skeletal and muscular disorders** | Parkinson's disease              | $1.16 \times 10^{-14}$ |                   | ANXA2, CAPZB, COPE, CSE1L, EEF1A1, EEF4G1, ENO2, GSTP1, HSF3A/HSF3B, HLA-B, HSPB1, LDHA, LDHB, MAP1B, MDH1, PARK7, PCNA, PEBP1, PGK1, PRDX2, PSMC1, PTGES3, Ran, RPL3, RPS3A, RPS4X, RTN4, SLC25A6, SOD1, STN1, TUBA18, UCHL1, VIM, VIP535 | 34                |
| **Cellular development, cellular growth and proliferation**              | Proliferation of tumor cell lines | $3.28 \times 10^{-14}$ | $-0.292$          | ACAT1, ACLY, ACTN4, AHS1A1, ALDOA, ANXA1, ANXA2, ANXA6, APEX1, ARF1, BSG, CIQBP, CACYPB, CALR, CAV1, CD44, CD59, CDK1, CSE1L, CTSB, CTNN, CYR61, DX5X, DYNCH1E, EEF1A1, EEF1A2, EEF3C, EEF4A1, EEF5A, EFR, EZR, FASN, FNLA, FNI, FUS, GADD, GAPDH, GNB2L1, H2AFY, HDGF, HMBG1, HNRNPA1, HNRNPA2B1, HNRNPK, HSP90AA1, HSP9A5, IGF2R, ILF3, IMM7, IPO7, IQGAP1, ITGB1, KPN2A, KRT8, LAGLS1, MAP1B, MAPK1, MAPRE1, MCM7, NAP, NCL, NPM1, NUMA1, PA2G4, PCNA, PDI3, PEPB1, PKF2, PFN1, PKM, PP2R2A, PRDX2, PRKC5H, PRMT5, PSMC1, PTP2B, PTP1B, PTPMA, RAN, ROHA, S100A6, SEPT9, SET, SFN, SFPQ, SLC25A6, SNS1, SOD1, STN1, STT1, TAGLN2, TCP1, TFRC, TRIM28, TUBB, UBA1, UCHL1, XRC5, XRC6, YBX1, YWHAQ, YWHAQ | 101               |
### Table 5. Cont.

| Categories | Diseases or Functions Annotation | $p$-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|-----------|-------------------|-----------|-------------------|
| Molecular transport, protein trafficking | Transport of protein | $3.57 \times 10^{-14}$ | 0.362 | AP1B1, ARF1, CALR, CAV1, CFL1, CSE1L, CTSA, DNAJ1A1, DNAJ2A1, EHD1, EIF5A, ERP29, GD12, HSPA9, IgG2B, IPO3, IPO7, IPO9, KPN2A, KPNB1, MAP1B, MYH9, NPM1, PDCD6, PDIA3, PICALM, RAB11A, RAB7A, RAN, SNX3, SOD1, SPTBN1, SQSTM1, TNPO1, VAPA, XPO1, YWHAH | 37 |
| Immunological disease | Allergy | $7.01 \times 10^{-14}$ | | AHCY, AHNAK, ALDOA, ANXA1, ANXA5, CAPG, CAPN1, CAPZB, CD44, CFL1, CNN3, CPNE1, DYSLS2, EF1A1, ENO1, FKBP1A, FKBP4, FLNA, GAPDH, H3F3A/H3F3B, HN1, HNRNPA, HSPA5, ID1, KRT1, LGALS1, MSN, MYH9, NLPH, PDIA3, PDGFD, PPIA, PRDX1, STAT1, TFRC, TKT, TPI1, TPM3, TUBB, VCL, VCP, VDAC2, XRC6, YXK | 44 |
| Cellular movement | Cell movement of tumor cell lines | $7.21 \times 10^{-14}$ | 0.345 | ACTN4, ANXA1, ANXA2, ARF1, ARPC1B, ARPC2, BSG, C1QBP, CALR, CAP1, CAPN1, CAPN2, CAPNS1, CAV1, CD44, CSE1L, CT5B, CTTN, CYR61, DYSLS2, ENAH, EKR, FLNA, FLNB, FLNC, FN1, GD1, GNBD1, GPI, HDGF, HNRRPA2B1, HNRNPK, HSP90AA1, ILF3, IQGAP1, ITGB1, KHDRBS1, KPN2A, KRT8, LASP1, LGALS1, MAPK1, MSN, MYH10, MYH9, NCL, PA2G4, PEBP1, PHB2, PPIA, PRDX2, PRM5, RHOA, SEPT9, SFN, SQSTM1, STAT1, STN1, TAGLN2, TNL1, TNC, TPM3, VCL, VCP, VIM, YBX1, YXK | 67 |
| Cell death and survival | Cell survival | $1.06 \times 10^{-13}$ | $-1.997$ | ACLY, ANXA5, AP2B1, APEX1, ATP5H, B2M, CALR, CAPN2, CAV1, CD44, CD89, CDK1, COPB2, CSE1L, CT5B, CYR61, DDXX, DDXX, DHX9, DNML1, EE2, EF5F1, EFR5C, EIF4A1, EIF4G1, EKR, FLNA, FN1, GLUD1, GNBD1, GSTP1, HDGF, HINT1, HMGB1, HNRRPA, HSDB1B10, HSP90A1, HSP90B1, HSPA4, HSPA5, HSPB1, HSPD1, HYOU1, IGF2R, IQGAP1, ITGB1, LDHA, LMNA, MAPK1, MVP, P4HB, PARK7, PCNA, PDI3, PEA15, PPM1G, PPCCA, PP2R1A, PRDX2, PRKDC, PRPF19, PSMA1, PSMA4, PSMA7, PSMC4, RAB11A, RHOA, RPL7, RPSA, S100A6, SET, SF3A1, SFN, SHMT2, SNDR1, SNRPD1, SOD1, SQSTM1, STAT1, STN1, TCPI, TRIM28, TUBB, TXNDC5, UCHL1, VCL, VCP, VDAC1, VIM, XPO1, XRC5, YBX1, YWHAZ | 96 |
| Cellular movement | Migration of cells | $1.22 \times 10^{-13}$ | $-2.069$ | ACTN4, ACTR3, AHCY, ALDOA, ANXA1, ANXA2, ANXA5, ARF1, ARHGDIA, ARPC2, BSG, C1QBP, CALR, CAP1, CAPG, CAPN2, CAPNS1, CAST, CAV1, CD44, CD89, CFL1, C1IC1, C1IC3, C1IC6, CLIC1, CTNNB1, CTNNA1, CTNNB1, CYR61, DRY1, DDXX, DDXX, EHD1, EKR, FLNA, FLNB, FLNC, FN1, G6PD, GNAI2, GNBD1, GPI, HARS, HDGF, HLA-A, HMGB1, HNRNPA2B1, HNRNPK, HNRNPL, HSP90AA1, HSP90B1, HSP90B1, HSPB1, HSPD1, HYOU1, IGF2R, ILF3, IQGAP1, ITGB1, KHDRBS1, KPN2A, KRT8, LMAB1, LASP1, LGALS1, LMNA, LMNB1, MAP1B, MAFK1, MAFK2, MARCKS, MCM3, MCM7, MSN, MYH10, MYH9, MYL12A, NACA, NCL, NPM1, P2AG4, PARK7, PDCD6, PPIB, PHB2, PPM1G, PLEC, PPIA, PRDX1, PRDX2, PRM5, RHOA, RN1H, RPSA, RTN4, S100A6, SEPT7, SFN, SOD1, STAT1, STN1, TARS, TNL1, TMOD3, TNC, TPM3, VCL, VCP, VIM, WARS, YBX1, YWHAE, YWHAZ, YWHAZ, YXK | 119 |
Table 5. Cont.

| Categories                               | Diseases or Functions Annotation | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------|----------------------------------|---------------|--------------------|----------------------------------------------------------------------------|---------------------|
| Gene expression, protein synthesis       | Translation of mRNA              | 2.07 × 10⁻¹³  | 1.632              | CALR, CAPRIN1, DDX3X, EEF1B2, EIF2S1, EIF3B, EIF5C, EIF5I, EIF5M, EIF4G1, EIF4H, EPRS, GAPDH, GNB2L1, HSPB1, ILF3, NACA, PPP1CA, RBM3, RPL23, RPS2, RPS3A, RPS4X, RPS5, RRBP1, SYNCRIP, WARS | 27                  |
| Cancer, respiratory disease              | Respiratory system tumor         | 3.89 × 10⁻¹³  | 0.316              | ACLY, AHNAK, AKR1B1, ALDOA, ALDOC, ALYREF, ANXA1, ANXA2, APEX1, ATIC, B2M, CAPRIN1, CAV1, CD44, CDK1, CYR61, DDX9, EEF1A1, EEF1B2, EEF4A1, ENAH, EN01, EN02, EZR, FASN, FDPS, FN1, G3BP1, GNB2L1, GPI, GTP1, H2AFY, HIST2H2AC, HLA-A, HSP90AA1, HSP90AB1, HSP90B1, HSPDI, IMPDH2, ITGB1, KRT8, LDHA, LGALS1, LOC102724594/U2AF1, MAP4, MSN, MYH9, MYL12A, NACA, NCL, NSFL1C, PABPC1, PCNA, PDCd6, PFKP, PKM, PPIA, PRDX1, PRDX2, PRPFI9, RHOA, RPL27, RPL7, RPS11, RPS27A, SERBP1, SFN, SHMT2, SNDF1, S QSTM1, STAT1, STIN1, TNC, TP1, TUBB, TUBB4B, VIM, YWHAE, ZYX | 79                  |
| Cancer                                   | Malignant neoplasm of thorax     | 4.70 × 10⁻¹³  | 0.949              | ACLY, AHNAK, ALDOA, ALDOC, ANXA2, APEX1, ATIC, B2M, CAPRIN1, CAV1, CD44, CDK1, CYR61, DDX9, EEF1A1, EEF1B2, EEF4A1, ENAH, EN01, EN02, EZR, FASN, FDPS, FN1, G3BP1, GNB2L1, GPI, GTP1, H2AFY, HIST2H2AC, HLA-A, HSP90AA1, HSP90AB1, HSP90B1, HSPDI, IMPDH2, ITGB1, KRT8, LDHA, LGALS1, LOC102724594/U2AF1, MAP4, MSN, MYH9, MYL12A, NACA, NCL, NSFL1C, PABPC1, PCNA, PDCd6, PFKP, PKM, PPIA, PRDX1, PRDX2, PRKDC, PRPPF19, RHOA, RPL27, RPL7, RPS11, RPS27A, SERBP1, SHMT2, SNDF1, SQSTM1, STAT1, STIN1, TPI1, TUBB, TUBB4B, VIM, X RCC5, XRCG6, YWHAE | 76                  |
| Gene expression                          | Expression of mRNA               | 6.12 × 10⁻¹³  | 0.865              | CALR, CAPRIN1, DDX3X, EEF1B2, EIF2S1, EIF3B, EIF5C, EIF5I, EIF5M, EIF4G1, EIF4H, EPRS, GAPDH, GNB2L1, HMBG1, HSPB1, ILF3, KHDRBS1, NACA, PEN1, PPP1CA, RBM3, RPL23, RPS24, RPS3A, RPS4X, RPS5, RRBP1, STAT1, SYNCRIP, WARS | 31                  |
| Cell morphology, cellular assembly and organization, cellular function and maintenance | Formation of cellular protrusions | 6.14 × 10⁻¹³  | ~0.837             | ACTN4, ACTR2, ACTR3, ARPC2, BASP1, BSG, CIQBP, CAP1, CAPG, CAPN2, CAPN5I, CAPRIN1, CAPZB, CAST, CAV1, CD44, CFL1, CSR1, CTTN, CYR61, DBN1, DNM1L, DYSL, EEF1A1, EHD1, ENAH, EZR, FASN, FLNA, FN1, GDH1, HMBG1, HRNPK, HSP90AA1, HSPB1, IQGAP1, ITGB1, KIF5B, LAB1, LASP1, MAP1B, MARCKS, MSN, MYH10, NNM, PM, PDIA3, PEN1, PHC3D, PICALM, PLEC, PPP2CA, PRKCSH, RAB11A, RANBP1, RHOA, RTN4, SEPT2, SOD1, SPTBN1, STIP1, STIN1, TNC, TPM3, TWF2, UCHL1, VAPA, VCL, VIM, YWHAH | 70                  |
| Cancer, respiratory disease              | Lung tumor                       | 7.06 × 10⁻¹³  | 0.316              | ACLY, AHNAK, AKR1B1, ALDOA, ALDOC, ALYREF, ANXA2, APEX1, ATIC, B2M, CAPRIN1, CAV1, CD44, CDK1, CYR61, DDX9, EEF1A1, EEF1B2, EEF4A1, ENAH, EN01, EN02, EZR, FASN, FDPS, FN1, G3BP1, GNB2L1, GPI, GTP1, H2AFY, HIST2H2AC, HLA-A, HSP90AA1, HSP90AB1, HSP90B1, HSPDI, IMPDH2, ITGB1, KRT8, LDHA, LGALS1, LOC102724594/U2AF1, MAP4, MSN, MYH9, MYL12A, NACA, NCL, NSFL1C, PABPC1, PCNA, PDCd6, PFKP, PKM, PPIA, PRDX1, PRDX2, PRPFI9, RHOA, RPL27, RPL7, RPS11, RPS27A, SERBP1, SHMT2, SNDF1, SQSTM1, STAT1, STIN1, TNC, TP1, TUBB, TUBB4B, VIM, YWHAE, ZYX | 77                  |
| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|---------------------------------|---------|-------------------|-----------|--------------------|
| Organismal survival | Organismal death | $9.82 \times 10^{-13}$ | 2.742 | ACLY, ACTA1, ACTG1, ACTN4, AIP, ANXA1, APEX1, ARHGDIA, ATP1A1, B2M, BSG, BUB3, CIQBP, CALR, CANX, CAP1, CAPN1, CAPN2, CAPNS1, CAPRIN1, CAPZB, CAST, CAV1, CD44, CD59, CDK1, CFL1, CLIC4, CSE1L, CTSA, CTSB, CTN, CYR61, DBI, DDX1, DDX5, DEXH9, DNM1L, DYN1CH1, EHD1, EIF2S1, EIF3M, EIF4A1, EIF6, ENAH, FASN, FKBP1A, FKBP4, FLNA, FLNB, FLNC, FN1, FUS, G6PD, GNA12, GSTP1, H3F3A/H3F3B, HADHA, HEXB, HIST1H1C, HMGBI, HNRNPK, HSP90AA1, HSP90ABI, HSP90BI, HSPA5, HYOU1, IGF2R, ILF2, ILF3, IEMPHD2, ITGB1, KHDRBS1, KIF5B, KRT1, KRT8, LMNA, LMNB1, LRP3, MAP1B, MAPK1, MSN, MYH10, MYH9, NASP, NPM1, NUMA1, PCNA, PDIA3, PEAN, PHB2, PHGDH, PICALM, PLEC, PLS3, PPIA, PPP2CA, PRDX1, PRKDC, PRMT5, PRPF19, PSMC1, PSMC4, PTBP1, PTGES3, RAD23B, RHOA, RPL14, RPL6, RPSA, RTN4, SERTPHN1, SF3B1, SMH2, Spy1, SQSTM1, SSRP1, STFI1, STIP1, TREC, TKT, TTN1, TP53, TP1, TRIM28, UBE2L3, UBE2N, VCL, VCP, VDAC1, VIM, WDR1, XRC5, XRC6, XBY1, XBY3, YWHAE | 139 |
| Infectious disease, renal and urological disease | Infection of kidney cell lines | $1.19 \times 10^{-12}$ | $-1.281$ | BSG, CTSB, GANAB, HMGB1, HNRNPH1, HSPA5, IFITM3, KHDRBS1, KPNB1, KRT18, MAP4, PCBP2, PCGM1, PLOD2, PSMA1, PSMA2, PSMA5, PSMA7, PSMC4, PTGES3, RNH1, RPL10A, RPL12, RPL18, RPL3, RPL5, SF3A1, SF3B1, SNRPD3, TAGLN2, TFRC, UBE2L3, YBX1, ZYX | 34 |
| Inflammatory disease, skeletal and muscular disorders | Inclusion body myopathy | $2.03 \times 10^{-12}$ | | CALR, CANX, HNRNPA1, HNRNPA2B1, HSPA5, HSPMA2, PSMA2, SQSTM1, VCP | 10 |
| Cancer, respiratory disease | Lung cancer | $2.29 \times 10^{-12}$ | 0.205 | ACLY, AHNAK, ALDOA, ALDCLC, ANXA2, APEX1, ATIC, B2M, CAPRIN1, CANX, CD44, CDK1, Cyr61, DDX9, EEF1A1, EEF1B2, EIF4A1, ENAH, ENSI, ENO2, EZR, FASN, FDPS, FN1, G3BP1, GNB2L1, GPI, GSP1, H2AFY, HIST2H2AC, HLA-A, HSP90AA1, HSP90ABI, HSP90BI, HSPFD1, IMPDH2, ITGB1, KRT8, LDHA, LGS1, LOC10272454, MAP4, MSN, MYH9, MYL12A, NACA, NCL, NPLIC, PABPC1, PCNA, PDCD6, PKP3, PKM, PPIA, PRDX1, PRDX2, PRPF19, RHOA, RPL2, RPL7, RPL17, RPS11, RPS27A, SERBP1, SMH2, SNM1, SQSTM1, STAF1, STMN1, TP1, TUBB, TUBB4B, VIM, YWHAE | 73 |
| Dermatological diseases and conditions, immunological disease, inflammatory disease, inflammatory response | Atopic dermatitis | $2.95 \times 10^{-12}$ | | AHCY, AHNAK, ANXA1, ANXA5, CAPG, CAPZB, CD44, CFL1, CN2N, CPNE1, DYSPL2, EEF1A1, ENO1, FKBP1A, FKBP4, FLNA, H3F3A/H3F3B, HN1, HNRNPR, ID1, KRT1, LGALS1, MSN, PHGDH, STAF1, TP1, TPM3, VCL, VCP, VDAC2, XRC6, ZYX | 32 |
| Developmental disorder, hereditary disorder, skeletal and muscular disorder | Distal myopathy | $4.20 \times 10^{-12}$ | | CALR, CANX, FLNC, HSP90BI, HSPA5, MATR3, PSMA2, PSMA4, SQSTM1, VCP | 10 |
| RNA post-transcriptional modification | Processing of RNA | $4.45 \times 10^{-12}$ | 0.640 | AARS, AHNAK, CIQBP, DDX39B, DDX5, FUS, HNRNPA1, HNRNPA2B1, HNRNPH1, HNRNPH3, HNRNPK, HNRNPL, HNRNPM, HNRNPU, KHDRBS1, KHSRP, LOC10272454/U2AF1, NPM1, PABPC1, PCBP2, PPIA, PRPF19, PTBP1, RBM3, RPL5, RPL7, RPS15, RPS24, RPS7, SF3A1, SF3B1, SFQ, SNRPD1, SYNCRIP, U2AF2 | 34 |
| Categories                                      | Diseases or Functions Annotation | p-Value     | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-------------------------------------------------|----------------------------------|-------------|--------------------|----------------------------------------------------------------------------|---------------------|
| Nucleic acid metabolism                         | Metabolism of nucleic acid component or derivative | \(7.96 \times 10^{-12}\) | -1.213             | ACLY, AHHCY, ALDOA, ANXA1, ATIC, ATP1A1, ATP5A1, ATP5B, ATP5H, CAV1, CCT8, CDK1, CS, CTSP1, DB1, DDX1, DDX39B, DDX39X, DDX39L, DDX39M, DYS1, EDRB1, FASN, FDS1, G3BP1, G6PD, GMP5, GNA2D, HMBG1, HSP90AA1, HSP9A, HSPD1, HSPF2, LONP1, MAPK1, MCM7, MDH1, MDH2, MYH10, MYH9, NNMT, OLA1, PGK1, PKM, PPA1, PSMC1, PSMC4, SET, SLC25A5, SOD1, TALD01, UAP1, VCP, VDAC1 | 54                  |
| Infectious disease, organismal injury and abnormalities | Infection of embryonic cell lines | \(1.06 \times 10^{-11}\) | -1.045             | BSG, GANAB, HMBG1, HRNRP11, HSP9A, IFTM1, HDHRKS1, KPBN1, MAP4, PCBP2, PG1, PLOD2, PSA1, PSA2, PSA3, PSA7, PMC4, PTGES3, RH1, RPL10A, RPL12, RPL18, RPL3, RPL5, SBSF1, SNSP3, TACLN2, TACRN, UBE2L3, YB1, YXY | 32                  |
| Infectious disease                              | Infection of epithelial cell lines | \(1.06 \times 10^{-11}\) | -1.045             | BSG, GANAB, HMBG1, HRNRP11, HSP9A, IFTM1, HDHRKS1, KPBN1, MAP4, PCBP2, PG1, PLOD2, PSA1, PSA2, PSA3, PSA7, PMC4, PTGES3, RH1, RPL10A, RPL12, RPL18, RPL3, RPL5, SBSF1, SNSP3, TACLN2, TACRN, UBE2L3, YB1, YXY | 32                  |
| Cellular movement                               | Invasion of cells                | \(1.64 \times 10^{-11}\) | -0.711             | ACAT1, ACY, ANX1A, ANX2A, APAX1, ARHGDIA, BSG, C1QBP, CALR, CAP1, CAPN2, CAPS1, CAV1, CD44, CDK1, CSE1L, CTSB, CTNN, CYR61, ENA1H, EZK, FKBPIA, FLNA, FN1, GNA2D, GNB2L1, GPA, HDF, HDLPB, HMBG1, HSP90A1, HSP90A1B, HSP90B1, HSP9A, IL3, IGGAP1, ITG8B, KRT8, LAPS1, LALS1, MAPK1, MKS, MHY10, NPM1, OTUB1, PA2G4, PERP1, PICALM, PKK, PTGES3, RHOA, RH1, RPS1, S100A6, SEPT9, SQSTM1, STAM1, TACRN, TACLN2, TACRN2, TACRN, UBE2L3, YB1, YXY | 63                  |
| Cell death and survival                         | Cell viability                   | \(3.09 \times 10^{-11}\) | -1.538             | ACILY, ANX5A, AP2B1, ATPX1, ATP5H, B2M, CALR, CAPN2, CAV1, CD44, CD59, CDK1, COB2, CTBB, CYR61, DDX5, DDX9, DNM1L, EEF2, EFC3, EIF4A1, EIF4G1, EZR, FN1, GLUD1, GNR2L1, GSP1, HDF, HINT1, HMBG1, HRNRP11, HSD17B10, HSP90A1, HSP90B1, HSP9A, HSBA5, HSBA1, HSBD1, HYO1, IGFB2, IGFRAP1, ITB8, LDHA, LMNA, MAPK1, MVP, PHRB, PARK7, PCNA, PDA1, PIA, PMG1, PP1CA, PP2CA, PP2R1A, PPCD2, PRCB, PRF19, PSA1, PSA4, PMC4, RAB11A, RHOA, RPL5, RPSA, S100A6, SFB1, SFN, SHM2, SN1, SNRPN1, SOD1, SQSTM1, STAT1, STAM1, TACRN, TRIM28, TXNDC5, UCHL1, VCP, VDAC1, XPO1, XRCC5, YBX1, YWHAZ | 85                  |
| Cancer, organismal injury and abnormalities, reproductive system disease | Cervical tumor                   | \(3.68 \times 10^{-11}\) | -1.538             | ACTR3, ALYREF, ANXA1, ANX2A, ANX5A, ATIC, CTBB, ENO1, GSP1, H2AFY, HST1H2B1, HST2H2AC, HLA-A, HLA-B, HSP90AA1, HSP90A1, HSP90B1, KRT1, KRT9, MAP4, MCM7, RPS12, TACRN, TACRN, TACRN2, TACRN3, TACRN, TACRN, UBE2L3, YB1, YWHAZ | 31                  |
| Developmental disorder, hereditary disorder, inflammatory disease, neurological disease, skeletal and muscular disorders | Nonaka myopathy                  | \(4.55 \times 10^{-11}\) | -1.538             | CALR, CANX, HSP90B1, HSP9A, PSMA2, PSMA4, SQSTM1, VCP | 8                  |
| Dermatological diseases and conditions, inflammatory disease, inflammatory response | Dermatitis                       | \(5.49 \times 10^{-11}\) | -1.538             | AHCY, AHNAK, ANXA1, ANX5A, ARHGDIA, ATP1A1, CALR, CAPG, CAPZB, CD44, CFL1, CNGB3, CPN1, DYS1, EDRB1, EEF1A1, ENO1, FKBPIA, FKBPIB, FN1, GHRP1, HSD17B10, HSP90A1, HSP90B1, HSP90B1, HSP9A, HRNRP11, ID1, KRT1, KRT9, LALS1, MSN, PHD3, PSN, STAT1, TIPI, TPM3, TUBB, TUBB4B, TUBB4E, TUBB5, TUBB6, TUBB8, TUBB11, TUBB12, VCP, VDAC2, XRCC6, YXY | 41                  |
Table 5. Cont.

| Categories | Diseases or Functions | Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|-----------------------|------------|---------|--------------------|-----------|---------------------|
| Infectious disease | Replication of influenza A virus |           | 6.00 × 10^{-11} | −0.322 | ANXA6, B2M, C14orf166, CLIC4, COPA, COPB1, COPB2, COPG1, CSE1L, EEF1A1, EIF3C, FPD5, HSP90AA1, HSPD1, IFTM3, ILF3, KPNB1, LONP1, MAPK1, PSMA1, PSMD2, RPS10, RPS27A, RPS5, RSA4A, SAE1, SF3B1, SFPQ, STAT1, TUBB, XPO1 | 32 |
| Cell cycle | M phase | 6.05 × 10^{-11} | −0.578 | ACTN4, BUB3, CAP1, CAPN2, CDK1, CFL1, FLNA, FN1, GNAI2, ITGB1, LMNA, MAPRE1, MCM4, MCM7, MSN, MYH10, MYH9, NPM1, NUMA1, PFB31A, RAB11A, RHOA, SEPT2, SEPT7, SEPT9, SSRP1, XRCC5, YBX1 | 28 |
| DNA replication, recombination, and repair, energy production, nucleic acid metabolism, small molecule biochemistry | Catabolism of ATP | 7.68 × 10^{-11} | | ACLY, ANXA1, ATP1A1, ATP5A1, ATP5B, ATP5H, CCR5, DDX1, DDX39B, DDX3X, DDX5, DDX9, G3BP1, HSP90AA1, HSPA8, LONP1, MCM7, MYH10, MYH9, NOL1, PSMC1, PSMC4, VCP | 23 |
| Cell death and survival | Cell death of neuroblastoma cell lines | 1.35 × 10^{-10} | −1.206 | ATP5A1, CAPN1, CAPN2, CAST, CCT2, CCT3, CCT4, CCT5, CCT6A, CCT7, CCT8, ENO1, FKBPA1, GAPDH, HSPA5, ITGB1, PARK7, PBPI, PRDX2, S100A6, SOD1, SQSTM1, TCP1, YWHAE | 24 |
| Hematological disease, immunological disease, inflammatory disease, inflammatory response, respiratory disease | Allergic pulmonary eosinophilia | 1.55 × 10^{-10} | | ALDOA, ENO1, GAPDH, HSPA5, MYH9, P4HB, PIA3, PRDX1, TKT, TPI1, TUBB | 11 |
| Cell morphology | Cell spreading | 1.72 × 10^{-10} | −0.793 | CAP1, CAPN2, CAST, CD44, CYR61, EHD1, FLNA, FLNB, FLNC, FN1, GNB2L1, IGF2R, IP09, ITGB1, LCA1S, MAP4, MAPK1, MARCKS, PFB1, PFBP1, RHOA, RBB1, RTN4, TNI1, TNC, UCHL1, VCL, VIM, YWHAZ, ZYX | 30 |
| Skeletal and muscular disorders | Myopathy | 1.81 × 10^{-10} | −2.236 | AARS, ACTA1, AINHAK, ATP1A1, BUB3, CALR, CANX, CAST, DYNC1H1, ECH51, FBK51A, FLNC, FN1, GARS, HARS, HEXB, HINT1, HLA-A, HMBG1, HRNRPA1, HRNRPA2B1, HSP90B1, HSP5A, HSPA1B, ITGB1, LMNA, LRP3R, MATR3, FLEC, PIPICA, PIP2CA, PSMA2, PSMA4, RAB7B, RHOA, SDHA, SOD1, SQSTM1, STMN1, TPM2, TPM3, TUBB, TUBB4B, UBA1, VCL, VCP | 46 |
| Molecular transport, protein trafficking | Internalization of protein | 2.17 × 10^{-10} | 1.900 | AP1B1, AP2B1, CAP1, CFL1, CLTC, DNAJ1A1, DNAJ2A, IPO5, IPO7, IPO9, KPNA2, KPNB1, PIA3, RAN, RHOA, SPTBN1, TUBB | 17 |
| Cell death and survival | Cell death of cervical cancer cell lines | 2.24 × 10^{-10} | −0.340 | ATP1A1, CALR, CCT4, CDK1, CTSB, DNM1L, DYNC1H1, EZF, FNLB, HNRNPK, IMMT, KHDRBS1, KPNB1, KRT18, LMNA, MAPK1, MSN, PCBP2, PKM, PPIA, PP2RA1, PRDX2, PRKDC, PRPF19, PTMA, RPS24, SOD1, SQSTM1, STAT1, TCP1, UCHL1, VCP, VDAC1, YWHAH | 34 |
| Cellular development, cellular growth and proliferation, connective tissue development and function | Proliferation of fibroblast cell lines | 2.34 × 10^{-10} | −0.983 | AAT1, AKR1B1, ALDOA, APEX1, ATIC, CAPRIN1, CAST, CAV1, CLTC, DDX3X, DPY30, EEFD1D, EIF5B, EIF5C, EIF9I, EGF2, FN1, GPD2, GNA2, GRN21L, HOGF, HINT1, HMG8L1, ITGB1, KHDRBS1, LMNA, MAPK1, NPM1, PRPF19, PSMA4, PTMA, RHOA, S100A6, STAT1, STIP1, STMN1, TFRC, TPM3, XRCC6 | 39 |
| Categories                              | Diseases or Functions Annotation | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-----------------------------------------|----------------------------------|---------------|-------------------|---------------------------------------------------------------------------|--------------------|
| Cancer, respiratory disease             | Stage 1-2 non-small cell lung cancer | $2.36 \times 10^{-10}$ |                   | ANXA2, B2M, EEF1A1, EIF4A1, FN1, MYL12A, PPIA, RPL27, RPL7, RPS11, RPS27A, SERBP1 | 12                 |
| Immunological disease                   | Immediate hypersensitivity        | $2.58 \times 10^{-10}$ |                   | AHCY, AHNAK, ANXA1, ANXA5, CAPG, CAPZB, CD44, CFL1, CNN3, CPNE1, DPYS12, EEF1A1, ENO1, FKBP1A, FKBP4, FLNA, H3F3A/H3F3B, HN1, HNRNPR, ID1, KRT1, LGALS1, MSN, PHGDH, PPIA, STAT1, TPI1, TPM3, VCL, VCP, VDAC2, XRC6, ZYX | 33                 |
| DNA replication, recombination, and repair | Metabolism of DNA                | $2.73 \times 10^{-10}$ | $-1.611$          | APEX1, BSG, CACYBP, CALR, CAPN2, CAST, CAV1, CDK1, DHX9, ENO1, HMGB1, HNRNPA1, HSD17B10, HSPB1, KPN2, KRT8, LMNA, MAPK1, MCM7, NAP1L1, NASP, NCL, NPM1, PCMI, PCNA, PEA15, PFN1, PPIA, RAN, RHOA, SET, SOD1, SSRP1, STAT1, SUPT16H, TMPO, XRC5, XRC6 | 38                 |
| Cellular assembly and organization      | Organization of organelle         | $3.33 \times 10^{-10}$ | $-1.732$          | ALDOA, ANXA2, CAPZB, CAV1, CD44, CFL1, CLIT, CTNNA1, DBN1, DNM11, DPYS12, ENAH, FKBP1A, FLNA, FN1, GAPDH, H3F3A/H3F3B, HEBX, ITGB1, KRT1, KRT9, LMNA, LONP1, MAPRE1, MSN, MYH9, NLOC4, NPM1, NSFLIC, NUMA1, PARK7, PCMI, PLS3, RHOA, RRBP1, SERPINH1, SOD1, SPTBN1, STOML2, SURF4, TIP1, TUBB, TUBC, VIM | 44                 |
| Cancer, respiratory disease             | Carcinoma in lung                 | $3.34 \times 10^{-10}$ | 0.555             | AHNAK, ALDOA, ALDOC, ANXA2, APEX1, ATIC, B2M, CAPRIN1, CAV1, CD44, CDK1, DHX9, EEF1A1, EEF1B2, EIF4A1, ENO1, ENO2, EZR, FASN, FDPS, FN1, G3BP1, GNB2L1, GPl, GSTP1, HIT2H2AC, HLA-A, HSP90AA1, HSP90AB1, HSP90B1, HSPD1, IMPDH2, ITGB1, LDHA, LOCI272494/1U2AF1, MAP4, MSN, MYH9, MYL12A, NACA, NSFLIC, PABPC1, PCNA, PDCD6, PFKP, PKM, PPIA, PRDX1, PRPF9, RPL27, RPL7, RPS11, RPS27A, SERBP1, STAT1, STMN1, TIP1, TUBB, TUBB4B, VIM, YWHAe | 61                 |
| Nucleic acid metabolism, small molecule biochemistry | Metabolism of nucleotide          | $4.07 \times 10^{-10}$ | $-1.647$          | ACLY, ALDOA, ANXA1, ATPI1A, ATPSA1, ATPSB, ATPSH, CAV1, CCT8, CDK3, CTS1, DD1, DDX3B, DDX3X, DDX5, DHX9, DNMI1, FASN, FDPS, FN1, G3BP1, GNB2L1, GPl, GSTP1, HIT2H2AC, HLA-A, HSP90AA1, HSP90AB1, HSP90B1, HSPD1, IMPDH2, ITGB1, LDHA, LOCI272494/1U2AF1, MAP4, MSN, MYH9, NLOC4, NSFLIC, NPLC4, PABPC1, PCNA, PDCD6, PFKP, PKM, PPIA, PRDX1, PRPF9, RPL27, RPL7, RPS11, RPS27A, SERBP1, STAT1, STMN1, TIP1, TUBB, TUBB4B, VIM, YWHAe | 46                 |
| DNA replication, recombination, and repair, nucleic acid metabolism, small molecule biochemistry | Hydrolysis of nucleotide          | $4.19 \times 10^{-10}$ | $-1.306$          | ATP1A1, CALR, CCT4, CCT5, CDK1, DNMI1, GNA12, HMGB1, HSPA5, HSPD1, IPOS, MAPK1, RAB7A, RAN, RANBP1, RHOA, STMN1, UBA1, XPO1 | 19                 |
| Infectious disease                      | HIV infection                     | $4.22 \times 10^{-10}$ | $-1.958$          | ANXA2, ARF1, ATPSB, B2M, CCT2, CD44, DDX3X, DHX9, DNJAJ2, FDPS, FN1, GANAB, GML, GPl, H3F3A/H3F3B, HMGB1, HNRNPH1, HNRNPU, IMPDH2, ITGB1, KHDRBS1, KPNB1, MAP4, PDI1A3, PDI1A6, PGMI, PLOD2, PSMA1, PSMA2, PSMA3, PSMA7, PSMC4, PSMF2, PTGES3, RAB1B, RANBP1, RNH1, RPL10A, RPL12, RPL18, SF3A1, SF3B1, SNRPD3, SPTAN1, SPTBN1, STIP1, TAILN2, TFCR, TF1W1, UAP1, UBE2L3, UQCRCC1, XPO1, YBX1, ZYX | 55                 |
| Categories                                      | Diseases or Functions Annotation | p-Value    | Activation z-Score | Molecules                                                                                           | Number of Molecules |
|------------------------------------------------|----------------------------------|-----------|-------------------|----------------------------------------------------------------------------------------------------|---------------------|
| Nucleic acid metabolism, small molecule biochemistry | Metabolism of purine nucleotide | 4.60 × 10⁻¹⁰ |                   | ACLY, ANXA1, ATP1A1, ATP5A1, ATP5B, ATP5H, CCT8, DDX1, DDX39B, DDX3X, DDH5, DDH9, G3BP1, G6PD, HSP90AA1, HSP9A8, LONP1, MCM7, MDH1, MDH2, MYH10, MYH9, OLA1, PSMC1, PSMC4, VCP | 26                  |
| Cancer, respiratory disease                     | Non-small cell lung cancer       | 4.91 × 10⁻¹⁰ |                   | AHNAK, ALDOA, ALDOC, ANXA2, APEX1, ATIC, B2M, CAPRIN1, CAV1, CD44, CDK1, DHX9, EEF1A1, EEF1B2, EEF1A3, ENO1, EZR, FASN, FDP5, FN1, G3BP1, GNB2L1, GPI, GSTP1, HIST2H2AC, HLA-A, HSP90AA1, HSP90AB1, HSP90B1, HSPD1, IMPDH2, ITGB1, LDHA, LOC102724594/U2AF1, MAP4, MSN, MYH9, MYL12A, NACA, NSFL1C, PABPC1, PCNA, PFKP, PKM, PPIA, PRDX1, PRPF19, RPL27, RPL7, RPS11, RPS27A, SERBP1, STAT1, STN1, TP11, TUBB, TUBB4B, VIM | 58                  |
| Immunological disease                           | Hypersensitive reaction          | 5.39 × 10⁻¹⁰ | 0.404             | AHCY, AHNAK, ANXA1, ANXA5, CALR, CAPG, CAPZB, CD44, CFL1, CUN3, CPNE1, DPYSL2, EEF1A1, ENO1, FKBPA1, FKBPA4, FLNA, GARS, H3F3A/H3F3B, HLA-A, HLA-B, HN1, HRNRNP, IDH1, KRT1, LGAL5I, MSN, PHGDH, PPIA, PSE2, SOD1, STAT1, TP11, TP3M, VCL, VCP, VDAC2, XRC5, ZYX | 39                  |
| Cancer, endocrine system disorders, organismal injury and abnormalities | Benign cold thyroid nodule       | 1.09 × 10⁻⁹  |                   | ANXA5, CALR, CTSB, GSTP1, HSP90AB1, PARK7, PRDX2, PRDX5 | 8                   |
| Cancer, organimial injury and abnormalities, reproductive system disease | Cervical cancer                  | 1.13 × 10⁻⁹  |                   | ACTR3, ANXA1, ANXA2, ANXA5, ATIC, CTSB, ENO1, GSTP1, H2AFY, HIST1H2BL, HIST2H2AC, HSP90AA1, HSP90AB1, HSP90B1, HSB1, KRT1, KRT9, MAP4, MCM7, RPS12, TAGLN, TFRC, TPM2, TPM3, TUBB, TUBB4B, XPO1, YWHAE | 28                  |
| Cellular assembly and organization, cellular function and maintenance | Organization of filaments       | 1.22 × 10⁻⁹  | −1.929            | ALDOA, ANXA2, CFL1, DBN1, DPYSL2, ENAH, FKBPA1, FLNA, FN1, GAPDH, ITGB1, KRT18, KRT9, MAPRE1, MSN, NUMA1, PCML, PL53, RHOA, RRRP1, SERPINH1, SOD1, TUBB, VIM | 24                  |
| Cancer, respiratory disease                     | Pulmonary metastasis             | 1.30 × 10⁻⁹  |                   | ATIC, B2M, EEF1A1, EEF4A1, FN1, MYL12A, PPIA, RHOA, RPL27, RPL7, RPS11, RPS27A, YWHAE | 13                  |
| Cellular assembly and organization              | Stabilization of filaments       | 1.55 × 10⁻⁹  | −0.454            | CFL1, COPB2, CTTN, DNM1L, DPYSL2, FLNA, IQGAP1, KRT18, KRT8, MAP1B, MAP4, MAPRE1, NUMA1, PKM, RHOA, SEPT7, STN1 | 17                  |
| Cancer, respiratory disease                     | Metastatic lung carcinoma        | 1.60 × 10⁻⁹  |                   | ATIC, B2M, EEF1A1, EEF4A1, FN1, MYL12A, PPIA, RPL27, RPL7, RPS11, RPS27A, YWHAE | 12                  |
| Cancer                                          | Metastasis                       | 1.88 × 10⁻⁹  | −1.645            | ANXA1, ANXA5, ATIC, B2M, C1QBP, CAPG, CAPN2, CAV1, CD44, CSE1L, CTSB, CTNN, CYR61, DPYSL2, EEF1A1, EEF4A1, ENAH, EZR, FASN, FDP5, FKBPA1, FLNA, FN1, FUS, GNB2L1, HMGBI, HSP90AA1, HSP90AB1, HSP90B1, HYOU1, ITGB1, KHDRBS1, KRT18, KRT8, LGAL5I, MAPK1, MYL12A, PLOD2, PPIA, PRDX2, RHOA, RNH1, RPL27, RPL7, RPS11, RPS27A, SND1, SQSTM1, STAT1, TUBB, TUBB4B, UBE2N, VIM, YWHAE, YWHAZ | 55                  |
Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|---------|--------------------|-----------|---------------------|
| Cellular movement | Migration of tumor cell lines | 1.96 × 10⁻⁹ | −0.054 | ACTN4, ANXA1, ANXA2, ARF1, ARPC2, BSG, C1QBP, CAPN2, CAPNS1, CAV1, CD44, CSE1L, CTTN, CYR61, DPYSL2, EZR, FLNA, FLNB, FN1, GNB2L1, HDGF, HNRNPA2B1, HNRNPK, HSP90AA1, ILF3, IQGAP1, ITGB1, KHDRBS1, KPN2, KRT8, LASP1, LGALS1, MAPK1, MSN, MYH10, MYH9, NCL, PHB2, PRDX2, PRMT5, RHOA, SFN, STAT1, STMN1, TNC, TPM3, VCP, VIM, ZYX | 50 |
| Cell morphology, connective tissue development and function | Cell spreading of fibroblast cell lines | 2.05 × 10⁻⁹ | 0.201 | CAST, EHD1, FLNA, FLNC, FN1, GNB2L1, IPO9, ITGB1, PTBP1, RTN4, VCL, VIM | 12 |
| Cancer, respiratory disease | Metastatic lung cancer | 2.05 × 10⁻⁹ | | ATIC, B2M, EEF1A1, EIF4A1, FN1, MYL12A, PPIA, RPL27, RPL7, RPS11, RPS27A, YWHAE | 12 |
| Gene expression | Expression of RNA | 2.21 × 10⁻⁹ | 1.310 | ACTR2, ACTR3, ALYREF, BAP51, BTF3, C14orf166, C1QBP, CALR, CAND1, CAPRIN1, CAV1, CBX3, CD44, CDK1, CSE1L, CYR61, DDX9, DXD5, DXH9, EEF2B2, EEFD1, EEFD2, EEF2S1, EEF3B, EEF3C, EIF3I, EIF4G1, EIF4H, ENO1, EPRS, EZR, FKBP1A, FLNA, FN1, FUBP3, GAPDH, GLO1, GNB2L1, GSTP1, H2AFY, HDGF, HEXB, HINT1, HIST1H1C, HMGBI, HNRNPA1, HNRNPA2B1, HNRNPK, HSPA4, HSPA8, HSPB1, ILF2, ILF3, IQGAP1, KHDRBS1, KPN2, LGALS1, LMNA, LRP, MAPK1, MATR3, MCM7, MSN, NACA, NONO, NPM1, PTP1B, PTP2, RBM3, RHOA, RPL23, RPL6, RPS1A, RPS4X, RPS5, RRP1, SET, SFOQ, SQSTM1, SPP1, STAT1, SYNCRIP, TAGLN, TEMPO, TNC, TRIM28, UBE2L3, VAPA, VIM, WARS, XPO1, XRC5, XRC6, YBX1, YBX3, YWHAH, YWHAQ, YWHAZ | 117 |
| Inflammatory response | Inflammation of organ | 2.36 × 10⁻⁹ | 0.481 | ACTN4, AHCY, AINHAK, ALDOA, ANXA1, ANXAS, ARHGDIA, ATPI1A1, B2M, BSG, CALR, CAPG, CAZ, CAV1, CD44, CFL1, CNN3, CPNE1, CTBP, CYR61, DDX9, DYSPL2, EEF1A1, ENO1, FKBP1A, FKBP4, FLNA, FUS, GAPDH, GNA12, GSTP1, H3F3A/H3F3B, HARS, HLA-A, HMGBI, HN1, HNRNPH, HSP90B1, HSPA5, ID1, IMPD1H2, KRT1, KRT18, KRT8, LGALS1, MSN, MYH10, MYH9, PAB1, PDI4, PDI2, PDI1, PDI1A3, PDI1M1, PHGDH, PI4KA, PPP2CA, PRDX1, PSM5, PSMD2, SGMN, SOD1, STAT1, TCT, TPI1, TPM3, UBB, UB4B, TUBB6, TUBB8, VCP, VCP, VDAC2, VIM, XRC5, YBX1, ZYX | 74 |
| Embryonic development, organismal survival | Death of embryo | 2.51 × 10⁻⁹ | 0.942 | BSG, CAPN2, CAPNS1, EIF6, FASN, IMPDL2, KIF5B, LRP, MAP2, MAP1B, NAP, NCAM, PCNA, PPIA, PHB2, PRPF19, PSC4, RPS4, SF3B1, TCT, TPM3, VCP | 20 |
| Cell cycle | Cell cycle progression | 2.53 × 10⁻⁹ | −1.218 | BUB3, C1QBP, CALR, CAPN2, CAST, CAV1, CAVT4, CD44, CD59, CDK1, CLTC, CSE1L, CYR61, DBL, DHX9, DYNCH1, EEF6, EZR, FASN, FKBP1A, FLNA, GNB2L1, GPI, H3F3A/HEF3B, HMGBI, HSPA5, HSPB1, ITGB1, KHDRBS1, KPNB1, KRT18, KRT8, LMNA, MAP2, MAPK1, MARCK3, MCM7, MYH10, NAP, NPM1, NUM1A, PA2G4, PCNA, PPIA, PPIA, PPIA, PPP2CA, PRDX1, PRTM5, PTMA, RAN, RBM3, RHOA, RPS24, SEPT9, SFN, SFPQ, SSR1, STAT1, STMN1, TCP1, TEMPO, TNC, TUBB, TUBB4C, TUBB6, VCP, XRC6, YWHAH, YWHAZ | 69 |
### Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|-----------------------------------|---------|--------------------|-----------|---------------------|
| Cell morphology | Morphology of cells | $2.61 \times 10^{-9}$ | | ACTA1, ACTN4, ACTR2, ANXA1, ANXA2, ARF1, ARHGDI1, ARPC2, B2M, BUB3, CALR, CAP1, CAPN1, CAPN2, CAPRIN1, CAP2B, CAST, CAV1, CD44, CD59, CDK1, C1, CLC4, CLTC, CTSB, CTS8, CTSB, CTN, DNAJA1, DNM1L, DPY30, DPYS, EHD1, EIF6, EZR, FASN, FLNA, FLNC, FN1, G3F3A, G3F3B, HADH, HADHA, HEXB, HLA-A, HMGBI, HSP90AA1 | 110 |
| Cancer, respiratory disease | Stage I non-small-cell lung carcinoma | $2.83 \times 10^{-9}$ | | B2M, EF1A1, EF4A1, FN1, MYL12A, PPIA, RPL27, RPL7, RPS11, RPS27A, SERBP1 | 11 |
| Cellular assembly and organization, tissue development | Formation of filaments | $3.49 \times 10^{-9}$ | $-0.462$ | ACTA1, ACTR3, ARF1, ARPC2, CAPN1, CAPZB, CAV1, CD44, CFL1, CTTN, DPYSL2, FKBP4, FN1, GNA12, GPl, HSP9A5, HSP9B1, ITGB1, KRT18, MAP1B, MAPK1, MAPRE1, NPM1, PFN1, RHOA, SERPINH1, SOD1, STN1, TCP1, TNC, TPM2, TUBB, TWF1, TWF2, VIM, ZYX | 36 |
| Infectious disease | Infection by HIV-1 | $4.09 \times 10^{-9}$ | $-1.626$ | ARF1, ATPSB, CCT2, CD44, DDX3X, DHX9, DNAJA2, GANAB, GML, H3F3A, H3F3B, HMGBI, HNRNP4H1, HNRNPJ, HNRNPK, HSP9A5, KPNB1, MAP4, PDIA3, PDIA6, PGM1, PLOD2, PSMA1, PSMA2, PSMA5, PSMA7, PSMC4, PSME2, PTGFS, RAB18, RANBP1, RNH1, RPL10A, RPL12, RPL18, S3F1A1, S3F1B1, SNRPA3, SPTA1, SPTB1, STIP1, TAGL1N2, TWF1, UAPI, UBE2L3, UQCRC1, XP01, YBX1, ZYX | 48 |
| Cancer | Malignant neoplasm of heart, mediastinum and pleura | $4.65 \times 10^{-9}$ | 1.982 | ATIC, B2M, EF1A1, EF4A1, FN1, MYL12A, PPIA, PRDX1, PRKDC, RHOA, RPL27, RPL7, RPS11, RPS27A, TUBB, TUBB4B, XRC5, XRC6, YWHAE | 19 |
| Cancer | Growth of tumor | $5.06 \times 10^{-9}$ | $-0.277$ | ALCY, ACTN4, AHCY, AKR1B1, ANXA1, ANXA2, BSG, CACYBP, CALR, CAPN2, CAV1, CD44, CD59, CTSB, CTTN, CYB61, EEF1A1, EZR, FASN, FLNA, FN1, GAPDH, GNB2L1, HDGF, HMGBI, HSP9A4, HSP9A5, HSP9A8, HSP9D1, HYOU1, ILF3, ITGB1, LAMB1, LDHA, LGALS1, MAPK1, NPM1, PARK7, PKN, PLEC, PPP2CA, RHOA, RPL22, RPS4X, S100A6, SET, SQSTM1, STAT1, STN1, TNC, TXLNA, UCHL1, XRC5, YBX1 | 54 |
| RNA post-transcriptional modification | Splicing of RNA | $5.23 \times 10^{-9}$ | 0.239 |  | 20 |
| Categories                          | Diseases or Functions Annotation              | p-Value    | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------|-----------------------------------------------|------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cell death and survival            | Cell death of connective tissue cells         | 5.91 × 10⁻⁹ | -0.258           | CAPN1, CD4, CDK1, CLIC4, CTSE, CYR61, DDX3X, DNM1L, EEF1A1, EEF2A1, EEF3B, EEF3C, EIF3, EIF6, ENO1, FKBP4, FLNA, FN1, FUS, GLO1, GPI, GSTP1, HINT1, HSPA5, HSPD1, IGF2R, ITGB1, KHDRBS1, KRT18, KRT8, LMNA, MAP4, MAPK1, PARK7, PRKDC, RHOA, RPL10, SERPINE1, STAT1, STKN1, TPI1, UBA1, VCP, VIM, XRC6, YWHAZ | 46                  |
| Cancer, hematological disease      | Blood tumor                                   | 6.43 × 10⁻⁹ | 1.121            | ACTG1, ANXA1, ANXA2, ANXA6, ATIC, B2M, CALR, CAV1, CD44, CDK1, CFL1, CSE11, CYR61, DNM1L, EEF1A1, FASN, FDPS, FKBP1A, FLNA, FN1, FUS, G3BP1, GMPs, GNB2LI, GTP1, HIST1H1C, HLA-A, HMBG1, HSPD1, IMPDH2, IQGAPI, KPN1, KRT1, LDHA, LGALS1, LOC10272594/U2AF1, LONP1, MARS, MYH10, NNM7, NONO, NPM1, PCNA, PDIA5, PICALM, PLOD2, PPI2CA, PRDX1, PRKDC, PSMA2, PSMB1, PSMD2, PSME1, RHOA, RPL3, RPL6, RPS12, RPS24, RPS4X, SF3B1, SHMT2, SNRPD3, SPTB1, STIP1, STKN1, TUBB, TUBB4B, TUBB6, TUBB8, TXLNA, UQRC2, VIM, XO1, XRC5, XRC6, YWHA5, YWHAZ | 78                  |
| Cell-to-cell signaling and interaction | Binding of cells                             | 6.68 × 10⁻⁹ | -0.441           | ANXA2, ANXA5, BSG, C1QBP, CALR, CAV1, CCT2, CCT3, CCT4, CCT5, CTT6A, CTT7, CTT8, CD44, CPAP4, CYR61, DDX3X, FN1, HLA-A, HMBG1, HSPA5, IGF2R, ITGB1, KRT1, MAP4, MSN, MYH9, NCL, PDIA3, PPP2CA, PRMT5, RHOA, RPSA, STIP1, STKN1, TCI1, TFRC, TLN1, TNC, VCL | 40                  |
| Cancer, hematological disease      | Hematologic cancer                            | 7.44 × 10⁻⁹ | 1.121            | ACTG1, ANXA1, ANXA2, ANXA6, ATIC, B2M, CALR, CAV1, CD44, CDK1, CFL1, CSE11, CYR61, DNM1L, EEF1A1, FASN, FDPS, FKBP1A, FLNA, FN1, FUS, G3BP1, GMPs, GNB2LI, GTP1, HIST1H1C, HLA-A, HMBG1, HSPD1, IMPDH2, IQGAPI, KPN1, KRT1, LDHA, LGALS1, LOC10272594/U2AF1, LONP1, MARS, MYH10, NNM7, NONO, NPM1, PCNA, PDIA5, PICALM, PPI2CA, PRDX1, PRKDC, PSMA2, PSMB1, PSMD2, PSME1, RHOA, RPL3, RPL6, RPS12, RPS24, RPS4X, SF3B1, SHMT2, SNRPD3, SPTB1, STIP1, STKN1, TUBB, TUBB4B, TUBB6, TUBB8, TXLNA, UQRC2, VIM, XO1, XRC5, XRC6, YWHA5, YWHAZ | 77                  |
| Cellular assembly and organization | Development of cytoplasm                      | 8.43 × 10⁻⁹ | -0.761           | ACTR3, ANXA1, ARF1, ARPC2, CAPN1, CAPZB, CAV1, CD44, CFL1, CORO1C, CTTN, DNM1L, DYSPL1, EEF2, FKBP4, FLNA, FN1, GDI1, GNA12, GPP1, HSPA5, IP09, ITGB1, MAP1B, MAPK1, MAPRE1, NPM1, PARK7, PFN1, RHOA, RKN1, STGM1, STOM2, TNC, TPM2, TUB8, TWF1, TWF2, ZYX | 38                  |
| Neurological disease               | Amyotrophic lateral sclerosis                 | 9.09 × 10⁻⁹ |                   | ANXA1, ANXA5, CAPN2, CCT2, CYR61, DB1, EEF1A1, EEF4A1, EZR, FASN, FUS, HN1, HNRNPC1, MAPK1, NNM7, PFKP, PFN1, RHOA, RTN4, S100A6, SOD1, TFRC, VCP, VIM | 24                  |
| Cell death and survival            | Cell viability of tumor Cell lines            | 9.74 × 10⁻⁹ | -0.894           | APEX1, ATP5H, B2M, CAPN2, CAV1, CD44, COPB2, DHX9, EEF2, EEF3C, EEF4A1, EGF1G1, FLNA, FN1, GLUD1, GNB2LI, GSTP1, HINT1, HMBG1, HSPA5, IGF2R, ITGB1, F4QB, PARK7, PCNA, PPM1G, PPI2CA, PPI2R1A, PRDX2, PRKDC, PRF9, PSMA1, PSMA4, PSMD4, RAB11A, RHOA, RPL27, RPSA, S100A6, S3A1, SFN, SNRPD1, SOD1, SQSTM1, TCI1, TRIM28, VCP, XO1, YBX1 | 53                  |
Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|---------------------------------|---------|--------------------|-----------|---------------------|
| Hereditary disorder, neurological disease, psychological disorders, skeletal and muscular disorders | Huntington’s disease | 1.18 × 10⁻⁸ | | ACAA1, AHCY, B2M, BAP-1, CAPNS1, CD44, CYC1, DDH3, DNAJ1A1, ENO2, FKBP4, GAPDH, GPI, HADH, HINT1, HNRNPU, HSP90AA1, HSPA5, HSPA6, LAMB1, LDHA, LDHB, MYL12A, NPM1, PCMT1, PCNA, PDE6H, PDLIM1, PN1, PG1, PKM, PLOD2, PPIA, PRDX2, PSME1, RAB11A, RANBP1, RPA1, SDHA, TPI1, TPM3, UCHL1, UQCRCL1, XRC6, YWHAZ | 45 |
| Cellular development, cellular growth and proliferation | Proliferation of breast cancer cell lines | 1.19 × 10⁻⁸ | 0.389 | ANXA2, ARF1, C1QBP, CAV1, CD44, CD59, CDK1, CSE1L, CYR61, EEF1A1, EEF1B2, EIF3C, FN1, GNB2L1, HNRNPK, HSPA5, ILF3, IGFB1, KRT18, LGALS1, MAPK1, PDL1, PFKP, PN1, PPP2R1A, PRDX2, PTMA, SEPT9, SFN, SOD1, TRIM28, UBA1, YBX1, YWHAQ | 35 |
| Carbohydrate metabolism | Glycolysis of cells | 1.30 × 10⁻⁸ | -1.474 | ALDOA, BSG, C1QBP, CAV1, ENO1, ENO2, GAPDH, GPI, LDHA, PFKP, PGAM1, PGK1, PGM1, PKM, TP1 | 15 |
| Cancer, respiratory disease | Metastatic non-small cell lung cancer | 3.13 × 10⁻⁸ | | ATIC, B2M, EEF1A1, EIF4A1, FN1, MYL12A, PPA1, RPL27, RPL7, RPS11, RPS27A | 11 |
| Protein synthesis | Polymerization of protein | 1.44 × 10⁻⁸ | | ACAA1, AHNAK, ALDOC, ANXA2, ANXA5, ANXA6, ARPC2, CAV1, CTNN1, CUTA1, DNM1, EEF1A1, EHD1, ENA1, HSD17B10, IMPDH2, LONP1, NPM1, PFKP, PN1, PRKCSH, RHOA, SEPT2, SEPT7, SEPT9, SHMT2, SQSTM1, STOML2, TRIM28, VCP, YWHAZ | 31 |
| Cell death and survival | Cell death of fibroblast cell lines | 1.61 × 10⁻⁸ | -0.361 | CAPNS1, CDK1, CLIC4, CTB5, CYR61, DDX3X, DNM1L, EEF1A1, EEF2S1, EEF3B, EEF3C, EEF3I, EIF6, ENO1, FKBP4, FN1, FUS, GLO1, G1P, GSTP1, HINT1, HSPA5, HSPD1, ITGB1, KRT18, KRT8, MAPK1, PARK7, RHOA, RPL10, STAT1, STMN1, UBA1, VCP, YWHAZ | 36 |
| Cellular assembly and organization, cellular function and maintenance | Organization of actin cytoskeleton | 2.12 × 10⁻⁸ | -1.937 | ACTR2, ALDOA, ARHDGIA, CALK, CAP1, CFL1, CORO1C, CSRP1, DBN1, DYSPL2, ENA1, EKR, FLNA, FLNB, FLNC, FN1, ITGB1, MSN, MYH10, MYH9, PL5, RAN, RHOA, SEPT2, SPTAN1, TLN1, TMOD3, TWF2 | 28 |
| Cancer | Malignant neoplasm of mediastinum | 2.27 × 10⁻⁸ | 1.982 | ATIC, B2M, EEF1A1, EIF4A1, FN1, MYL12A, PPA1, PRDX1, PRKDC, RHOA, RPL27, RPL7, RPS11, RPS27A, TUBB4B, XRC5, XRC6, YWHAE | 18 |
| Metabolic disease | Amyloidosis | 2.45 × 10⁻⁸ | | ALCY, ATP5A1, B2M, CANX, CAPN1, CAST, CAV1, CDK1, CT5B, DHX9, DNM1L, DYSPL2, EEF1C, EEF2, EIF2B1, EIF5, EIF5S, G3BP1, GAPDH, GNB2L1, HNRNPA1, HNRNPA2B1, HNRNPL1, HSPA5, HSPD1, LGALS1, PCNA, PICALM, PRDX1, PRKDC, PSMB1, PSMB2, RAN, SET, SOD1, STIP1, TAGL2, TUBB, UBXN4, UCHL1, VIM, VPS35, YWHAZ | 43 |
| Nucleic acid metabolism, small molecule biochemistry | Biosynthesis of purine ribonucleotide | 2.57 × 10⁻⁸ | -2.378 | ALDOA, ATP5A1, ATP5B, CAV1, CDK1, DNM1L, HMGB1, HSPD1, NNMT, PKM, PPA1, SLC25A5, SOD1, VCP, VDAC1 | 15 |
| Categories               | Diseases or Functions Annotation | p-Value   | Activation z-Score | Molecules                                                                 | Number of Molecules |
|--------------------------|----------------------------------|-----------|--------------------|---------------------------------------------------------------------------|---------------------|
| Neurological disease     | Neurological signs               | $2.58 \times 10^{-8}$ |                    | ACAA, AHCY, B2M, BASP1, CBP5, CAV1, CD44, CYC1, DD1, DNAJ1, ENO2, FKBP4, GADD1, GPL, HADH, HINT1, HNRNPA2B1, HNRNPU, HSP90AA1, HSP9A5, HSPA5, HSPA8, LAMB1, LDHR, LDHB, MYL12A, NPM1, PCMT1, PCNA, PDE6H, PDLIM1, PFI1, P3K, PLOD2, PPIA, PRDX2, PSME1, RAB11A, RANBP1, RPSA, SDHA, SOD1, TPI1, TPM3, UCHL1, UQCRCL, XRC6, YWHAZ | 48                  |
| Cancer                   | Epithelial cancer                | $3.20 \times 10^{-8}$ | $-0.050$           | AARS, ACAA, AAT, ACY1, ACTG1, ACTN1, ACTN4, ACTR2, AHCY, AKR1B1, ALDOA, ALDOC, ANXA1, ANXA2, ANXA5, APIB1, APEX1, ARF1, ARHGDIA, ARPC2, ATC, ATP6A1, ATP5B, B2M, BASP1, BSG, C14orf166, C1QBP, CACYPB, CAND1, CAX3, CAPG, CAPN2, CAPRIN1, CAST, CAV1, CBX3, CCT2, CCT4, CCT5, CCT6A, CCT7, CD9, CD44, CD59, CDK1, CLIC1, CLTC, COPA, COPB1, COPB2, COPE, COPG1, CORO1C, COTL1, CRIP2, CSE1L, CTNNA1, CTSP1, CTSA, CTSS, CTTN, CUTA, CYC1, CYR61, DBI, DBN1, DD1, DD1B, DD1X, DD3X, DHX9, DLAT, DAI1A1, DAI1A2, DNAJC5, DMI1, DIPSY2, DYNCI1H, DYNCI2H, ECHS1, EEFAB1, EEFAB2, EEFAB3, EFAB2, EFAB3, EFAB4, EFAB5, ENA1, ENO1, ENO2, EPRS, ESPI, ETA, ETR, ETR1, ETR2, ETR3, FAD, FAF1, FLNA, FLNB, FLNC, FN1, FUBP3, FUS, G3BP1, G3BP2, GANAB, GARS, GCN1L1, GD2, GLUD1, GMI, GHAB, GNAS1, GNB2L1, GOL, GSTP1, H2AFY, H3F3A/H3F3B, HADHA, HARS, HDGE, HLD, HNX, HINT1, HIST1H1C, HIST1H2B, HIST2H2Z, HLA-A, HLA-B, HMGB1, HN1, HNRNPA1, HNRNPA2B1, HNRNPA3, HNRNPH1, HNRNPH3, HNRNPK, HNRNP1, HNRNP2, HNRNP4, HNRNP6, HSP90AA1, HSP90AB1, HSP90B1, HSP9A5, HSPA5, HSPA6, HSPA8, HSPD1, HYOU1, IARS, ID1, ILF2, ILF3, IMM, IMPDH2, IPOS, IPOS, IQGAP1, ITG41, KHDRBS1, KHSRP, KIF5B, KNAM2, KPNB, KPNB1, KRT1, KRT18, KRT8, KRT9, LAMB1, LASP1, LDHA, LGALS1, LMNA, LMNB1, LOC10274594/U2AF1, LON1P1, LR2PRC, LRRCC5, MAP1B, MAP4, MAP8, MAPR2, MAR1, MAT3, MCM3, MCM4, MCM6, MDM2, MDH2, MSN, MVP, MYH9,MYIP, MYL12A, NACA, NAP1L3, NAP1L4, NAST, NCL, NMT1, NONO, NPEPPS | 350                  |
| Categories                                           | Diseases or Functions Annotation | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------------------|----------------------------------|------------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cancer                                               | Metastatic carcinoma             | 3.23 × 10⁻⁸      |                   | ATIC, B2M, CSE1L, EEF1A1, EFB1A1, FKBPA1, FN1, HSP90AA1, HSP90AB1, HSP90B1, MYL12A, PPIA, RPL7, RPS11, RPS27A, TUBB, TUBB4B, YWHAE | 19                  |
| Neurological disease                                 | Dyskinesia                       | 3.44 × 10⁻⁸      |                   | ACAT1, AHCY, B2M, BASP1, CAPN5, CAV1, CD44, CYC1, DDX1, DNAA1, ENO2, FKBPA4, GAPDH, GPI, GAPDH, HINT1, HNRNPU, HSP90AA1, HSP90AB1, HSP90B1, HSPA5, HSPA8, LAMB1, LDHA, LDHB, MYL12A, NPM1, PCMT1, PCNA, PDE6H, PDLIM1, PFN1, PKG1, PLOD2, PPIA, PRDX2, PSEME1, RAB11A, RANBP1, RPSA, SDHA, TPI1, TPM3, UCHL1, UQCC1, XRCC6, YWHAZ | 46                  |
| Cellular assembly and organization                   | Formation of cytoskeleton        | 3.46 × 10⁻⁸      | −0.867            | ACTR3, ARF2, CAPN1, CAPZB, CAV1, CD44, CFL1, CORO1C, CTNN, DYSPL2, ERK29, FKBPA4, FNA, FN1, CDH1, GNA12, GPI, ITGB1, MAP1B, MAPK1, MAPRE1, NPM1, PFK1, RHOA, STMN1, TNC, TPM2, TUBB, TUBB2, TWF2, ZYX | 32                  |
| Inflammatory disease                                 | Chronic inflammatory disorder     | 3.62 × 10⁻⁸      |                   | ACLY, ACTA1, ACTN4, ALDOA, ANXA1, ARF1, ATIC, B2M, BSG, CALR, CAPG, CD59, COL1, CTSD, DDX9B, DDX5, EIF1G, EIF2, ENO1, EPO, FKBPA3, FKBPA4, HSP3A, HSP3B, HLA-A, HMC4, HHX2, HNRNPU, HSP90AA1, HSP90B1, HSPA8, HSPD1, IMPDH2, KHSRP, KRT18, LKB1, LDHB, LGAL1, MAPRE1, MYL12A, NONO, P4HB, PCMI, PIDA3, PDLIM1, PKG1, PKM, PRDX1, PRDX2, PRDX5, PSMB1, PSM2, PTA, RHOA, RPS24, RPS3, RPSA, SND1, STAT1, TFCR, TPM2, TRMD2, UCHL1, VARS, VIM | 62                  |
| Cell morphology, connective tissue development and function | Shape change of fibroblast cell lines | 3.74 × 10⁻⁸ | −0.342 | CAST, EHD1, FLNA, FLNC, FN1, GNB2L1, IPO9, ITGB1, MARCKS, PTBP1, RHOA, RT1N4, VCL, VIM | 14                  |
| Cell morphology, cellular assembly and organization, cellular function and maintenance | Formation of lamellipodia | 3.90 × 10⁻⁸ | 0.308 | ACTN4, ACTR3, ARPC2, BSG, C1QBP, CAP1, CAPZB, CD44, CFL1, CYR61, DNM1L, EZR, FN1, HSP90AA1, HP1B1, LSP1, RHOA, TWF2, VCL | 19                  |
| Categories                                                                 | Diseases or Functions Annotation                                                                 | p-Value                          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|----------------------------------|--------------------|--------------------------------------------------------------------------|---------------------|
| Cell cycle, cell morphology, cellular assembly and organization, cellular movement | Elongation of filaments                                                                           | $4.03 \times 10^{-8}$            | $-1.000$           | ACTN4, CAP1, FN1, MAPRE1, PFN1, SEPT7, SEPT9                             | 7                   |
| Cell death and survival                                                  | Neuronal cell death                                                                               | $4.08 \times 10^{-8}$            | 0.202              | AARS, AP2B1, CAPN1, CAPNS1, CAPRIN1, CAST, CDK1, CTSB, DNML1, FKBP1A, FN1, FUS, G6PD, GAPDH, GLUD1, GPI, HMGBl, HSD17B10, HSP90AB1, HSP90AB1, HSP9B1, HSPD1, HYOU1, ITGB1, LDHA, LGAL5, MAP1B, MAPK1, NPM1, P4HB, PARK7, PDA3, PEAI5, PRDX2, RHOA, RPS5, SDHA, SET, SOD1, STAT1, STIP1, TCP1, UCHL1, VAPA, XRC5, XRC6, YWHAH, YWHAZ | 49                  |
| Cell-to-cell signaling and interaction, cellular assembly and organization, tissue development | Quantity of focal adhesions                                                                       | $4.08 \times 10^{-8}$            | 1.463              | CAPNS1, CAV1, FLNA, FLNB, FN1, GNB2L1, ITGB1, MYH9, RHOA, SPTAN1          | 10                  |
| Carbohydrate metabolism                                                  | Glycolysis                                                                                       | $4.46 \times 10^{-8}$            | $-1.946$           | ALDOA, BSG, CIQB, CAV1, DNML1, ENO1, ENO2, GAPDH, GPI, LDHA, FFKP, PGAM1, PKG1, PGM1, PKM, TPI1 | 16                  |
| RNA post-transcriptional modification                                    | Processing of mRNA                                                                               | $4.53 \times 10^{-8}$            | $-0.128$           | CIQB, DDX39B, DDX5, HNRNPA1, HNRNPA2B1, HNRNPH3, HNRNPK, HNRNPM, KHDRBS1, LOC10272494/U2AF1, NPM1, PABPC1, PCBP1, PRPF19, PTBP1, SF3A1, SF3B1, SFQ, SNRNP1, U2AF2 | 20                  |
| Molecular transport                                                      | Transport of molecule                                                                            | $4.60 \times 10^{-8}$            | $-1.226$           | ACAT2, ALYREF, ANXA1, ANXA2, ANXA6, AP1B1, ARFI, ATP1A1, AT5PB, B2M, BSG, CALR, CANX, CAV1, CD44, CFL1, CLIC1, CLIC4, CPNE1, CSE1, CTS5, DDX39B, DDX3X, DNAJ1, DNAJ2, DNML1, DPyS2, EHDI, EIF5A, ERP29, FKBP4, FN1, FUS, GDI2, GNAJ2, HNRNPA2B1, HPSAB, HPSA9, IGF2R, IP05, IP07, ITGB1, KHDRBS1, KIF3B, KPN2, KRT8, LASP1, LGAL5, MAP1B, MYH9, NPM1, P4HB, PDCD6, PDL1, PIA14, PEAI5, PICALM, PLIN3, PPIA, RAB1A, RAB7A, RAN, RHOA, RRB1, RTN4, S100A6, SEC13, SEPT2, SLC25A3, SLC25A5, SLC34A2, SNX3, SOD1, SPTBN1, SQSTM1, STAT1, STOML2, TFCR, TNP1, U2AF2, VAPA, VDAC1, XPO1, YWHAH, YWHAZ, YWHAZ | 89                  |
| Cellular development                                                    | Differentiation of cells                                                                           | $4.66 \times 10^{-8}$            | $-1.742$           | ACly, ACTR3, ALYREF, ANXA1, ANXA2, ANXA6, AT5PB, B2M, BASP1, BSG, CIQB, CACYBP, CALR, CAND1, CAPN1, CAPZB, CAST, CAV1, CBX3, CD44, CDK1, CFL1, CLIC1, CLIC4, CLT, CSBP1, CTSB, CYR61, DBN1, DDX5, DHX9, DNML1, DPyS2, EIF5A, ENO1, EZR, FASN, FLNB, FLNC, FN1, GAPDH, GLO1, GNB2L1, H2AFY, H3F3A/H3F3B, HMGBl, HNRNPA2B1, HNRNPK, HNRNPL, HNRNPu, HSP90AA1, HSP90AB1, HSP90B1, HSP9B1, HSPD1, IARS, IGF2R, ITGB1, KHDRBS1, KRT1, KRT8, LGAL5, LMNA, LMNB1, LONP1, MAP1B, MAPK1, NAP1L1, NNM7, NPEPS5, NPM1, P2X4, PDA3, PDI5, PHGDH, PICALM, PKM, PPIA, PP1CA, PRDX2, PRKDC, PRMT5, PRPF19, RHOA, RNH1, RLP22, RPS11, RPS3, RPS5, RRBP1, RTN4, SFN, SFQ, SNRDI, SOD1, SQSTM1, STAT1, STIN1, SYNCRIP, TAGLN, TAGLN2, TFCR, TNC, TNC2, TPM2, TPM4, VIM, XPO1, XRCC5, XRCC6, YBX1, YBX3, YWHAH, YWHAQ | 115                 |
| Categories                  | Diseases or Functions Annotation                              | p-Value       | Activation z-Score | Molecules                                                                 |
|-----------------------------|---------------------------------------------------------------|---------------|-------------------|--------------------------------------------------------------------------|
| Cancer                      | Neoplasia of epithelial tissue                               | $4.68 \times 10^{-8}$ | 0.453             | AARS, ACAT1, ACAT2, ACLY, ACTG1, ACTN1, ACTN4, ACTR2, ACTR3, AHNAK, AIP, AKR1B1, ALDOA, ALDOC, ANXA1, ANXA2, ANXA5, API1B1, APEX1, ARF1, ARFGD1A, ARPC2, ATIC, ATP5A1, ATP5B, B2M, BASP1, BSG, C14orf166, C1QB, CACYBP, CALR, CAND1, CANX, CAPG, CAPN2, CAPR1N1, CAST, CAV1, CBX3, CCT2, CCT4, CCT5, CCT6A, CCT7, CCT8, CD44, CD59, CDK1, CLC1, CLC4, COP1, COPB1, COPB2, COPE, COPG1, CORO1C, CRT1K, CRIP2, CSE1L, CTNNA1, CTPS1, CT5A, CT5B, CTN, CUTA, CYC1, CYR61, DBI, DBN1, DDX39B, DDX39, DDX5, DDX9, DLT, DNAA1, DNAA2, DNAA5, DNM1L, DPYSL2, DYNCH1, DYNC1I2, ECHS1, EEFLA1, EEFLD1, EEFLD2, EEFLS1, EIF2S2, EIF3A, EIF4A1, EIF4G1, ENAH, ENO1, ENO2, EPRS, ESY1, ETA, EZR, FASN, FDP5, FKBP1A, FLNA, FLNB, FLNC, FN1, FUBP3, FUS, G3BP1, G6PD, GANAB, GARS, GCN1L1, GD2, GLUD1, GML, GMP5, GNA12, GNB2L1, GPR, GSTP1, H2AFY, HSF3A, HSF3B, HADHA, HARS, HDGF, HDLBP, HEXB, HINT1, HIST1H1C, HIST1H2BL, HIST2H2AC, HLA-A, HMG1B, HN1, HNRP1A1, HNRP1A2, HNRP2, HNRP4, HSP90AA1, HSP90AB1, HSP90B1, HSPAP, HSPA6, HSPH1, HSPD1, IAP1, ID1, IFIT3, IGF2R, ILF2, ILF3, IMMT, IMPDH2, IPO5, IPO7, IPO9, IQGAP1, ITGB1, KHDRBS1, KHSRP, KIF5B, KNAP2, KPN3, KPNB1, KRT1, KRT18, KRT8, KRT9, LAB, LAH, LAL, LMNB1, LOC102724994, LONF1, LPPRPC, LRPC9, MAP1B, MAP2, MAPRE1, MARCKS, MARS, MATR3, MCM3, MCM4, MCM6, MDH1, MDH2, MSN, MPVR, MYH10, MYH9, MYL12A, NACA, NAP1L1, NAP1L4, NASS, NCL, NNMT, NONO, NPEPPS, NPLCP4, NPM1, NSF1, NUMA1, OLA1, O4B1, PA2G1, PABPC1, PAAH1B2, PAICS, PAR7, PCB1, PCBP1, PCBP2, PCB1, PCM1, PCNA, PDCD6, PDE4A, PDE5A, PDML1, PDXK, PEA15, FPK, PFG, PFM1, PGAM1, PNG1, PK1, PHGDH, PICL, PKM, PLEC, PLOD2, PP1, PPM1G, PPPICA, PPPI2CA, PRD1X, PRDX1, PRDX2, PRKCSH, PRKDC, PRMT5, PPRP19, PSM1A, PSCM1, PSCM4, PSM2D, PTP1B, PTP, PTPF, PYGB, PYGL, QARS, RANBP1, RARS, RHOS, RLO10, RLO12, RLO21, RLO22, RLO27, RPL4, RPL5, RPL7, RPL7A, RPL8, RPLP0, RPN1, RPN2, RPS11, RPS12, RPS2, RPS24, RPS27A, RPS7, RRBP1, RNT4, S100A6, SDHA, SEPT9, SERBP1, SERBP2, SF3A1, SF3B1, SF5, SFPO, SFGFR1, SLCA2, SLCA5, SLCA8, SNCL, SOD1, SODI, SPTAN1, SPTB2, SSRP1, STAT1, STIP1, STMN1, SYNSCRIPT, TAP1, TDL, TAR5, TCP1, TFCR, TLN1, TMPO, TNFRAS, TNPO1, TPI1, TPM4, TUBB, TUBB4B, TUBB6, TUBB8, TWRF, TXNDC5, UAP1, UBA1, UBE2N, UBKX4, UCHL1, VARS, VCL, VCP, VIM, VPS53, WARS, WDR1, XPO1, XRCC5, XRCC6, YBX1, YBX3, YHAB, YHWA3, YHWA4, YHWA5, YHWA6, YHWA7, YHWA8, ZYX | 355 |
| Categories                                                                 | Diseases or Functions Annotation | p-Value       | Activation z-Score | Molecules                                                                                           | Number of Molecules |
|---------------------------------------------------------------------------|----------------------------------|---------------|-------------------|----------------------------------------------------------------------------------------------------|---------------------|
| Hereditary disorder, skeletal and muscular disorders                      | Autosomal recessive myopathy     | 4.96 x 10⁻⁸   |                   | AHNAK, CALR, CANX, FN1, HINT1, HSP90B1, HSPA5, ITGB1, LMNA, Plec, PSM2, PSM4, SQSTM1, VCP             | 14                  |
| Infectious disease                                                        | Infection of tumor cell lines    | 5.02 x 10⁻⁸   | -1.728            | ACTR2, AP1B1, AP2B1, ARF1, ARPC2, ATP5B, CCT2, CLTC, COPA, COPB1, COPB2, COPG1, DXDXX, DNAJ2A, EEF3I, G3BP1, GML, H3F3A/H3F3B, HMGBI1, HNRNPK, HNRNPu, HSPA9, IFITM3, IGF2R, MAP4, PDA3, PA6, PICA1M, PSM2, RAB1B, RANBP1, SPTAN1, SPTB1A, STAT1, STIP1, TFRC, TF21, UAPI, UQCCRC1, XPO1 | 40                  |
| Cancer                                                                    | Abdominal neoplasm              | 5.10 x 10⁻⁸   | -1.025            | AARS, ACAT1, ACAT2, ACY, ACTG1, ACTN1, ACTN4, ACTR2, ACTR3, AHCY, AHNAK, AKR1B1, ALDOA, AYREF, ANX1, ANXA2, ANXA5, AP1B1, APEX1, ARF1, ARHDIGIA, ARPC2, ATIC, ATP5A1, ATP5B, B2M, BAP3, BG1, C1orf66, CACYBP, CALR, CAND1, CANX, CAP1, CAPG, CAIP2, CAST, CAV1, CBX3, CCT2, CTT, CCT5, CTTA, CD44, CD59, CDK1, CLIC1, CLTC, COPA, COPB1, COPB2, COPE, COPG1, COROIC, COT1, CRIE2, CSE1L, CTNNA1, CTPS1, CTSA, CTSS, CTTN, CUTA, CYC1, CYR61, DBI, DBN1, DXD1, DXD9B, DXD1X, DXD5, DXD6, DXH9, DLAT, DNAJ1A, DNAJ2A, DNAJ2C, DNM1L, DPYS1L | 350                  |
|                                                                          |                                  |               |                   | DYNCH1, DYNCH2, EC8S1, EE1F2A1, EE1B2, EE1F2D, EE2F1, EE2F1B, EE2F15, EE2F1A, EE2F1A, ENAH, ENOA, ENOC, EPS1, EPS1F, ESY1, EAS1, FDPS, FKBPA1, FLNA, FLNB, FLNC, FN1, FUPB3, FUS, G3BP1, G6PD, GANAB, GADPH1, GARS, GCN2L1, GDE2, GLUD1, GML, GMP5, GNA2A, GN2B2, GPR1, GSR1, H2AFY, H3F3A/H3F3B, HADHA, HARS, HDCG, HDLBP, HEXB, HINT1, HIST1H1C, HIST1H2B1, HIST2H1C, HIST2H2AC, HLA-A, HLA-B, HMBG1, HNI1, HNRNP1A, HNRNP2A1, HNRNP3A, HNRNP3H1, HNRNP3H, HNRNP4, HNRNP4, HNRNP5, HNRNP7, HSPD17B10, HSP90AA1, HSP90AB1, HSP90B1, HSP9A5, HSP9A8, HSPA9, HSPB1, HIV1, IDS1, IFT53, IGF2R, IF2L, IF2F, IFMT1, IMPT4H2, IP30, IP07, IP09, IQC1A, IFTG1, KHDRBS1, KHSRP, KIP2B, KPI2A, KPR1, KRT1, KRT1B, KRT18, KRT6, LAMB1, LAMA1, LAMA2, LAMA3, LMNA, LMNB1, LOC102724594/LOC2, LONP1, LRP4C, LRRCS9, MAP1B, MAP3, MAPR1, MARS, MATR3, MCM3, MCM4, MCM6, MCM7, MDM2, MDH2, MSN, MVP, MYH10, MYH9, NACA, NAPL1, NAPL4, NAPL, NCL, NNMT, NONO, NPEPS1, NPLC4, NPM1, NSFL1C, NUMA1, OLAL, PA4B1, PA2G, PABPC1, PAES, PCB1P1, PCBP2, PCM1, PCNA, PDI3, PIA4D, PIULM1, PDXK, PEAK1, PFKP, PEN1, PCAM1, PGD, PGK1, PGM1, PHGDH, PICALM, PKM, PLEC, PLIN3, PLOD2, PL9, PPM1G, PPR1CA, PPR2CA, PRDX1, PRDX2, PRKCSH, PRKDC, PSMA1, PSMA7, PSMC1, PSMC4, PSM2, PTB1P1, PTM, PTH1, PUN60, PYBG, PYG1, QARS, RAN, RANBP1, RAM, RBM3, RHOA, RPL12, RPL22, RPL27, RPL4, RPL5, RPL6, RPL7A, RPL8, RPL9, RNP1, RNP2, RPS11, RPS25, RPS26, RPS4X, RPS7, RBP1, RTN4, S100A6, SDHA, SEPT9, SERBP1, SFINH1, SET, SFB1, SFB2, SFPQ, SHBDBCL1, SHMT2, SLC25A3, SLC25A5, SLC33A2, SN1DI, SOD1, SPTAN1, ST5, SQSTM1, SRRP1, STAT1, STIP1, STIM1, SYNCRIP, TALGN, TALDO1, TARS, TCF1, TFRC, TNL1, TNP01, TP11, TPM2, TM3, TP4, TUBB, TUBB4B, TUBB8, TWLI, TWL2, TXNDC5, UAPI, UBA1, UBE2N, UBXN4, UCHL1, YARS, VCI, VCP, VM, VPS35, WARS, XPO1, XRC4C, XRC5, YBX1, YB2, YHWHAE, YWHAG, YWHAH1, YWHAQ, YWHAZ, ZYX |
Table 5. Cont.

| Categories | Diseases or Functions Annotation | $p$-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|----------|-------------------|-----------|---------------------|
| RNA post-transcriptional modification | Splicing of mRNA | $5.56 \times 10^{-8}$ | 0.239 | C1QB, DDX39B, DDX5, HNRNPA2B1, HNRNPH3, HNRNPK, HNRNPM, NPM1, PRPF19, PTBP1, SF3A1, SF3B1, SFQ, SNRPD1, U2AF2 | 15 |
| Cell morphology | Shape of cells | $7.25 \times 10^{-8}$ | | ACTN4, CAPN1, FLNA, GIP, IGF2R, ITGB1, MYH10, RHOA, TPM3 | 9 |
| Cell morphology, cellular assembly and organization, cellular development, cellular function and maintenance | Formation of plasma membrane projections | $7.91 \times 10^{-8}$ | $-0.331$ | ACTN3, BASP1, CAPN1, CAPRIN1, CAPZB, CAV1, CD44, CSR1, CYR61, DBN1, DNM1L, DYSLS2, EHD1, EZR, GDI1, HMG1, HNRNPK, ITGB1, KIF5B, LAMB1, MAP1B, MSN, MYH10, NNMT, PDI3, PP1, PHGDH, PICALM,PPP2CA, PRKCSH, RAB11A, RHOA, RTN4, SEPT2, SOD1, SPTBN1, STIP1, STN1, TNC, UCHL1, VAPA, VIM, YWHAH | 43 |
| Cell cycle, cellular movement | Cytokinesis | $8.89 \times 10^{-8}$ | $-0.943$ | ACTN4, CAP1, CFL1, FN1, GNAI2, ITGB1, LMNA, MAPRE1, MSN, MYH10, MYH9, NPM1, PP1, RAB11A, RHOA, SEPT2, SEPT7, SEPT9, SSRP1, YBX1 | 20 |
| Cellular movement | Cell movement of breast cancer cell lines | $1.01 \times 10^{-7}$ | 0.407 | ANXA1, ANXA2, ARF1, ARPC1B, CAPN2, CAV1, CSE1L, CTNN, ENAH, FLNA, FN1, GNR2L1, GIP, ILF3, ITGB1, KHDRBS1, KPNA2, KRT8, LPS1, MAP1K1, MYH9, RHOA, SEPT9, SFN, VIM | 25 |
| Post-translational modification, protein folding | Refolding of protein | $1.08 \times 10^{-7}$ | | B2M, DNAJ1A, DNAJ2A, FKBPLA, HSP90AA1, HSPA8, HSPD1 | 7 |
| Cell death and survival | Cell viability of myeloma cell lines | $1.08 \times 10^{-7}$ | $-0.376$ | COP2, EIF3C, EIF4A1, EIF4G1, HSP90B1, PSMA1, PSMA4, PSMC4, RAB11A, RPL27, SF3A1, SOD1, XPO1 | 13 |
| Cell morphology, cellular assembly and organization, cellular development, cellular function and maintenance, nervous system development and function, tissue development | Neuritogenesis | $1.09 \times 10^{-7}$ | $-0.401$ | ACTN3, BASP1, CAPRIN1, CAPRIN2, CAPZB, CAV1, CD44, CSR1, CYR61, DBN1, DNM1L, DYSLS2, EHD1, EZR, GDI1, HMG1, HNRNPK, ITGB1, LAMB1, MAP1B, MSN, MYH10, NNMT, PDI3, PP1, PHGDH, PICALM,PPP2CA, PRKCSH, RAB11A, RHOA, RTN4, SEPT2, SOD1, SPTBN1, STIP1, STN1, TNC, UCHL1, VAPA, VIM, YWHAH | 42 |
| Free radical scavenging | Synthesis of reactive oxygen species | $1.15 \times 10^{-7}$ | $-0.019$ | AKR1B1, ANXA1, ARHGDIA, CA1, CD44, CLIC1, CTNN, CYR61, DNM1L, FN1, G6PD, GNB2L1, GSTP1, HMG1, HNRNPK, HSDB1B10, HSP90AB1, HSPA9, HSPB1, IMMT, IQGAP1, ITGB1, LDHA, LONP1, MAPK1, PARK7, PPIA, PRDX1, PRDX2, RHOA, S100A6, SOD1, SQSTM1, TALGN, TFRC, VDAC1, YWHAZ | 37 |
| Free radical scavenging | Metabolism of reactive oxygen species | $1.17 \times 10^{-7}$ | $-0.644$ | AKR1B1, ANXA1, ARHGDIA, CA1, CD44, CLIC1, CTNN, CYR61, DNM1L, FN1, G6PD, GNB2L1, GSTP1, HMG1, HNRNPK, HSDB1B10, HSP90AB1, HSPA9, HSPB1, IMMT, IQGAP1, ITGB1, LDHA, LONP1, MAPK1, PARK7, PPIA, PRDX1, PRDX2, RHOA, S100A6, SOD1, SQSTM1, TALGN, TFRC, VDAC1, YWHAZ | 38 |
### Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|---------|--------------------|-----------|---------------------|
| Cancer     | Breast or colorectal cancer      | 1.22 × 10⁻⁷ | 0.555              | AARS, ACAT1, ACAT2, ACLY, ACTN1, AHHCY, AHNAK, AKR1B1, ALDOA, ALDOC, ANXA1, ANXA2, ARHGDA1, ATIC, ATP5A1, B2M, BSG, C1QB, CACYBP, CAPG, CAPN2, CAV1, CBX3, CCT3, CTT4, CTT5, CD44, CDK1, COPA, COPB2, CSE1L, CTSB, CYC1, CYR61, DBI, DBN1, DDX1, DDX3X, DDX5, DLAT, DNAJ1, DNAJC8, DYSPL, DYNCH1, DYNCI12, ECHS1, EEF1A1, EEF1D, EEF2, EIF5B, EIF5C, EIF4A1, EIF4G1, ENA4, ENS1, ESYT1, ETOA, FASN, FDP5, FKBP1A, FLNA, FLNB, FLNC, FN1, FUBP3, FUS, G3BP1, G6PD, GARS, GCN1L1, GLO1, GML, GMPS, GNA2, GSTP1, H2AFY, HIF3A/HIF3B, HIDE, HIST1H1C, HLA-A, HLA-B, HNRNPA1, HNRNPA3, HNRNPH3, HNRNPL, HNRNPM, HNRNPU, HSP90AA1, HSP90AB1, HSP90BI1, HSPA5, HSPA9, HSPD1, IDI1, IFITM3, IGF2R, IFL2, IFL3, IMMT, IPO7, IQGAP1, ITGB1, KHSRP, KIF5B, KPN2, KPN3, KRT1, KRT18, KRT8, KRT19, LAMB1, LASP1, LDHA, LGALS1, LMNA, LMNB1, LONP1, LRPPRC, MAP1B, MAPRE1, MARS, MATR3, MCM3, MCM4, MCM6, MDH1, MDH2, MIP, MYH10, MYH9, NACA, NAPL1, NAPL4, NCL, NMT, NPEPS1, OLA1, PAFH1, PAICS, PCBP1, PCNA, PDCD6, PFKP, PFN1, PGAM1, PGD, PGK1, PGM1, PKM, PLEC, PLIN3, PLOD2, PL5S, PPP1CA, PPP2CA, PPP2R1A, PRDX1, PRDX5, PCKS5H, PKD2, PMA7, PTP1B, PTPA, PTEN, PYGB, RANBP1, RARS, RHOA, RPL4, RPL5, RPL6, RPL9, RPN2, RPS24, RPS3, RTN4, S100A6, SEPT9, SERT, SERT, SHMT2, SLC25A5, SLC25A6, SOD1, SPTAN1, SRRP1, STAT1, STIP1, SYNCRIP, TALG, TALN, TARS, TCA1, TFCR, TLRN1, TMPO, TNC, TNP1, TPI1, TPI4, TUBA1B, TUBB, TUBB4B, TUBB6, TUBB8, UBA1, VCL, VDAC2, VIM, VPS35, WDR1, XPO1, XRCC6, YBX1, YWHAH, YWHAQ, YWHAZ, YZK |
|            | Endocytosis                       |         |                    | ACTN4, ANXA5, ANXA6, ATP5B, CANX, CAP1, CAV1, CD44, CLTC, CORO1C, CTTN, DYSPL2, EHD1, EZR, GNB2L1, HNRNPK, HSPA5, HSPA9, HYOU1, IGF2R, IQGAP1, ITGB1, MAP1B, NCL, PICALM, RAB7A, RHOA, SFPQ, TLN1 |
|            | Neurological disease, psychological disorders | 1.30 × 10⁻⁷ | −0.427              | ACTN4, ANXA5, ANXA6, ATP5B, CANX, CAP1, CAV1, CD44, CLTC, CORO1C, CTTN, DYSPL2, EHD1, EZR, GNB2L1, HNRNPK, HSPA5, HSPA9, HYOU1, IGF2R, IQGAP1, ITGB1, MAP1B, NCL, PICALM, RAB7A, RHOA, SFPQ, TLN1 |
|            | Dementia                          |         |                    | ACTN4, ANXA5, ANXA6, ATP5B, CANX, CAP1, CAV1, CD44, CLTC, CORO1C, CTTN, DYSPL2, EHD1, EZR, GNB2L1, HNRNPK, HSPA5, HSPA9, HYOU1, IGF2R, IQGAP1, ITGB1, MAP1B, NCL, PICALM, RAB7A, RHOA, SFPQ, TLN1 |
| Cancer, respiratory disease | Diverse non-squamous non-small cell lung cancer | 1.39 × 10⁻⁷ |                     | AHNAK, ALDOA, ATIC, CAPR1N1, CAV1, CD44, CDK1, DHX9, DENN1, DYSPL2, EEF1G, EEF2, EIF5B, EIF5S, EIF8, G3BP1, G6BP1, HNRNPA1, HNRNPA2B1, HNRNPU, HSP90AB1, HSP90BI1, IGF2R, ITGA6, ITGB1, KIF5B, KPN1, LAMP1, LAMB1, LAMP2, LAMB3, LCP1, LNK, LRPPRC, MAP1B, MAPRE1, MARS, MATR3, MCM3, MCM4, MCM6, MDH1, MDH2, MIP, MYH10, MYH9, NACA, NAPL1, NAPL4, NCL, NMT, NPEPS1, OLA1, PAFH1, PAICS, PCBP1, PCNA, PDCD6, PFKP, PFN1, PGAM1, PGD, PGK1, PGM1, PKM, PLEC, PLIN3, PLOD2, PL5S, PPP1CA, PPP2CA, PPP2R1A, PRDX1, PRDX5, PCKS5H, PKD2, PMA7, PTP1B, PTPA, PTEN, PYGB, RANBP1, RARS, RHOA, RPL4, RPL5, RPL6, RPL9, RPN2, RPS24, RPS3, RTN4, S100A6, SEPT9, SERT, SERT, SHMT2, SLC25A5, SLC25A6, SOD1, SPTAN1, SRRP1, STAT1, STIP1, SYNCRIP, TALG, TALN, TARS, TCA1, TFCR, TLRN1, TMPO, TNC, TNP1, TPI1, TPI4, TUBA1B, TUBB, TUBB4B, TUBB6, TUBB8, UBA1, VCL, VDAC2, VIM, VPS35, WDR1, XPO1, XRCC6, YBX1, YWHAH, YWHAQ, YWHAZ, YZK |
| Skeletal and muscular disorders | Caveolinopathy | 1.42 × 10⁻⁷ |                     | ACTN4, ANXA5, ANXA6, ATP5B, CANX, CAP1, CAV1, CD44, CLTC, CORO1C, CTTN, DYSPL2, EHD1, EZR, GNB2L1, HNRNPK, HSPA5, HSPA9, HYOU1, IGF2R, IQGAP1, ITGB1, MAP1B, NCL, PICALM, RAB7A, RHOA, SFPQ, TLN1 |
Table 5. Cont.

| Categories | Diseases or Functions | Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------|------------|---------|-------------------|-----------|-------------------|
| Cellular movement | Invasion of tumor cell lines | | 1.49 \times 10^{-7} | -0.733 | ACAT1, ANXA1, APEX1, ARHCGIA, BSG, CALR, CAP1, CAPNS1, CAV1, CD44, CSE1L, CTSB, CTTN, ENAH, EZR, FNI, GN2B1L1, GPI, HDGE, HMGBl, HSP90AA1, ILF3, IQGAP1, ITGB1, KRT8, LGALS1, MAPK1, MARCKS, PA2G4, PEBP1, PKM, PTGES3, RHOA, RPSA, SI00A6, SEPT9, SQSTM1, STMN1, TAGLN, TAGLN2, VCP, Vim, YWHAQ | 43 |
| Cellular movement | Cell movement of connective tissue cells | | 1.54 \times 10^{-7} | -0.391 | CAPN1, CAPN2, CAPNS1, CAV1, CD44, CYR61, EHD1, ENAH, EZR, FLNB, FNI, GN2B1L1, HMGBl, IGF2R, ITGB1, LGALS1, MAPK1, MYH10, PLEC, STMN1, VCL, ZYX | 22 |
| Cancer | Follicular adenoma | | 1.67 \times 10^{-7} | | ANXA5, CALR, CTSB, GSTP1, HSP90AB1, PARK7, PRDX2 | 7 |
| Neurological disease, psychological disorders | Tauopathy | | 1.70 \times 10^{-7} | | ACYL, ATP5A1, CANX, CAPN1, CAV1, CDK1, CTBS, DHX9, DNML1, DYSPL2, EEF1G, EEF2, EEF2S1, EPRS, FDS, G3BP1, GAPDH, GN2B1L1, HNRNPA1, HNRNPA2B1, HNRNPU, HSP5, HSPD1, LGALS1, PARK7, PCNA, PICALM, PRDX1, PRKDC, RAN, SET, SOD1, STIP1, TAGLN, TUBB, TUBB4B, UBA4A, UCHL1, Vim, VPS35, YWHAZ | 41 |
| Cancer | Metastatic malignant solid tumor | | 1.70 \times 10^{-7} | | ATIC, B2M, CAV1, CSE1L, EEF1A1, EEF1A2, FBN1, FKBP1A, FNI, HSP90AA1, HSP90AB1, HSP90BI1, MYL12A, PPA1, RPL27, RPS11, RPS27A, TUBB, TUBB4B, YWHAE, YWHAZ | 21 |
| Cell death and survival | Cell death of central nervous system cells | | 1.85 \times 10^{-7} | 0.374 | CAPN1, CAPNS1, CAST, CDK1, DNML1, FUS, GAPDH, HMGBl, HSP90AA1, HSP90AB1, HSPB1, HSPD1, HYOU1, MAP1B, MAPK1, NPM1, P4HB, PARK7, PEA15, RHOA, RPS3, SOD3, STIP1, TCP1, VAPA, YWHA8 | 26 |
| Molecular transport, protein trafficking | Import of protein | | 2.01 \times 10^{-7} | 0.816 | CFL1, DNAJAI, DNAJ2A, IPOS, IPO7, IPO9, KPNA2, KPNB1, PDL1, RAN, SPTBN1, XPO1 | 12 |
| Nucleic acid metabolism, small molecule biochemistry | Synthesis of purine nucleotide | | 2.04 \times 10^{-7} | -2.561 | ALDOA, ATP5A1, ATP5B, CAV1, CDK1, DNML1, FASN, G6PD, GMPS, HMGBl, HSPD1, IMPDH2, NNMT, PKM, PPA1, SL23A5, SOD1, VCP, VDAC1 | 19 |
| Cancer, organisational injury and abnormalities | Lymphatic neoplasia | | 2.22 \times 10^{-7} | 0.882 | ACTG1, ANXA1, ATIC, B2M, CALR, CD44, CFL1, CSE1L, CYR61, DNML1, EEF1A1, FKBP1A, FUS, GMPS, GN2B1L1, GSTP1, HIST1H1C, HMGBl, HSP90AA1, HSP90AB1, HSP90BI1, HSPD1, IMPDH2, IQGAP1, ITGB1, KHDRBS1, KRT1, LDHA, LGALS1, LOC110224594/U2AF1, LONP1, MARS, MYH10, NNMT, NPM1, PICALM, PLOD2, PRDX1, PRKDC, PSMB1, PSMD2, PSME1, RHOA, RPL10, RPL3, RPL6, RPS12, RPS2, RPS24, RPS4X, SF3B1, SHMT2, SNRPD3, SPTBN1, STMN1, TUBB, TUBB4B, TUBB6, TUBB8, TXLNA, UQCRCl1, XPO1, XRCC5, XRC6, YWHAZ | 66 |
| Energy production, nucleic acid metabolism, small molecule biochemistry | Synthesis of ATP | | 2.47 \times 10^{-7} | -2.160 | ALDOA, ATP5B, CAV1, CDK1, DNML1, HMGBl, HSPD1, NNMT, PKM, SL23A5, SOD1, VCP, VDAC1 | 13 |
| Categories                                                                 | Diseases or Functions Annotation                                                                 | p-Value         | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------|-------------------|---------------------------------------------------------------------------|--------------------|
| Cell morphology, cellular assembly and organization, cellular development, cellular function and maintenance, nervous system development and function, tissue development | Morphogenesis of neurites                                                                         | 2.71 × 10⁻⁷    | -0.815            | ACTR3, CAPNS1, CAPRIN1, CAPZB, CAV1, CD44, CSRP1, CYR61, DBN1, DNM1L, DPYSL2, EHD1, EZR, HMBG1, HNRNPK, ITGB1, LAMB1, MAP1B, MYH10, NNMT, PDA3, PFN1, PHGDH, PICALM, RAB11A, RHOA, RTN4, SEPT2, SOD1, TNC, VAPA, YWHAH | 32                 |
| Cell death and survival                                                   | Apoptosis of neurons                                                                               | 2.84 × 10⁻⁷    | 1.726             | AARS, CAPN1, CAPRIN1, CAST, CDK1, CTSB, DNM1L, FN1, G6PD, GAPDH, GLUD1, GPI, HSD17B10, HSP90AB1, HSPA5, HSPB1, HSPD1, HYOU1, LGALS1, MAP1B, MAPK1, NPM1, P4HB, PARK7, PEAI5, PRDX2, RHOA, RPS3, SET, SOD1, STAT1, XRCC5, XRC5, YWHAH | 34                 |
| Nucleic acid metabolism, small molecule biochemistry                     | Biosynthesis of nucleoside triphosphate                                                              | 2.93 × 10⁻⁷    | -2.160            | ALDOA, ATP5B, CAV1, CDK1, CTPS1, DNM1L, HMBG1, HSPD1, NNMT, PKM, SLC25A5, SOD1, VCP, VDAC1 | 14                 |
| Cellular development, skeletal and muscular system development and function, tissue development | Differentiation of osteoblasts                                                                     | 3.01 × 10⁻⁷    | -1.093            | ALYREF, ATP5B, CAPNS1, CLC1, CLTC, CYR61, DDX5, DHX9, FASN, FN1, GNB2L1, HSPA5, HSPB1, IARS, MAPK1, RPS11, RPS15, RRPB1, SOD1, STAT1, STM1, SYNCRIP, TNC, TPM4, VIM | 25                 |
| Cell-to-cell signaling and interaction, cellular movement, hematological system development and function, immune cell trafficking, tissue development | Detachment of granulocytes                                                                         | 3.22 × 10⁻⁷    | 0.254             | ANXA1, ANXA5, ITGB1, RHOA                                                | 4                  |
| Cellular movement, connective tissue development and function             | Cell movement of fibroblasts                                                                        | 3.30 × 10⁻⁷    | -0.142            | CAPN2, CAPNS1, CAV1, CD44, CYR61, EHD1, ENAH, EZR, FLNB, FN1, HMBG1, IGF2R, ITG1B, MAPK1, MYH10, PLEC, STM11, VCL, ZYX | 19                 |
| Cancer, organismal injury and abnormalities                               | Lymphoid cancer                                                                                   | 3.34 × 10⁻⁷    | 0.818             | ACTG1, ANXA1, ATIC, B2M, CALR, CD44, CFL1, CSE1L, CYR61, DNM1L, EEF1A1, FBSP1A, FN1, FUS, GMP5, GNB2L1, GTP1, HIST1H1C, HMBG1, HSP90AA1, HSP90AB1, HSP90B1, HSPD1, IMPDH2, IQGAP1, ITG1B, KHDRBS1, KRT1, LDHA, LGALS1, LOC10272594/12A1F1, LONP1, MARS, MYH10, NNMT, NPM1, PICALM, PRDX1, PRKDC, PSMB1, PSMD2, PSME1, RHOA, RPL3, RPL6, RPS12, RPS2, RPS24, RPS4X, SF3B1, SMIT2, SNRPD3, SPTBN1, STM11, TUBB, TUBB4B, TUBB6, TUBB8, TXLNA, UQCR1C, XP01, XRCC5, XRC6, YWHAZ | 64                 |
| Metabolic disease, neurological disease, psychological disorders          | Alzheimer’s disease                                                                               | 3.37 × 10⁻⁷    |                   | ACLY, ATP5A1, CANX, CAPN1, CAV1, CDK1, CTSB, DHX9, DNM1L, DPYSL2, EEF1G, EEF2, EIF2S1, EPRS, FDS5, G3BP1, GAPDH, GNB2L1, HNRNP1A1, HNRNP2B1, HNRNP4, HSPA5, HSPD1, LGALS1, PCNA, PICALM, PRDX1, PRKDC, RAN, SET, SOD1, STI1, TAGLN, TUBB, UBNA4, UCHL1, VIM, VPS35, YWHAZ | 39                 |
| Categories                               | Diseases or Functions | Annotation                     | p-Value   | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------|-----------------------|--------------------------------|-----------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cancer, tumor morphology                 | Invasion of tumor     |                                | 3.40 × 10^{-7} | -1.402            | AHCY, ANXA2, BSG, CAPN2, CAV1, CD44, CTSB, CTTN, EZR, FASN, FKBP1A, FLNA, FN1, HDLBP, HMGBl, HNRNPA1, HSPAS, ITGB1, LGALS1, MAPK1, PARK7, ROHA, VIM | 23                  |
| Hereditary disorder, neurological disease| Autosomal dominant neuropathy |                                | 4.17 × 10^{-7} |                   | AARS, DYN1C1H1, FUS, GARS, HSPB1, HSPD1, RAB7A, SOD1, UCHL1               | 9                   |
| Gene expression                          | Binding of DNA        |                                | 4.32 × 10^{-7} | -1.045            | ALYREF, APEX1, CALR, CAV1, CDK1, CFI1, FN1, GADD46, GNBP2L1, GSTP1, H3F3A/H3F3B, HMGBl, LGALS1, LMNA, MAPK1, NCL, NPM1, PCNA, PPIA, PRDX1, PRDX4, PRKDC, ROHA, SET, SFQP, SNDA1, SOD1, STAT1, TAGLN, TRIM28, UBE2N, XRC3, YBX1, YBX3, YWHA, YWHAEG, YWHAZ | 38                  |
| Cell-to-cell signaling and interaction, tissue development | Adhesion of connective tissue cells |                                | 5.10 × 10^{-7} | -1.487            | ANXA2, CALR, CD44, CYR61, FN1, IGF2R, IPO9, IQGAP1, ITGB1, MAPK1, PLEC, ROHA, RPL22, TLN1, TNC, VCL, ZYX | 17                  |
| Cellular movement                        | Cell movement of fibroblastoma cell lines |                                | 5.20 × 10^{-7} | -1.621            | ARPC2, CTTN, FLNA, FLNB, FLNC, FN1, GIP1, HNRNPK, TPM3 | 9                   |
| Lipid metabolism, small molecule biochemistry | Binding of lipid     |                                | 5.48 × 10^{-7} | 0.823             | ANXA2, DNAJA1, FKBP4, FN1, HMGBl, HSP90AB1, MAP4, PTGES3, RPSA, SFN, STIP1, STMN1 | 12                  |
| DNA replication, recombination, and repair| Double-stranded DNA break repair |                                | 5.75 × 10^{-7} | 0.116             | CDK1, DX1, FUS, KPNA2, NPM1, OTUB1, PCNA, PRKDC, PRPF19, TRIM28, UBE2N, VCP, XRC5, XRC6 | 14                  |
| Cell signaling, DNA replication, recombination, and repair, nucleic acid metabolism, small molecule biochemistry | Hydrolysis of GTP |                                | 5.79 × 10^{-7} | -1.580            | CALR, CDK1, DNM1L, GNAI2, IPO5, RAB7A, RAN, RANBP1, ROHA, STMM1, XPO1 | 11                  |
| Cell death and survival                  | Cell death of breast cancer Cell lines |                                | 6.10 × 10^{-7} | -0.856            | ARHGDA1, B2M, CAV1, CD44, CDK1, CSE1L, CYR61, FASN, FN1, HINT1, HSPA5, HSPB1, HSPD1, KPN2A, KRT18, MAPK1, PEA15, PEBP1, PRKDC, ROHA, SLC25A6, SNDA1, SSRP1, STAT1, STMM1, TFC, VCP | 27                  |
| Connective tissue disorders, skeletal and muscular disorders | Arthropathy |                                | 7.25 × 10^{-7} | -0.277            | ACLY, ACTA1, ALDOA, ANXA1, ARF1, ATIC, B2M, CALR, CAPN2, CD44, CD59, CTSB, DDx39B, EEG1F, EEG2, ENU1, FAS, FDP5, FKBP1A, FN1, GNAI2, GIP, H3F3A/H3F3B, HLA-A, HLA-B, HMGBl, HNRNPA1, HNRNPA3, HSP90B1, HSP90A1, HSP90B1, HSP9A1, HSP9B1, KHSRP, LDHB, LGALS1, MAPRE1, MYL12A, NONO, PCMI1, PDI1A3, PGK1, PHB2, PRDX1, PRDX2, PRDX5, PTMA, RPS24, RPS3, RPSA, SNDA1, STAT1, TFC, TMP2, TRIM28, TUBB, TUBB4B, UBA1, VARS, VIM | 59                  |
| Cancer, gastrointestinal disease, hepatic system disease | Cholangiocarcinoma |                                | 7.33 × 10^{-7} |                   | ANXA1, ANXA2, GNB2L1, HSP90AA1, HSP90AB1, PGK1, PKM, RPL4, RPLP0, VIM | 10                  |
| Categories                                                                 | Diseases or Functions Annotation | $p$-Value  | Activation z-Score | Molecules                                                                 | Number of Molecules |
|----------------------------------------------------------------------------|----------------------------------|------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Endocrine system disorders, gastrointestinal disease, immunological disease, inflammatory disease | Autoimmune pancreatitis          | 7.47 x $10^{-7}$ |                  | CALR, CAPG, COTL1, P4HB, PKM, PRDX2, UCHL1                               | 7                   |
| Cellular assembly and organization, cellular compromise                     | Formation of cytoplasmic inclusions | 7.50 x $10^{-7}$ |                  | FUS, KRT18, KRT8, SOD1, SQSTM1, UCHL1                                      | 6                   |
| Cell death and survival                                                     | Cell death of colon cancer Cell lines | 7.75 x $10^{-7}$ | 1.899             | AHSA1, CAPN2, CD44, CDK1, CSE1L, FASN, GSTP1, HINT1, HSPD1, IGF2R, ITGB1, KRT18, LMNA, PARK7, PPIA, RHOA, SFN, SFPQ, SQSTM1, STAT1, VCP, XRC5, YWHAE, YWHAH | 24                  |
| Cancer                                                                     | Abdominal cancer                 | 8.21 x $10^{-7}$ | -0.593            | AARS, ACAT1, ACAT2, ACLI, ACTG1, ACTN1, ACTN4, ACTR2, ACTR3, AHCY, AHNAK, AKR1B1, ANXA1, ANXA2, ANXA5, AP1B1, APEX1, ARF1, ARHGDIA, ARPC2, ATIC, ATP5A1, ATP5B, B2M, BASPI, BSG, C14orf166, CACYBP, CALR, CAND1, CANX, CAP1, CAPG, CAPN2, CAST, CAV1, CBX3, CCT2, CCT4, CCT5, CCT6A, CCT8, CD44, CD39, CDK1, CLCL1, CLTC, COPA, COPB1, COPB2, COPE, COPI, CORO1C, COTL1, CRIP2, CSE1L, CTNNA1, CTPS1, CTSA, CTSh, CTTN, CUTA, CYC1, CYR61, DBI, DBN1, DD1, DDX39B, DDX9, DDX9, D1AT, DNAJ1, DNAJ2, DNAJC8, DNAJ1L, DYSPL2, DYN1H1, DYN1L2, ECHS1, EEF1A1, EEF1B2, EEF1D, EEF2, EIF2S1, EIF2S2, EIF3, EIF4AI1, ENA4, ENO1, ENO2, ESRT5, FAS, FASIN, FDP5, FKBP1A, FLNA, FNLB, FNCL, FN1, FUBP3, FUS, G3BP1, G6PD, GANAB, GADPH, GARS, GCN1L1, GD2, GLU1, GML, GMS, GNA2, GN2I1L1, GPI, GSTP1, H2AFY, H3F3A/H3F3B, HADHA, HARS, HDGE, HDLP1, HEBX, HINT1, HIST1H1C, HIST1H2BL, HIST2H2AC, HLA-A, HLA-B, HMG1, HN1, HNRNPA1, HNRNPA2B1, HNRNPA3, HNRNPH1, HNRNPH3, HNRNPK, HNRNP2L, HNRNP4, HNRNP5, HNRNP6, HNRPA0A1, HNRPA0B1, HNRPA2B2, HNAP4, HSPA1A, HSPA1B, HSPA1H, HSPA2, HSPA8, HSPB1, HSPD1, HYOU1, IARS, ID1, IFTM3, IGF2R, ILEF2, IMMT, JEMPDB2, JPO5, JPO7, JPO9, JQCP1, ITGB1, KHDRBS1, KHSRP, KIF5B, KPN2, KPN3, KPN1, KRT1, KRT8, KRT9, LAMB1, LDHA, LGALS1, LMNA, LMB18, LOCI0272594/U2AF1, LONP1, LRPPRC, LRRRC59, MAP1B, MAP4, MAPK1, MAPRE1, MARS, MATR3, MCM3, MCM4, MCM6, MCM7, MDD1, MDC2, MEF2, MNV, MNP, MHY110, MYH9, NACA, NAPIL1, NAPIL4, NASP, NCL, NMNT, NONO, NPEPPS, NPLC4, NPM1, NSF1I1C, NUMA1, OLAI1, P4HB, PAGC4, PAPC1, PAICS, PCBP1, PCBP2, PCMB1, PCNA, PDIA3, PDIA4, PDI1M1, PDKX, PEA15, PFK, PFN1, PGAMA, PCD, PGK1, PMG1, PHGDH, PICALM, PKM, PLEC, PLIN3, PLD2, PL5, PPM1G, PPP1CA, PPP2CA, PPP2R1A, PRDX1, PRDX2, PRKCSH, PRKDC, PSA1A, PSA1B, PSA1M, PSAC1, PSAC2, PSAC4, PSM2, PTB1B, PTMA, PTRF, PUF60, PYGB, PYGL, QARS, RAN, RANBP1, RARS, RBM3, RHAO, RPL1, RPL2, RPL4, RPL5, RPL7A, RPL8, RPLP0, RN1, RPN2, RPS2, RPS24, RPS4, RPS7, RRP1P, RTN4, S100A6, SDHA, SEPT9, SERBP1, SERPHN1, SET, SFD1A, SF3B1, SFQ, SH3BGR1, SHMT2, SL2C25A3, SL2C25A5, SL3C3A2, SNN1, SOD1, SPTAN1, SPTBN1, SQSTM1, SRRP1, STAT1, STIP1, SYNCRIP, TAGLN, TALDO1, TARS, TCFP1, TFR1, TLNI, TPMO, TNC, TNPO1, TPI1, TPI2, TPM3, TPM4, TUBB, TUBB4B, TUBB8, TW2F, TNX2D5, UAP1, UBA1, UBE2N, UBA4N, UCHL1, VARS, VCL, VCP, VIC, VIM, VPS35, WAR1, XPO1, XRC5, XRC6, YBX1, YBX3, YWHAE, YWHAH, YWHAJ, YWHAQ, YWHAZ, ZYX | 342 |
### Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|---------|-------------------|-----------|--------------------|
| Drug metabolism, endocrine system development and function, lipid metabolism, small molecule biochemistry | Binding of progesterone | $8.87 \times 10^{-7}$ | $-0.277$ | DNAJA1, FKBP4, HSP90AB1, PTGES3, STIP1 | 5 |
| Connective tissue disorders, inflammatory disease, skeletal and muscular disorders | Arthritis | $8.98 \times 10^{-7}$ | $-0.277$ | ACLY, ACTA1, ALDOA, ANXA1, ARF1, ATIC, B2M, CALR, CAPN2, CD44, CD59, CTSA, DDX39B, EEF1G, EE2, ENO1, FASN, FDS, FKBP1A, FN1, GNAI2, GPI, H3F3A/H3F3B, HLA-A, HLA-B, HMBG1, HNRNPA1, HNRNPA3, HSP90B1, HSPA5, HSPA8, HSPD1, KHSRP, LDHB, LGALS1, MAPRE1, MYL12A, NONO, PCM1, PDEA3, PGK1, PHB2, PRDX1, PRDX2, PRDX5, PTMA, RPS24, RPS3, RPSA, SN1D1, STAT1, TRIF, TFM2, TRIM28, TUBB, TUBB4B, VARS, VIM | 58 |
| Cellular compromise, cellular function and maintenance | Endoplasmic reticulum stress response | $9.28 \times 10^{-7}$ | $1.069$ | AARS, CALR, CTSA, DNAJA1, HSP90AA1, HSP90AB1, HSPA5, HSPD1, HYOU1, SERPINH1, SLC38A2, SQSTM1, UCHL1, VCP | 15 |
| Cell death and survival | Cell death of cerebral cortex cells | $9.41 \times 10^{-7}$ | $1.181$ | CAPN1, CAPNS1, CAST, CDK1, FUS, GAPDH, HMBG1, HSPA5, HSPB1, HSPD1, HYOU1, MAP1B, P4HB, PAK7, PEA15, RPS3, SOD1, STIP1, TCP1, VAPA, YWHAB | 21 |
| Connective tissue disorders, immunological disease, inflammatory disease, skeletal and muscular disorders | Rheumatoid arthritis | $9.82 \times 10^{-7}$ | | ACLY, ACTA1, ALDOA, ANXA1, ARF1, ATIC, B2M, CALR, CTSA, DDX39B, EEF1G, EE2, ENO1, FDS, FKBP1A, H3F3A/H3F3B, HLA-A, HMBG1, HNRNPA1, HNRNPA3, HSP90B1, HSPA5, HSPA8, HSPD1, KHSRP, LDHB, LGALS1, MAPRE1, MYL12A, NONO, PCM1, PDEA3, PGK1, PRDX1, PRDX2, PRDX5, PTMA, RPS24, RPS3, RPSA, SN1D1, STAT1, TRIF, TFM2, TRIM28, VARS, VIM | 46 |
| Cellular assembly and organization, cellular function and maintenance | Bundling of microtubules | $1.03 \times 10^{-6}$ | $0.218$ | DNM1L, MAP1B, MAPRE1, NUMA1, RRB1P, SEPT9, SRRP1 | 7 |
| Cellular movement | Migration of breast cancer Cell lines | $1.21 \times 10^{-6}$ | $0.280$ | ANXA1, ANXA2, ARF1, CAPN2, CAV1, CSE1L, CTTN, FLNA, FN1, GNB2L1, ILF3, ITGB1, KHDRBS1, KPN2A2, KRT8, LASP1, MAPK1, MYH9, RHOA, SFN, VIM | 21 |
| Cellular compromise | Collapse of intermediate filaments | $1.58 \times 10^{-6}$ | | KRT18, KRT8, PLEC, RHOA | 4 |
| Connective tissue disorders, inflammatory disease, skeletal and muscular disorders | Rheumatic disease | $1.66 \times 10^{-6}$ | $-0.277$ | ACLY, ACTA1, ALDOA, ANXA1, ARF1, ATIC, B2M, CALR, CAPN2, CD44, CD59, CTSA, CTSA, DDX39B, EEF1G, EE2, ENO1, FASN, FDS, FKBP1A, FN1, GNAI2, GPI, H3F3A/H3F3B, HLA-A, HLA-B, HMBG1, HNRNPA1, HNRNP4A3, HSP90B1, HSPA5, HSPA8, HSPD1, KHSRP, LDHB, LGALS1, MAPRE1, MYL12A, NONO, PCM1, PDEA3, PGK1, PHB2, PPP2CA, PRDX1, PRDX2, PRDX5, PTMA, RHOA, RPS24, RPS3, RPSA, SN1D1, STAT1, TRIF, TFM2, TRIM28, TUBB, TUBB4B, UBE2L3, VARS, VIM | 62 |
| Categories                                                                 | Diseases or Functions Annotation                                   | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|---------------------------------------------------------------------|------------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Organismal injury and abnormalities, reproductive system disease          | Adenomyosis                                                        | $1.67 \times 10^{-6}$ |                   | ALDOA, ANXA2, DDX6, GPI, IQGAP1, ITGB1, LDHA, MYH10, PRDX5, VDAC1          | 10                  |
| DNA replication, recombination, and repair, energy production, nucleic acid metabolism, small molecule biochemistry | Hydrolysis of ATP                                                  | $1.72 \times 10^{-6}$ | $-0.164$          | ATP1A1, CCT4, CCT5, CDK1, HMGB1, HSPA5, HSPD1, MAPK1, UBA1                | 9                   |
| Cell-to-cell signaling and interaction, tissue development                | Detachment of blood cells                                          | $1.74 \times 10^{-6}$ | 0.293             | ANXA1, ANXA5, FN1, ITGB1, RHOA                                            | 5                   |
| Cell death and survival                                                   | Cell death of muscle cells                                         | $1.79 \times 10^{-6}$ | 1.087             | ALDOA, CALR, CAPN1, CAV1, CYR61, EEF1A1, EEF1D, GAPDH, GNA12, HADHA, HLA-B, HMGB1, HSPB1, HSPD1, LMNA, MAPK1, MDH1, NCL, PARK7, PLEC, PSMB1, RRM3, RHOA, RPSA, S100A6, STAT1, ZYX | 27                  |
| Cell-to-cell signaling and interaction, tissue development               | Adhesion of tumor cell lines                                       | $1.86 \times 10^{-6}$ | $-0.235$          | ANXA1, ANXA2, BSG, CIQBP, CAV1, CD44, CD59, CYR61, ERP29, FLNA, FN1, GNR2L1, HMGB1, ITGB1, MAPK1, MARCKS, MYH9, PTGES3, RHOA, RPSA, UCHL1, VCL, ZYX | 23                  |
| Cardiovascular system development and function, cellular movement        | Migration of endothelial cells                                     | $1.90 \times 10^{-6}$ | $-2.222$          | ANXA2, CAV1, CYR61, FLNA, FLNB, FN1, G6PD, HMGB1, HSP90AB1, HSPA5, HSPB1, IGF2R, ITGB1, LGALS1, MAPK1, MARCKS, NCL, PDCD6, PKM, RHOA, RTN4, SEPT7, TARS, VIM, WARS, YWHAZ | 26                  |
| Cancer, cellular development, cellular growth and proliferation, tumor morphology | Proliferation of tumor cells                                       | $2.04 \times 10^{-6}$ | $-1.588$          | ACLY, ACTN4, AHCY, AKR1B1, ANXA1, ANXA2, BSG, CACYBP, CAV1, CD44, CTSB, CYR61, EEF1A1, ESR, FASN, FN1, HDGE, HMGB1, HSP5, LDHA, LGALS1, MAPK1, NPM1, PARK7, PPP2CA, RHOA, RPS4X, S100A6, SQSTM1, STAT1, STN1, TNLNA, UCHL1, XRC5   | 34                  |
| Cellular assembly and organization                                        | Binding of zona pellucida                                          | $2.10 \times 10^{-6}$ |                   | CCT2, CCT3, CCT4, CCT5, CCT6A, CCT7, CCT8, TCP1                          | 8                   |
| Cellular function and maintenance                                         | Engagement of cells                                                | $2.23 \times 10^{-6}$ | $-0.600$          | ACTN4, ANXA1, ANXA5, CALR, CAPG, CAV1, CD44, CLIC4, CLTC, CORO1C, EHD1, ESR, FN1, GNRL1, HMGB1, HYOU1, IQGAP1, ITGB1, MAP1B, MAPK1, MYH9, NCL, NPM1, PFF1, PICALM, RAB7A, RHOA, SFPQ, SNX3, VIM | 30                  |
| Cancer, respiratory disease                                               | Non small cell lung adenocarcinoma                                 | $2.24 \times 10^{-6}$ |                   | AHNAK, ALDOA, ALDOC, ATIC, CAPRIN1, CAV1, CD44, CDK1, DHX9, EEF1B2, EEF4A1, EN01, ESR, G3BP1, GPI, HIST2HE2AC, HLA-A, IMPDH2, LDHA, LOC102724594/U2AF1, MAP4, MSN, MYH9, NACA, NSF11C, PCNA, PFKP, PKM, PRDX1, PRPF19, SERBP1, TP11, TUBB4B | 33                  |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | Peripheral t-cell lymphoma                                         | $2.47 \times 10^{-6}$ |                   | CYR61, FN1, NNMT, PSMB1, PSMD2, TUBB, TUBB4B, TUBB6, TUBB8               | 9                   |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation | p-Value     | Activation z-Score | Molecules                                                                                       | Number of Molecules |
|----------------------------------------------------------------------------|----------------------------------|-------------|--------------------|-------------------------------------------------------------------------------------------------|---------------------|
| Cell death and survival                                                   | Cell death of brain              | $2.52 \times 10^{-6}$ | 0.904              | CAPN1, CAPNS1, CAST, CDK1, DNM1L, FUS, GAPDH, HMGB1, HSPA5, HSPB1, HSPD1, HYOU1, MAP1B, P4HB, PARK7, PEA15, RPS3, SDHA, SOD1, STAT1, STIP1, TCP1, VAPA, YWHAH | 24                  |
| Cancer                                                                    | Metastatic cancer                | $2.58 \times 10^{-6}$ |                    | ATIC, B2M, CAPG, CAV1, CSE1L, DYSLS1, EEF1A1, EIF4A1, FDP5, FKBPIA, FLNA, FNI, HSP90AA1, HSP90AB1, HSP90B1, KRT18, MYL12A, PLOD2, PPIA, RPL27, RPL7, RPS11, RPS27A, STAT1, TUBB, TUBB4B, YWHAE | 27                  |
| Free radical scavenging                                                  | Production of reactive oxygen species | $2.60 \times 10^{-6}$ | 0.372              | AKR1B1, ANXA1, ARHGDIA, CAV1, CD44, CTN, DNM1L, FN1, G6PD, CNB2L1, HMGB1, HNRNPK, HSP90AB1, HSP90B1, KRT18, IMMT, LDHA, LONP1, MAPK1, PARK7, PPIA, PRDX1, PRDX2, RHOA, SOD1, SQSTM1, TAGLN, VDCA1, YWHAZ | 28                  |
| Cellular movement                                                        | Migration of fibrosarcoma cell lines | $2.60 \times 10^{-6}$ | $-1.394$           | ARPC2, CTTN, FLNA, FLNB, FLNC, FN1, HNRNPK, TPM3                                              | 8                   |
| Cellular growth and proliferation                                         | Outgrowth of cells               | $2.75 \times 10^{-6}$ | $-0.580$           | APEX1, BASP1, CDK1, CYR61, DNM1L, DYSLS1, EZR, FKBPIA, FUS, HMGB1, HSP90AA1, IQGAP1, ITG8, LGALS1, MAP1B, MAPK1, MARCKS, MYH10, MYH9, NPM1, P4HB, RAB11A, RHOA, RTN4, SLC25A5, SNX3, SOD1, STIP1B1, TNC, VAPA, VIM, YWHAH | 32                  |
| Cancer, hematological disease, immunological disease                     | Waldenstrom’s macroglobulinemia  | $2.79 \times 10^{-6}$ |                    | ANXA2, ANXA6, CAV1, CDK1, FASN, FKBPIA, FUS, G3BPI, KPN2A, NONO, PCNA, PPI2CA, PSMB1, PSMB2, STIP1, XRC6, YWHAE | 18                  |
| Cancer, gastrointestinal disease                                         | Upper gastrointestinal tract tumor | $2.84 \times 10^{-6}$ |                    | AKR1B1, ALYREF, ANXA1, ATIC, BSG, CANX, CAV1, CD44, COPB2, CSTB, CTNN1A1, CTNN, DDX39B, EZR, FAS, FKBPIA, FUS, G3BPI, KPN2A, NONO, PCNA, PPI2CA, PSMB1, PSMB2, TTN1, XRC6, YWHAE | 46                  |
| Molecular transport, RNA trafficking                                      | Transport of RNA                 | $3.04 \times 10^{-6}$ | $-1.969$           | ALYREF, DDX39B, DDX3X, EIF5A, FUS, HNRNP2B1, KDHRBS1, RAN, U2AF2, XPO1                        | 10                  |
| Cancer, hematological disease, immunological disease                     | Plasma cell dyscrasia            | $3.09 \times 10^{-6}$ |                    | ANXA2, ANXA6, CAV1, CDK1, DNM1L, FUS, FKBPIA, FLNA, FNI, G3BPI, HLA-A, KPN2A, NONO, PCNA, P16A6, PPI2CA, PSMB1, PSMB2, STIP1, VIM, XRC6, YWHAE, YWHAZ | 25                  |
| Cell cycle                                                               | Arrest in interphase             | $3.10 \times 10^{-6}$ |                    | ANXA2, CAV1, CD44, CDK1, CSE1L, CYR61, FAS, FKBPIA, FLNA, FNI, ITG8, LGALS1, LMNA, MAPK1, MCM7, PCDC6, PPI2CA, PRKDC, PTGES3, RHOA, RPL23, RPL5, RPL7A, SFN, SPTAN1, STAT1, TCF1, TFCRC, TFCP2, TMPO, YWHAE | 30                  |
| Cell signaling, post-translational modification, protein synthesis        | Actin capping of filament barbed ends | $3.12 \times 10^{-6}$ |                    | CAPG, CAPZA1, CAPZB, TWF1, TWF2                                                             | 5                   |
| Cellular movement                                                        | Cell movement of bone cancer cell lines | $3.21 \times 10^{-6}$ | $-1.584$           | ACTN4, CAPN2, CAV1, CTNS, FN1, STMN1, TNL1, VCP                                              | 8                   |
| Categories                                                                 | Diseases or Functions Annotation | p-Value     | Activation z-Score | Molecules                                                                                                           | Number of Molecules |
|---------------------------------------------------------------------------|---------------------------------|-------------|-------------------|---------------------------------------------------------------------------------------------------------------------|---------------------|
| Hematological system development and function, inflammatory response, tissue development | Aggregation of blood platelets  | 3.42 × 10⁻⁶ | −0.977            | ACTG1, AKR1B1, CAPN1, CAST, CLIC1, CSRP1, FLNA, GNA12, HSPB1, ITGB1, LGALS1, MAPK1, MYH9, MYL12A, P4HB, PDIa3, TLN1, VCL | 18                  |
| Cancer                                                                    | Cancer                          | 3.45 × 10⁻⁶ | −1.084            | AARS, ACAT1, ACAT2, ALCY, ACTG1, ACTN1, ACTN4, ACTR2, ACTR3, ACY, AHCY, AHNAK, AKR1B1, ALDOA, ALDOC, ANXA1, ANXA2, ANXA5, ANXA6, APOB1, APEX1, ARF1, ARHGDA, ARFC2, ATIC, ATP5A1, ATP5B, B2M, BASP1, BSG, C1orf166, CIQBP, CACYBP, CALR, CAND1, CANX, CAP1, CAPG, CAPN1, CAPN2, CAPR1N, CAPZA1, CAV1, CBX3, CCT2, CCT3, CCT4, CCT5, CCT6A, CCT7, CCT8, CD44, CD59, CDK1, CFI, CLIC1, CLIC, CMM, COP1, COPB1, COPB2, COPE, COPG1, CORO1C, COTL1, CRIP2, CSE1H, CSTB, CTNNAL1, CTPI1, CTSA, CTSB | 406                 |

Table 5. Cont.
| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|---------|-------------------|-----------|--------------------|
| Cell morphology | Blebbing | $3.47 \times 10^{-6}$ | 0.053 | CTTN, DPYS1, EZR, HSPB1, LMNA, LMNB1, MARCKS, RHOA, SPTAN1 | 9 |
| Hereditary disorder, neurological disease, organismal injury and abnormalities, skeletal and muscular disorders | Charcot-Marie-tooth disease type 2 | $3.75 \times 10^{-6}$ | | AARS, DYNC1H1, GARS, HSPB1, LMNA, RAB7A | 6 |
| Endocrine system development and function, small molecule biochemistry | Binding of hormone | $3.75 \times 10^{-6}$ | 0.250 | DNAJA1, FKBP4, HSP90AB1, PTGES3, SFN, STIP1 | 6 |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | Classic Hodgkin disease | $3.75 \times 10^{-6}$ | | FKBP1A, LGALS1, TUBB, TUBB4B, TUBB6, TUBB8 | 6 |
| Cellular assembly and organization, cellular function and maintenance | Stabilization of microtubules | $3.80 \times 10^{-6}$ | 0.247 | COPB2, DNM1L, DPYS1, IQGAP1, MAP1B, MAP4, MAPRE1, NUMA1, PKM, RHOA, SEPT7, STMN1 | 12 |
| Cell morphology, cellular function and maintenance | Transmembrane potential of mitochondria | $4.05 \times 10^{-6}$ | $-0.508$ | ANXA6, B2M, CLIC1, CLIC4, HSPA4, HSPB1, HSPD1, IMMT, LDHA, LGALS1, LONP1, PARK7, PHB2, SLC25A6, SOD1, STOML2, VCP, VDAC1, YWHAE | 19 |
### Table 5. Cont.

| Categories                                | Diseases or Functions Annotation | p-Value                | Activation z-Score | Molecules                                                                                      | Number of Molecules |
|-------------------------------------------|----------------------------------|------------------------|--------------------|-----------------------------------------------------------------------------------------------|---------------------|
| Cancer, gastrointestinal disease          | Digestive organ tumor            | 4.26 × 10⁻⁶           | −0.321             | AARS, ACAT1, ACAT2, ACAT1, ACTG1, ACTN1, ACTR2, ACTR3, AHCC, AHNAK, AKR1B1, ALYREF, ANXA1, ANXA2, AP2B1, APEX1, ARF1, ARHGDEA, ATIC, ATP5A1, ATP5B, B2M, BSG, CACYBP, CANX, CAPG, CAPN2, CAST, CAV1, CX3, CCTX, CTTA, CTT8, CD44, CD59, CLC1, CLTC, COPA, COPB2, COPG1, COTL1, CRIP2, CSE1L, CTST, CTNNA1, CTPS1, CTSA, CTSB, CTTN, CUX1, CYF6, DB1, DBN1, DDX1, DDX9B, DDX3X, DDX5, DDX8, DLAT, DNAA1, DNAJC8, DNML1, DPYSL2, DYN1H1, DYN1C2, ECHS1, EE1F1A, EE1F2D, EEIF2, EEIF3, EEIF4A1, EEIF4G1, ENA4, ENO1, ENO2, EFRS, ESY7, EZR, EASN, FKBP1A, FLNA, FLNB, FLNC, FN1, FUBP3, FUS, G3BP1, G6PD, GANAB, GARS, GCN1L1, GD2, GLUD1, GMI, GMPS, GNA12, GNB2L1, GPl, GSTP1, H2AFY, HSF3A/HSF3B, HADHA, HEDGE; HIDLBP; HFXB, HINT1, HIST1H1C, HLA-A, HLA-B, HMG81, HNRNPA1, HNRNPA2B1, HNRNPA3, HNRNPH1, HNRNPH3, HNRNPK, HNRNPFL, HNRNPMA, HNRNPQ, HSP90AA1, HSP90B1, HSP90Bob1, HSP9A5, HSPA8, HSPF9, HSPD1, HYOU1, IARS, IDH1, IFTM3, IGF2R, ILF2, ILF3, IMMT, IMPDH2, IP5X, IP5Y, IQGAP1, ITGB1, KHDRBS1, KHDRBS2, KHSRP, KIF5B, KPN2A, KPN2B, KPN3A, KPN8B, KRT1, KRT18, KRT8, LAMAI, LDEHA, LGA5L1, LMNA, LNB1, LOC101725949/U2AF1, LONIP1, LRPPRC, LRRC59, MAP1B, MAP4, MAPRE1, MARS, MATR3, MCM3, MCM4, MCM6, MCM7, MDD1, MDH2, MVP, MYH10, MYH9, NACA, NAP1L1, NAP1L4, NASP, NCL, NNMT, NPEPP5, NPLOC4, NPM1, NUMA1, OLAI1, PBX4, PAXG4, PAICS, PCBP1, PCBP2, PM1, PCNA, PDI4A, PKP2, PN31, PGAM1, PGM1, PHGDH, PKM2, PLEC, PLIN3, PLOD2, PLN3, PPM1C, PPM1A, PPM1B, PPM1C, PPM2CA, PPM2RA1, PREDX1, PKRCSH, PRKDC, PSMA7, PSMB1, PSMB2, PTBP1, PTMA, PTE, PUFX, PYGB, PYGL, QARS, RAN, RANBP1, RARS, RHODA, RPL10, RPL12, RPL22, RPL4, RPL5, RPL7A, RPL10, RN, RPS2, RPS24, RPS4X, RPSBP1, RTN4, ST10A6S, SDHA, SEP7P, SERBP1, SERBP1H1, SET, SF3A1, SF3B1, SFN, SFPQ, SRB3R3L3, SLC38A2, SOD1, SODI, SPTANI, SPTBN1, SQSTM1, SSRP1, STAT1, STIP1, STN1, SYNCRIP, TAGLN, TALDO1, TAR5, TCP1, TERC, TNC, TNPO, TNPO1, TPO1, TPM2, TPM4, TUBB, TUBB4B, TBUBB, TUBW2, UAP1, UBA1, UBE2N, UBXN4, UCHL1, VARS, VCL, VCP, VIM, ZPS3, WARS, XRC5, XRC6, YBX1, YBX3, YWHAE, YWHAH, YWHAJ, YWHAZ |
| Cellular assembly and organization, tissue development | Polymerization of filaments | 4.45 × 10⁻⁶ | 0.934 | ACTR3, ARPC2, CAP2B, CAV1, CFL1, FKBP4, MAP1B, MAPRE1, PFNI, RHODA, STM1, TUBB, TF31, TF2 | 14 |
| Cellular assembly and organization, cellular development, cellular growth and proliferation, nervous system development and function, tissue development | Growth of neurites | 4.55 × 10⁻⁶ | −1.344 | APEX1, BASP1, CAV1, CDK1, CSRPI, DNML1, DPYSL2, EZR, FKBP4, FNI, HMG81, IQGAP1, ITGB1, LGALS1, MAP1B, MAPK1, MARCKS, MYH10, MYH9, PDEA3, RAB11A, RHODA, RTP4, SEPT9, SLC25A5, SNX3, SOD1, SPTB11, TNC, VAPA, VCL, VIM, YWHAZ | 33 |
| Categories                                      | Diseases or Functions Annotation | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------------|---------------------------------|---------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Hematological disease                          | Blood protein disorder          | $4.60 \times 10^{-6}$ |                   | ANXA2, ANXA6, ARHGDIA, B2M, CAV1, CDK1, FASN, FDPS, FKBP1A, FLNA, FN1, FUS, G3BP1, HLA-A, KPNAA2, NONO, PCNA, PDI6, PPF2CA, PSMA2, PSMB1, PSMD2, STIP1, VIM, XRC6C, YWHAE, YWHAZ | 27                  |
| Hereditary disorder                             | Autosomal dominant disease      | $4.66 \times 10^{-6}$ |                   | AARS, ACTA1, ACTG1, ACTN4, AHNAK, CAV1, DNML, DYNCH1H1, EF2, EIF4G1, FKBP1A, FLNB, FLNC, FN1, FUS, GARS, HNRNP, HNRNPA2B1, HSPB1, HSPD1, KRT1, KRT9, LMNA, LMNB1, MYH9, PARK7, RAB7A, SOD1, STAT1, TNC, TPM2, TPM3, UCHL1, VCP, VPS35 | 35                  |
| Cancer, immunological disease, organinal injury and abnormalities | Lymphatic node tumor           | $4.71 \times 10^{-6}$ | 0.000              | ANXA1, ATIC, B2M, CSE1L, CYR61, FKBP1A, FN1, FUS, HIST1H1C, HMGB1, IQGAP1, ITGB1, KHRDSB1, LONP1, NNMT, PRDX1, PRKDC, PSMB1, PSMD2, RHOA, RPS2, SF3B1, SHMT2, STIN1, TUBB, TUBB4B, TUBB6, TUBB8, TULNA, UQCCRC1, XPO1, XRC6C, YWHAZ | 33                  |
| Molecular transport                             | Nuclear export                  | $4.97 \times 10^{-6}$ |                   | ALYREF, CALR, CSE1L, DDX39B, EIF5A, HNRNP, HSPA9, KHRDSB1, NPM1, RAN, XPO1 | 11                  |
| Cell death and survival                         | Apoptosis of colon cancer cell lines | $5.12 \times 10^{-6}$ | 1.294              | AHS1A, CD44, CDK1, CSE1L, FASN, GSTP1, HINT1, HSPD1, IGF2R, ITGB1, KRT18, PARK7, PPA, RHOA, SFN, SFQ, STAT1, VCP, XRC6C, YWHAZ | 20                  |
| Cellular movement                               | Cell movement of pericytes      | $5.37 \times 10^{-6}$ | $-0.928$          | CD44, FN1, GNB2L1, HMGB1, LGALS1, MAPK1, MYH10 | 7                  |
| Molecular transport, protein synthesis, protein trafficking | Localization of protein         | $5.46 \times 10^{-6}$ | $-0.324$          | APEX1, ARHGDIA, BTF3, C1QBP, CAV1, CUTA, FKBP1A, FKBP4, GNB2L1, HLA-A, HYOU1, ITGB1, NPM1, PICALM, SEPT2, SQSTM1, TFRC | 17                  |
| Cellular movement                               | Migration of connective tissue cells | $5.46 \times 10^{-6}$ | 0.420              | CAPNS1, CAV1, CD44, CYR61, EHD1, FLNB, FN1, GNB2L1, HMGB1, ITGB1, LGALS1, MAPK1, MYH10, PLEC, STIN1, VCL, ZYX | 17                  |
| Hereditary disorder, skeletal and muscular disorders | Autosomal dominant myopathy    | $6.79 \times 10^{-6}$ |                   | AARS, AHNAK, DYNCH1H1, GARS, HSPB1, LMNA, RAB7A | 7                  |
| Neurological disease                            | Lower motor neuron disease      | $6.79 \times 10^{-6}$ |                   | DYNCH1H1, GARS, HNRNP, HNRNPA2B1, HSPB1, UBA1, VCP | 7                  |
| Cancer, endocrine system disorders              | Thyroid adenoma                 | $6.79 \times 10^{-6}$ |                   | ANXA5, CALR, CTSB, GSTP1, HSP90AB1, PARK7, PRDX2 | 7                  |
| Cell death and survival                         | Apoptosis of cervical cancer cell lines | $7.05 \times 10^{-6}$ | $-0.772$          | CCT4, CDK1, CTSB, DNML, DYNCH1H1, EZR, FLNB, HNRNPK, IMMT, KHRDSB1, MAPK1, MSN, PCBP2, PPIA, PRKDC, PRPF19, PTMA, RPS24, STAT1, TCP1, UCHL1, VDAC1 | 22                  |
### Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value   | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------|----------------------------------|-----------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cell morphology | Shape change of tumor cell lines | $7.13 \times 10^{-6}$ | $-1.937$ | ANXA5, CAP1, CAPN2, DPYSL2, FLNA, FLNB, FN1, ITGB1, MAPK1, MARCKS, MYH9, PPIN1, RHOA, TNC, UCHL1 | 15                  |
| Energy production, molecular transport, nucleic acid metabolism, small molecule biochemistry | Concentration of ATP | $7.22 \times 10^{-6}$ | $-1.019$ | ALDOA, ATP5B, CAV1, DNM1L, ENO1, HSD17B10, KRT8, LDHA, LRPPRC, PKM, SQSTM1, STOML2, VDAC1 | 13                  |
| Cell death and survival | Cell death of brain cells | $7.42 \times 10^{-6}$ | $1.086$ | CAPN1, CAPNS1, CAST, CDK1, DNM1L, FUS, GAPDH, HMGBI, HSPA5, HSPB1, HPD1, HYOU1, MAP1B, P4HB, PARK7, PEA15, RPS3, SOD1, STIP1, TCP1, VAPA, YWHAH | 22                  |
| Cancer, gastrointestinal disease | Digestive tract cancer | $7.58 \times 10^{-6}$ | $0.345$ | AARS, ACAT1, ACAT2, ACY1, ACTG1, ACTN1, ACTR2, ACTR3, AHCY, AHNAK, AKR1B1, ANXA1, ANXA2, AP1B1, APEX1, ARF1, ARHGDIA, ATIC, ATP5A1, ATP5B, B2M, BSG, CACBP, CAND1, CAPI, CAPN2, CAST, CAV1, CBX3, CCT4, COT1, CRIP2, CSE1L, CSTB, CTNNB1, CTSP1, CTSA, CTSG, CTTN, CUX1, CYR61, DBI, DBN1, DDX1, DDX9B, DDX9X, DDX5, DDX9, DLA1, DNAJ1A1, DNAJ6, DNM4L, DYSPL2, SYNCH1, YNYC1, ECHS1, EEF1A1, EEF1D, EEF2, EIF3L, EIF4A1, EIF4G1, ENAH, ENO1, ENO2, EPRS, ESID1, EZR, FASN, FKBPL1, FLNA, FLNB, FLNC, FN1, FUBP3, FUS, G6BP, GANAB, GARS, GCN1L1, GD2, GLUD1, GML, GMPS, GNAI2, GNB2L1, GPI, GTP1, H2AFY, HSF3A/HSF3B, HADHA, HDGF, HDLBP, HEXB, HINT1, HINT1H1C, HLA-A, HLA-B, HMGBI, HNRNPA1, HNRNPA2B1, HNRNPC3, HNRNPF1, HNRNPF3, HNRNPK, HNRNP1, HNRNPM, HNRNPV, HSP90AA1, HSP90AB1, HSP90BI1, HSPA5, HSPA6, HSPA9, HSPD1, HYOU1, IARS, ID1, IFITM3, IKG2R, ILF2, ILF3, IMMT, IMPDE2, IPO5, IPO7, IQGAP1, ITGB1, KHDRBS1, KHSRP, KIF5B, KPN2A, KPN3, KPNB1, KRT1, KRT18, KRT8, KRT9, LAMB1, LDHA, LGALS1, LMNA, LMNB1, LOC10274694, U2AF1, LONP1, LRPPRC, LRRC59, MAP1B, MAP4, MAPRE1, MARS, MATK, MCM3, MCM4, MCM6, MCM7, MDM1, MDH2, MVP, MYH10, MYH9, NACA, NAP1L1, NAP1L4, NAPC, NCL, NNM1, NPEPS, NPLC4C, NPM1, NUMA1, OLA1, P4HB, PA2G4, PAICS, PB2P1, PCBP2, PCBP1, PCBP2, PCBP3, PCNA, PDI4A, PKF1, PPIN1, POGM, PGD, PGM1, PHGDH, PKM, PLEK, PLIN3, PLOD2, PL53, PPM1G, PPACA, PPACCA, PPF2R1A, PRDX1, PRKCSH, PRKDC, PSMA7, PSMC1, PSMD2, PTBP1, PTPA, PTP1B, PTP2B, PTP4B, PUC2, PVG2, PVL1, QRPS, RAN, RANBP1, RARS, RHOA, RPL10, RPL12, RPL22, RPL4, RPL7A, RPLPO, RNPL1, RPS2, RPS24, RPS4X, RRP8l, RTN4, S100A6, SDHA, SEPT9, SERBP1, SERPIN1H, SET, SF3A1, SF3B1, SFN, SFQ, SH3BGL3, SLC38A2, SN1D1, SOD1, SPTAN1, SPTBN1, SQSTM1, SSRP1, STAT1, STIP1, STIP1, SYGCR1, TAGLN, TALDO1, TARS, TCP1, TFRC, TTN1, TMPO, TNC, TNPO1, TPI1, TPM2, TPM4, TUBB, TUBB4B, TUBB8, TW2, UAP1, UBE1, UBE2N, UBXN4, UCHL1, UARS, VCL, VCP, VIM, VPS35, WARS, XCCO, YBX1, YBX3, YWHAE, YWHAH, YWHAH, YWHAZ | 294 |
### Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|---------|--------------------|-----------|---------------------|
| **Cancer, gastrointestinal disease** | Malignant neoplasm of digestive system | $7.58 \times 10^{-6}$ | 0.345 | AARS, ACAT1, ACAT2, AGLY, ACTG1, ACTN1, ACTR2, ACTR3, AHHCY, AHNACK, AKR1B1, ANXA1, ANXA2, AP1B1, ARF1, ARHGDI, ATIC, ATP5A1, ATP5B, B2M, BSG, CACYBP, CANX, CAPP, CAP2, CAST, CAV1, CBX3, CTT4, CTT5, CTT6A, CTT8, CD44, CD59, CLIC1, CLTC, COPA, COPB2, COPG1, COT1L1, CRIP2, CSE1L, CTHB, CTNN1, CTA, CYC1, CYR61, DB1, DBN1, DDX1, DDX39B, DDX39, DDX5, DHX9, DIT, DNAAJ1, DNACB, DNMT1, DPYSL2, DYNCH1H1, DYNCH1H2, ECHS1, EEF1A1, EEF1D, EEF2, EEF3I, EIF4A1, EIF4G1, ENAH, ENO1, ENO2, EPFS, ESY1, EZR, FASN, FKBP1A, FLNA, FLNB, FLNC, FN1, FUBP3, FUS, G3BP1, G6PD, GANAB, GARS, GCN1L1, GD2, GLUD1, GML, GMPS, GNA2, | 294 |
| **Molecular transport** | Export of molecule | $7.90 \times 10^{-6}$ | -1.118 | ALYREF, ANXA6, CALR, CSE1L, DDX39B, EIF5A, HSPA9, KHRDHS8, RAN, SEC13, U2AF2, XPO1, YWHA | 13 |
| **Cellular assembly and organization** | Quantity of filaments | $8.03 \times 10^{-6}$ | -0.914 | CFL1, FN1, GNB2L1, KRT18, MAP1B, MAP4, MARCKS, PLEC, RHOA, SERPINH1, SPTAN1, STNP1, SQSTM1, SSP1, STAT1, STIP1, SYNCRIP, TAL1, TALD1, TARS, TCP1, TFC, TLNI, TEMPO, TNC, TMF1, TPM2, TPM4, TUBB, TUBB4B, TUBB8, TFW2, UAP1, UBA1, UBE2N, UBXN4, UCH1, VARS, VCL, VCP, VIN, VPS35, WARS, XRC6, YBX1, YBX3, YWHAEE, YWHAH, YWHAEE, YWHA | 14 |
| **Cell-to-cell signaling and interaction, reproductive system development and function** | Binding of sperm | $8.32 \times 10^{-6}$ | | CCT2, CCT3, CCT4, CCT5, CCT6A, CCT7, CCT8, TCP1 | 8 |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation | p-Value        | Activation z-Score | Molecules                                                                 | Number of Molecules |
|----------------------------------------------------------------------------|----------------------------------|----------------|--------------------|---------------------------------------------------------------------------|--------------------|
| Connective tissue disorders, developmental disorder, metabolic disease, skeletal and muscular disorders | Paget's disease of bone           | $8.37 \times 10^{-6}$ |                    | FDP5, HNRNPA1, HNRNPA2B1, SQSTM1, VCP                                    | 5                  |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | Refractory classical hodgkin lymphoma | $8.37 \times 10^{-6}$ |                    | FKB1A, TUBB, TUBB4B, TUBB6, TUBB8                                      | 5                  |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | Relapsed classical hodgkin lymphoma | $8.37 \times 10^{-6}$ |                    | FKB1A, TUBB, TUBB4B, TUBB6, TUBB8                                      | 5                  |
| Infectious disease                                                        | Infection of hepatoma cell lines  | $8.85 \times 10^{-6}$ | $-0.425$           | ACTR2, AP1B1, AP2B1, ARPC1B, CLTC, G3BP1, HMGB1, IFITM3, TFRC            | 9                  |
| Cancer, gastrointestinal disease                                          | Upper gastrointestinal tract cancer | $8.86 \times 10^{-6}$ |                    | ANXA1, ATIC, BSG, CANX, CAV1, CD44, COP82, CSTB, CTNNA1, CTTN, DDX39B, EZR, FASN, FKB1A, FN1, FUS, GTP1, H3F3A/H3F3B, HEDGE, HINT1, HLA-B, HNRNPH1, HSP90AA1, HSP90AB1, HSP90B1, IGF2R, IPO5, LGALS1, NPM1, P4HB, PA2G4, PLOD2, RAN, RHOA, RPL10, RPL22, SFN, TAGLN, TNC, TUBB, TUBB4B | 41                 |
| Hematological disease, organismal injury and abnormalities                | Myelodysplastic syndrome          | $9.44 \times 10^{-6}$ |                    | CALR, LOC102724594/U2AF1, NPM1, PDI1A3, RPL3, RPL4, RPL5, RPL6, RPL7, RPLP0, RPLP1, RPS27A, RPS4X, SF3B1 | 14                 |
| Cancer                                                                    | Osteosarcoma                      | $9.56 \times 10^{-6}$ |                    | CD44, FASN, FDP5, HINT1, HSP90AA1, HSP90AB1, HSP90B1, IMPDH2, PRDX1, STOML2, TUBB, TUBB4B | 12                 |
| Cellular function and maintenance                                         | Uptake of cells                   | $9.91 \times 10^{-6}$ | 0.555              | C1QBP, CAV1, ITGB1, NCL, OTUB1, RHOA, RPSA, SNX3                          | 8                  |
| Cellular development, cellular growth and proliferation                   | Proliferation of carcinoma Cell lines | $1.06 \times 10^{-5}$ | $-0.759$           | ACLY, ANXA1, ANXA2, BSG, C1QBP, CAV1, CYR61, DYNC1H1, GAPDH, H2AFY, HMGB1, HNRNPA2B1, IGF2R, ITGB1, MAPK3, MAPRE1, PTBP1, S100A6, SFT, SLC25A6, SOD1, STMN1, TRIM28, UCHL1 | 24                 |
| Cell death and survival                                                   | Apoptosis of breast cancer Cell lines | $1.16 \times 10^{-5}$ | $-1.394$           | ARHGDIa, B2M, CAV1, CD44, CDK1, CSE1L, CYR61, FASN, FN1, HINT1, HSPA5, HSPB1, HSPD1, KIF2A2, KRT18, MAFK1, PEA15, PEBP1, SND1, STAT1, TFRC, VCP | 22                 |
| Categories                                                                 | Diseases or Functions Annotation                                                                 | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cell-to-cell signaling and interaction, connective tissue development and function, tissue development | Adhesion of fibroblast Cell lines                                                                 | $1.18 \times 10^{-5}$ | $-1.591$         | CALR, CD44, CYR61, FN1, IQGAP1, ITGB1, MAPK1, RHOA, VCL                   | 9                   |
| Cellular assembly and organization, cellular compromise                     | Formation of cellular inclusion bodies                                                             | $1.21 \times 10^{-5}$ | 0.246             | CTSB, DNAJA1, FUS, HSPA4, KRT18, KRT8, PSMC4, SOD1, SQSTM1, TCP1, UCHL1  | 11                  |
| Cell-to-cell signaling and interaction                                      | Binding of lymphoma cell lines                                                                   | $1.31 \times 10^{-5}$ | $-0.881$         | ANXA2, CD44, FN1, ITGB1, NCL, RHOA, TFRC                                  | 7                   |
| Organismal injury and abnormalities, renal and urological disease          | Nephrosis                                                                                         | $1.35 \times 10^{-5}$ |                 | ACTN4, ANXA1, ARHGDIA, CLTC, FKBP1A, IMPDH2, ITGB1, LAMB1, PDLIM1         | 9                   |
| Cancer, gastrointestinal disease, respiratory disease                       | CDKN2A positive oropharyngeal squamous cell carcinoma                                              | $1.35 \times 10^{-5}$ |                 | HSP90AA1, HSP90AB1, HSP90B1                                              | 3                   |
| Cancer, respiratory disease                                                | Advanced stage primary laryngeal cancer                                                            | $1.35 \times 10^{-5}$ |                 | HSP90AA1, HSP90AB1, HSP90B1                                              | 3                   |
| Gene expression                                                            | Binding of Y box                                                                                   | $1.35 \times 10^{-5}$ |                 | APEX1, YBX1, YBX3                                                        | 3                   |
| Connective tissue disorders, developmental disorder, hereditary disorder, metabolic disease, skeletal and muscular disorders | Familial Paget’s disease of bone                                                                    | $1.35 \times 10^{-5}$ |                 | HNRNPA1, HNRNPA2B1, VCP                                                  | 3                   |
| Cellular movement                                                          | Initiation of migration of fibrosarcoma cell lines                                                | $1.35 \times 10^{-5}$ |                 | FLNA, FLNB, FLNC                                                         | 3                   |
| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|---------|-------------------|-----------|--------------------|
| Cancer, organismal injury and abnormalities, reproductive system disease | Locally advanced cervical cancer | $1.35 \times 10^{-5}$ | HSP90AA1, HSP90AB1, HSP90B1 | 3 |
| Cancer, immunological disease, organismal injury and abnormalities, reproductive system disease | Node positive cervical cancer | $1.35 \times 10^{-5}$ | HSP90AA1, HSP90AB1, HSP90B1 | 3 |
| Cell morphology, cellular assembly and organization, cellular development, cellular growth and proliferation, nervous system development and function, tissue development | Outgrowth of neurites | $1.36 \times 10^{-5}$ | −1.232 | APEX1, BASP1, CDK1, DNM1L, DPYSL2, EZR, FKBPD4, FN1, HMGBl, IQGAP1, ITGB1, LGALS1, MAP1B, MAPK1, MARCKS, MYH10, MYH9, Pdia3, RAB11A, RhoA, RTN4, SLc25A5, SNX3, SODI, SPTBN1, TNC, VAPA, VIM, YWHAZ | 29 |
| Cancer, tumor morphology | Invasion of malignant tumor | $1.38 \times 10^{-5}$ | −2.111 | AHCY, BSG, CAPN2, CD44, CTSB, CTTN, EZR, FASN, HMGBl, HNRNPA1, HSPA5, ITGB1, LGALS1, MAPK1, VIM | 15 |
| Cellular assembly and organization, cellular function and maintenance | Quantity of cellular protrusions | $1.38 \times 10^{-5}$ | 0.905 | ACTG1, ACTR2, ARPC2, BSG, CANX, CAPZB, CTTN, ENAHz, EZR, FN1, MAP1B, MSN, SODI, T1N1, TPM3 | 15 |
| Cell cycle | Interphase | $1.57 \times 10^{-5}$ | 0.828 | ANXA2, CAPNS1, CAV1, CD44, CDK1, CSE1L, CYR61, DDX3X, FASN, FKBPD4, FLNA, FN1, GNB2L1, GPI, ITGB1, LGALS1, LMNA, MAPK1, MCM7, NASS1, NPM1, PCNA, PDCD6, PEAI5, PPIACA, PRKDC, PTGES3, RHOA, RL120, RPL5, RPL7A, SNF, SPTAN1, STAT1, TCP1, TFCR, TMPO, XRCC5, YWHAG, YWHAX | 40 |
| Cell morphology, cellular function and maintenance | Repair of cells | $1.62 \times 10^{-5}$ | 0.131 | APEX1, KPN2, NPM1, OTUB1, PCNA, PRKDC, UE2N, XRCC5, XrCC6, YBX1 | 10 |
| Protein synthesis | Oligomerization of protein | $1.63 \times 10^{-5}$ | | ACAT1, AHNK, ANXA5, ANXA6, CAV1, CTNNB1, CUX1, EEF1A1, EHD1, LONP1, NPM1, PRKCSH, SEPT7, SEPT9, SQSTM1, STOML2, TRIM28, VCP, YWHAB | 19 |
| Cellular movement | Migration of pericytes | $1.68 \times 10^{-5}$ | −0.600 | CD44, FN1, GNB2L1, HMGBl, LGALS1, MYH10 | 6 |
| Cellular development, nervous system development and function, tissue development | Development of neurons | $1.85 \times 10^{-5}$ | −0.428 | ACTR3, BASP1, CAPN1, CAPRIN1, CAPZB, CAV1, CD44, CSR1P1, CYR61, DBN1, DNM1L, DPYSL2, EHD1, ENAH, EZR, GDI1, HMGBl, HNRNPK, HSPBI, ITGB1, LAMB1, MAP1B, MSN, MYH10, NNMT, Pdia3, Pfn1, PHGDH, PICALM, PPI2CA, PRKCSH, RAB11A, RHOA, RTN4, SEPT2, SOD1, SPTBN1, STIP1, STMN1, TNC, UCHL1, VAPA, VIM, YWHAG, YWHAX | 45 |
### Table 5. Cont.

| Categories                                           | Diseases or Functions Annotation                                                                 | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------|------------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Hereditary disorder, neurological disease, organismal injury and abnormalities, skeletal and muscular disorders | Autosomal dominant Charcot-Marie-Tooth disease type 2                                             | $1.88 \times 10^{-5}$ |                    | AARS, DYNC1H1, GARS, HSPB1, RAB7A                                         | 5                   |
| Cell morphology, hair and skin development and function | Cell spreading of epithelial cell lines                                                          | $1.88 \times 10^{-5}$ | $-1.446$          | CYR61, FLNA, FN1, ITGB1, VIM                                              | 5                   |
| Cell morphology, cellular function and maintenance, DNA replication, recombination, and repair | Double-stranded DNA break repair of cells                                                         | $1.91 \times 10^{-5}$ | 0.131              | KPNA2, NPM1, OTUB1, PCNA, PRKDC, UBE2N, XRCC5, XRCC6                     | 8                   |
| Cell death and survival                              | Apoptosis of central nervous system cells                                                         | $1.76 \times 10^{-5}$ | $-0.963$          | CAPN1, CAST, CDK1, DNM1L, GAPDH, HSP90AA1, HSPA5, MAP1B, NPM1, P4HB, PEA15, RHOA, RPS3, SODI, YWHAB | 15                  |
| Cell cycle                                           | Arrest in G1 phase                                                                               | $1.97 \times 10^{-5}$ |                    | CYR61, FASN, FBKB1A, FN1, ITGB1, LGALS1, LMNA, MAPK1, MCM7, PPP1CA, PRKDC, PTGES3, RHOA, RPL23, RPL5, RPL7A, SPTAN1, TFRC, TMPO, YWHAG | 20                  |
| Cellular function and maintenance                    | Cellular homeostasis                                                                             | $1.98 \times 10^{-5}$ | 0.822              | AKR1B1, ALDOA, ANXA1, ANXA2, ANXA6, ARF1, ATP1A1, B2M, BSG, CALR, CAPN1, CAPNS1, CAST, CAV1, CLIC1, CLIC4, CLTC, CTTN, CYR61, DNM1L, EEF1D, EIF2S1, EIF4G1, FBKB1A, FN1, GP1, H2AFY, HADH, HEXB, HMGBI, HRNRPL, HSP90A1A1, HSP90B1, HSPA4, HSPA5, HSPB1, HSPDI, IGF2R, JIMM1, ITGB1, KIF5B, KRT18, KRT8, LDHA, LGALS1, LONP1, MAPK1, PAFAH1B2, PARK7, PCM1, PHB2, PICALM, PPIA, PPP1CA, PPP2CA, PRDX2, PRKDC, PSMD2, PYGL, RAB11A, RAB7A, RPL22, SEPT9, SERPINH1, SLC25A6, SOD1, SQSTM1, STAT1, STOML2, TFRC, TUFM, UBE2N, VCP, VDAC1, XRCC3, XRCC6, YWHAE | 77                  |
| Tissue development                                   | Growth of connective tissue                                                                      | $2.07 \times 10^{-5}$ | 0.381              | ANXA2, ATIC, CAPNS1, CAV1, CD44, CLIC, CTGB, CYR61, DX5, DNM1L, FN1, GNAI2, GP1, GSTP1, HDGF, HRNRIPA281, HSPB1, ITGB1, KHDRBS1, LGALS1, LMNA, LMNB1, MAPK1, MYH10, MYH9, NPM1, PA2G4, PGK1, PRDX4, PRKDC, PTGES3, RBM3, RHOA, SERPINH1, SFN, STAT1, STOM1, TPM3, VCL, YBX1 | 40                  |
| Post-translational modification, protein folding     | Folding maturation of protein                                                                     | $2.09 \times 10^{-5}$ |                    | AIP, CALR, FBKB1A, PRDX4                                                  | 4                   |
| Cellular movement                                    | Invasion of breast cancer cell lines                                                              | $2.24 \times 10^{-5}$ | 0.051              | BSG, CALR, CAV1, CD44, CSE1L, CTGB, CTTN, ENAH, EZR, FN1, HSP90A1A1, ILF3, IQGAPI, KRT8, MAPK1, PTGES3, RHOA, SEPT9, STOM1 | 19                  |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation | p-Value            | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|----------------------------------|--------------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cellular function and maintenance, inflammatory response                  | Phagocytosis                     | $2.34 \times 10^{-5}$ | $-0.334$           | ANXA1, ANXA5, CALR, CAPG, CAV1, CD44, CLIC4, CLTC, CORO1C, EHD1, GNB2L1, HMGB1, ITGB1, MAPK1, MSN, MYH9, NPM1, PFN1, RAB7A, RHOA, SNX3, VIM | 22                  |
| Cellular development, cellular growth and proliferation, connective tissue development and function, tissue development | Proliferation of fibroblasts    | $2.34 \times 10^{-5}$ | 0.428              | ANXA2, CAV1, CD44, DD5X, DNM1L, FN1, GPl, GSTP1, HDGF, HSPB1, ITGB1, LMNA, LMNB1, MAPK1, NPM1, PA2G4, PGK1, PRDX4, PRKDC, PTGES3, RBM3, RHOA, STAT1, VCL, YBX1 | 25                  |
| Protein trafficking                                                       | Targeting of protein             | $2.35 \times 10^{-5}$ |                    | AIP, CALR, CSE1L, EIF5A, HSPA9, RAB7A, RAN, XPO1, YWHAQ, YWHAE, YWHAG, YWHAQ, YWHAZ | 13                  |
| Hematological system development and function, tissue development         | Aggregation of blood cells       | $2.36 \times 10^{-5}$ | $-1.292$           | ACTG1, AKR1B1, CAPN1, CAST, CD44, CLIC1, CRSPl, FLNA, GNA12, HSPB1, ITGB1, LGALS1, MAPK1, MYH9, MYL12A, P4HB, PDIR3, TLN1, VCL | 19                  |
| Cellular movement, connective tissue development and function             | Cell movement of fibroblast Cell lines | $2.39 \times 10^{-5}$ | $-0.697$           | ACTR2, ACTR3, ARPC2, CD44, CLIC4, CTNN, DDX3X, EHD1, FN1, GPl, HMGB1, ITGB1, MAPRE1, NPM1, RHOA | 15                  |
| Cellular development, tissue development                                   | Differentiation of bone cells    | $2.43 \times 10^{-5}$ | $-1.093$           | ALYREF, ATP5B, CAPNS1, CLIC1, CLTC, CYR61, DDX3, DHX9, FASN, FN1, GLO1, GNB2L1, H3F3A/H3F3B, HNRNPu, IARS, MAPK1, RPS11, RPS15, RRBP1, SND1, SQSTM1, STAT1, STMM1, SYNGR1, TFCR, TNI, TPRM, VIM | 28                  |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | Lymphocytic cancer              | $2.48 \times 10^{-5}$ | 1.450              | ANXA1, ATIC, B2M, CD44, CSE1L, CYR61, FKBP1A, FN1, HST1H1C, HMGB1, IQGAP1, LGALS1, LONP1, NMMT, NPM1, PRDX1, PRKDC, PSMB1, PSMD2, RHOA, RPS2, SF3B1, SHMT2, SPTBN1, STMN1, TUBB, TUBB4B, TUBB6, TUBB8, TLN1A, UQCR1C, XPO1, XRCC5, XRCC6, YWHAZ | 35                  |
| Cancer, cellular development, cellular growth and proliferation, tumor morphology | Proliferation of cancer cells    | $2.63 \times 10^{-5}$ | $-1.887$           | AHCY, AKR1B1, BSG, CACYBP, CAV1, CD44, CTSB, CYR61, EEF1A1, EZR, FASN, HDGF, HMGB1, LDAH, LGALS1, MAPK1, NPM1, PPP2CA, RHOA, RPS4X, S100A6, SQSTM1, STAT1, STMM1, TLN1A, XRCC5 | 26                  |
| Cell-to-cell signaling and interaction                                      | Fusion of cells                  | $2.74 \times 10^{-5}$ | 1.580              | ANXA1, ANXA5, CAPN2, CAV1, CD44, CTSP, FLNC, LGALS1, MAPK1, MYH9, RHOA, SOD1, STAT1 | 13                  |
| Cell morphology, cellular assembly and organization, cellular development, cellular function and maintenance, nervous system development and function, tissue development | Branching of neurons            | $2.75 \times 10^{-5}$ | $-0.900$           | ACTR3, BASPI, CAPNS1, CAPZB, CAV1, CRSPl, CYR61, DBN1, DNM11, DPYSI2, EZR, HMGB1, HNRNPK, ITGB1, MAP1B, NNT, PDLA3, PFN1, RHOA, RTN4, SOD1 | 21                  |
## Table 5. Cont.

| Categories                                      | Diseases or Functions Annotation                                                                 | p-Value     | Activation z-Score | Molecules                                                                                       | Number of Molecules |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------|--------------------|-------------------------------------------------------------------------------------------------|---------------------|
| Cell morphology                                 | Cell spreading of tumor Cell lines                                                              | $2.96 \times 10^{-5}$ | $-1.711$          | CAP1, CAPN2, FLNA, FLNB, FN1, ITGB1, MARCKS, PFN1, RHOA, TNC, UCHL1                          | 11                  |
| Dermatological diseases and conditions, inflammatory disease | Lichen planus                                                                                   | $2.96 \times 10^{-5}$ |                   | B2M, CFL1, EEF1A1, EIF5A, ENO1, FKBPA1, HLA-A, HLA-B, IFITM3, PFN1, PSME2                      | 11                  |
| Cellular assembly and organization, cellular function and maintenance | Formation of vesicles                                                                          | $3.07 \times 10^{-5}$ | $0.707$           | ANXA2, ANXA5, ARF1, CAST, CLTC, FLNA, IQGAP1, MARCKS, PICALM, RAB11A, RHOA, SNX3              | 12                  |
| Immunological disease                           | Systemic autoimmune syndrome                                                                   | $3.10 \times 10^{-5}$ |                   | ACTN4, ACTR3, CAPNS1, CSRP1, CYR61, EEF1A1, ENAH, EZR, FN1, IQGAP1, ITGB1, MAP1B, MARCKS, RHOA, TNC | 15                  |
| Cell morphology, cellular assembly and organization, cellular function and maintenance | Formation of filopodia                                                                         | $3.11 \times 10^{-5}$ | $-2.546$          | ACTN1, CAPN1, CAV1, CTTN, EHD1, EZR, FN1, GNA12, GB2L1, ITGB1, RHOA, STN1, VCL, VIM           | 14                  |
| Cell-to-cell signaling and interaction, cellular assembly and organization, cellular function and maintenance, tissue development | Formation of focal adhesions                                                                  | $3.12 \times 10^{-5}$ | $-2.245$          | ACTN1, CAPN1, CAV1, CTTN, EHD1, EZR, FN1, GNA12, GB2L1, ITGB1, RHOA, STN1, VCL, VIM           | 14                  |
| Cellular growth and proliferation, tissue development | Proliferation of connective tissue cells                                                       | $3.14 \times 10^{-5}$ | $0.548$           | ANXA2, ATIC, CAPNS1, CAV1, CD44, CLTC, CTSB, CYR61, DDX5, DNM1L, FN1, GNA12, GIL, GSTP1, HSF3BP, ITGB1, KHDRBS1, LGS1, LMNA, LMB1, MAPK1, NPM1, PA2G4, PGK1, PRDX4, PRKDC, PTGES3, RBM3, RHOA, SERPINH1, SFN, STAT1, STN1, TFM3, VCL, YBX1 | 37                  |
| Hematological disease, immunological disease    | Eosinophilia                                                                                    | $3.45 \times 10^{-5}$ |                   | ALDOA, ENO1, GAPDH, HLA-A, HLA-B, HSP5A5, MYH9, P4HB, PDI3, PRDX1, TKT, TP1, TUBB             | 13                  |
| Cellular assembly and organization, cellular function and maintenance | Organization of actin filaments                                                                | $3.56 \times 10^{-5}$ | $-1.633$          | ALDOA, CFL1, DBN1, DypsL2, ENAH, FLNA, FN1, ITGB1, MSN, PLS3, RHOA                           | 11                  |
| Cancer                                           | Benign neoplasia                                                                                 | $3.63 \times 10^{-5}$ | $1.591$           | AICAT1, AIP, ALDOA, ALDOC, ANXA1, ANXA2, ANXA5, CALR, CD44, CTSB, CYR61, DBN1, DDX5, DDX6, FKBPA1, GSTP1, HINT1, HSDB7B10, HSP90AB1, IFITM3, IQGAP1, KPN1A3, LGS1, MAPK1, MDH1, MYH10, NPEP9S, PARK7, PCNA, PEA15, PRDX1, PRDX2, PRDX5, RPL27, RPS15, SF3A1, SP1B1N, TCF1, VCP, ZYX | 41                  |
| Categories                                                                 | Diseases or Functions Annotation          | p-Value     | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|-------------------------------------------|-------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cancer, gastrointestinal disease                                          | Oral cancer                               | 3.66 × 10⁻⁵ |                   | ANXA1, ATIC, BSG, EZR, FASN, FN1, H3F3A/H3F3B, HSP90AA1, HSP90AB1, HSP90B1, LGALS1, NPM1, PLOD2, RPL10, TAGLN, TNC, TUBB, TUBB4B   | 18                  |
| Cell death and survival                                                  | Cell death of lymphoma Cell lines         | 3.67 × 10⁻⁵ | 1.961             | ANXA2, ARHGDIa, CD59, EZR, GLO1, HNRNP4A1, HSPB1, LGALS1, LMNB1, LONP1, MAPK1, MSN, NCI, RAD23B, RPLP0, YWHAG, YWHAZ     | 17                  |
| Cell cycle, cell morphology, cellular assembly and organization, cellular movement | Elongation of actin filaments             | 3.68 × 10⁻⁵ | −1.969            | ACTN4, CAP1, FN1, PFN1                                                   | 4                   |
| Infectious disease                                                       | Infection by Marburg virus                | 3.68 × 10⁻⁵ | −0.000            | HSPA5, RPL18, RPL3, RPL5                                                  | 4                   |
| Carbohydrate metabolism, nucleic acid metabolism                         | Pentose shunt of monosaccharide          | 3.68 × 10⁻⁵ |                   | G6PD, PGD, TALDO1, TKT                                                   | 4                   |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | Non-Hodgkin’s disease                      | 3.72 × 10⁻⁵ |                   | ANXA1, ATIC, B2M, CSE1L, CYR61, FKBP1A, FN1, HIST1H1C, HMGB1, IQGAP1, LONP1, NNMT, PRDX1, PRKDC, PSMB1, PSMD2, RHOA, RPS2, SF3B1, SHMT2, STMN1, TUBB, TUBB4B, TUBB6, TUBB8, TNLNA, UQRC2C1, XPO1, XRCC5, YWHAZ | 30                  |
| Organismal injury and abnormalities                                       | Nodule                                    | 3.73 × 10⁻⁵ |                   | ANXA5, CALR, CTSB, GSTP1, HMGB1, HSP90AB1, PARK7, PRDX2, PRDX5            | 9                   |
| Cell death and survival                                                  | Cell death of cortical neurons            | 3.77 × 10⁻⁵ | 0.671             | CAPN1, CAPNS1, CAST, CDK1, FUS, GAPDH1, HMGB1, HSPA5, HSPB1, HSPD1, MAP1B, PARK7, PEA15, TCP1, YWHA8                      | 15                  |
| Cell morphology, connective tissue development and function              | Morphology of fibroblast cell lines       | 3.85 × 10⁻⁵ |                   | CAV1, CTTN, DMPY30, FN1, KRT18, KRT8, MARCKS, PTBP1, RHOA, RTN4           | 10                  |
| Infectious disease                                                       | Replication of flaviviridae               | 3.85 × 10⁻⁵ | −0.905            | DDX3X, DDX6, DNAJ4, FASN, G3BP1, HMGB1, IFITM3, MVP, PPIA, YBX1           | 10                  |
| Cell death and survival                                                  | Cell viability of neuroblastoma cell lines| 3.96 × 10⁻⁵ | 0.537             | APEX1, HSP90AB1, HSPB1, P4Hb, S100A6, SOD1, SQSTM1, VCP                 | 8                   |
| Cellular compromise                                                      | Stress response of cells                  | 4.00 × 10⁻⁵ | 0.174             | CALR, CTB, DNAJ4, HNRNP4A1, HSD17B10, HSP90B1, HSPA5, PRDX1, SLC38A2, SOD1, SQSTM1, VCP, YBX1 | 13                  |
| Cancer, respiratory disease                                              | Laryngeal tumor                           | 4.00 × 10⁻⁵ |                   | ANXA1, CD44, HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                  | 7                   |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|----------------------------------|------------------|-------------------|---------------------------------------------------------------------------|--------------------|
| DNA replication, recombination, and repair                                | DNA damage                       | 4.01 × 10⁻⁵      | 1.228             | CALR, FN1, G6PD, GNA12, GSTP1, HSPB1, LONP1, NPM1, PARK7, PDIA3, PRDX1,  | 16                 |
|                                                                           |                                  |                  |                   | PRKDC, SOD1, SQSTM1, XRCC5, YWHAE                                          |                    |
| Cellular development, cellular growth and proliferation, nervous system   | Proliferation of neuronal cells   | 4.31 × 10⁻⁵      | -1.654            | APEX1, B2M, BASP1, CA3, CDK1, CML1, CSRP1, CTNNA1, DNMT1, DPYSL2, EZR,  | 36                 |
| development and function, tissue development                              |                                  |                  |                   | FKBP4, FN1, HMG1, IQGAP1, ITGB1, LGALS1, MAP1B, MAPK1, MARCK5, MYH10,    |                    |
|                                                                           |                                  |                  |                   | MYH9, PDIA3, RAB11A, RHOA, RTN4, SEPT9, SLC25A5, SNX3, SOD1, SPTBN1,    |                    |
|                                                                           |                                  |                  |                   | TNC, VAPA, VCL, VIM, YWHAZ                                                 |                    |
| Cellular movement                                                         | Cell movement of hepatic stellate cells | 4.34 × 10⁻⁵     | -0.600            | CD44, GNB2L1, HMG1, LGALS1, MAPK1, MYH10                                   | 6                  |
| Cancer, respiratory disease                                               | Laryngeal squamous Cell carcinoma | 4.34 × 10⁻⁵      |                   | CD44, HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                            | 6                  |
| Cellular movement                                                         | Migration of bone cancer cell     | 4.34 × 10⁻⁵      | -1.091            | ACTN4, CAPN2, CA3, FN1, STN1, VCP                                          | 6                  |
|                                                                          | lines                             |                  |                   |                                                                          |                    |
| Cell morphology                                                           | Shape change of epithelial cell   | 4.34 × 10⁻⁵      | -1.000            | CYR61, FLNA, FN1, ITG1, MAPK1, VIM                                         | 6                  |
| Molecular transport, protein trafficking                                  | Nuclear transport of protein      | 4.54 × 10⁻⁵      |                   | CALR, CSE1L, EIF5A, HSPA9, KPNB1, RAN, TNPO1, XPO1                       | 8                  |
| Cancer                                                                    | Growth of malignant tumor         | 4.65 × 10⁻⁵      | -1.175            | AHCY, AKR1B1, BSG, CACYP, CA3, CD4, CTSB, CYR61, EEF1A1, EZR, FASN, GNB2L1,  | 29                 |
|                                                                          |                                   |                  |                   | HDGF, HMG1, LDHA, LGALS1, MAPK1, NPM1, PKM, PIP2CA, RHOA, RPS4X, S100A6,  |                    |
|                                                                          |                                   |                  |                   | SQSTM1, STAT1, STN1, TNC, TXLNA, XRCC5                                    |                    |
| Cell morphology, cellular assembly and organization, cellular development,| Branching of neurites             | 4.69 × 10⁻⁵      | -0.668            | ACTN4, CAPNS1, CAPZB, CA3, CSRP1, CYR61, DBN1, DNMT1, DPYSL2, EZR, HMG1,  | 20                 |
| cellular function and maintenance, embryonic development, nervous system  |                                   |                  |                   | HNRNPK, ITGB1, MAP1B, NNMT, PDIA3, PFN1, RHOA, RTN4, SOD1                |                    |
| development and function, tissue development                              |                                   |                  |                   |                                                                          |                    |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation                        | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|----------------------------------------------------------|---------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cell-to-cell signaling and interaction, cellular function and maintenance, inflammatory response | Phagocytosis of cells                                    | $4.69 \times 10^{-5}$ | $-0.618$          | ANXA1, ANXA5, CALR, CAPG, CAV1, CD44, CLIC4, CLTC, CORO1C, EHD1, GNB2L1, HMBG1, ITGB1, MAPK1, MYH9, NPM1, PFK1, RHOA, SNX3, VIM | 20                  |
| Cell-to-cell signaling and interaction                                    | Binding of stem cells                                    | $5.32 \times 10^{-5}$ |                  | C1QBP, ITGB1, TLN1                                                         | 3                   |
| Tissue morphology                                                          | Collapse of epithelial tissue                            | $5.32 \times 10^{-5}$ |                  | KRT18, KRT8, RHOA                                                          | 3                   |
| Cell-to-cell signaling and interaction, tissue development                 | Growth of focal adhesions                                 | $5.32 \times 10^{-5}$ |                  | FLNA, FLNB, VIM                                                            | 3                   |
| Molecular transport, protein trafficking                                   | Import of green fluorescent protein                       | $5.32 \times 10^{-5}$ |                  | KPNA2, KPNB1, RAN                                                          | 3                   |
| Cell-to-cell signaling and interaction, hair and skin development and function | Binding of epithelial cell lines                         | $5.36 \times 10^{-5}$ | $-0.294$          | ANXA2, ANXA5, CAV1, ITGB1, PPP2CA, PRMT5                                  | 6                   |
| Cancer, gastrointestinal disease, respiratory disease                      | Oropharyngeal tumor                                       | $5.36 \times 10^{-5}$ |                  | HSP90AA1, HSP90AB1, HSP90B1, PCNA, TUBB, TUBB4B                              | 6                   |
| Protein degradation, protein synthesis                                     | Catabolism of protein                                     | $5.52 \times 10^{-5}$ | $0.237$           | CALR, CANX, CAPN1, CAPN2, CAPNS1, CAST, CAV1, COPG1, CSTB, CTSB, FLNA, GAPDH, HSP90B1, HSPA5, HSPD1, IPO9, ITGB1, LONP1, MYH9, NACA, NPEPPS, PARK7, PDIA3, PPP2CA, PSMD4, PSMD2, SNX3, SOD1, SQSTM1, TPP1, UBE2L3, UBE2N, UBXN4, UCHL1, VCP, XPO1 | 36                  |
| Cell cycle                                                                 | Arrest in cell cycle progression                          | $5.60 \times 10^{-5}$ |                  | C1QBP, CALR, CAV1, CD44, FASN, FKBPA1A, KHDRBS1, LMNA, MAP4, MAPK1, NPM1, PA2G4, PFCM1, PPM1G, PRMT5, RHOA, SEN, SSRP1, STAT1, TCP1, TNC, XRCC6, YWHAE | 23                  |
| Infectious disease                                                         | Infection by flaviviridae                                 | $5.71 \times 10^{-5}$ | $0.460$           | ACTR2, AP1B1, AP2B1, ARPC1B, CLTC, G3BP1, HMBG1, IFITM3, STAT1, TFRC       | 10                  |
| Cell cycle                                                                 | G1 phase                                                 | $5.92 \times 10^{-5}$ | $-0.221$          | CAPN1, CDK1, CYR61, FASN, FKBPA1A, FN1, GNB2L1, GPI, ITGB1, LGALS1, LMNA, MAPK1, MCM7, NASP, PPP1CA, PRKDC, PTGES3, RHOA, RPL23, RPL5, RPL7A, SPTAN1, TFRC, TMPO, YWHA, YWHAQ | 26                  |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | CD30-positive peripheral t-Cell lymphoma                  | $6.02 \times 10^{-5}$ |                  | TUBB, TUBB4B, TUBB6, TUBB8                                                | 4                   |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation          | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|----------------------------------------------------------------------------|--------------------------------------------|------------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cardiovascular system development and function, organ morphology          | Contraction of left ventricle              | $6.02 \times 10^{-5}$ | 0.849              | CAPNS1, ITGB1, LMNA, RHOA                                                 | 4                   |
| Cellular assembly and organization, cellular function and maintenance      | Formation of caveolae                      | $6.02 \times 10^{-5}$ | $-1.009$           | ANXA6, CAV1, PICALM, PTRF                                                | 4                   |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | Systemic large-cell KI-1 lymphoma         | $6.02 \times 10^{-5}$ |                    | TUBB, TUBB4B, TUBB6, TUBB8                                               | 4                   |
| Cancer, gastrointestinal disease                                           | Stomach tumor                              | $6.30 \times 10^{-5}$ |                    | AKR1B1, ALYREF, ANXA1, CANX, CAV1, CD44, COPB2, CTNNA1, DDX398, FKBPA1, FUS, GSTD1, HDGE, HINT1, HNRNPH1, IGF2R, IPO5, P4HB, PA2G4, RHOA, RPL22, TUBB4B, XRC6 | 23                  |
| Cell morphology, cellular function and maintenance, DNA replication, recombination, and repair | Double-stranded DNA break repair of tumor cell lines | $6.57 \times 10^{-5}$ | 0.878              | KPNA2, NPM1, OTUB1, UBE2N, XRC5, XRC6                                    | 6                   |
| Cancer                                                                     | Head and neck cancer                       | $6.57 \times 10^{-5}$ | 1.756              | ACTN1, ANXA1, ATIC, BSG, CAV1, CD44, CTTN, DDX3X, EZR, FASN, FLNA, FN1, GSTD1, H3F3A/H3F3B, HNRNPK, HSP90A1, HSP90B1, HSP90B2, HSP90B3, LDHA, LGALS1, MARCKS, MCM7, NPM1, PCMI, PKM, PLOD2, PRDX1, PRKDC, PRMT5, RPL10, SET, SF3B1, SEN, SPTBN1, STAT1, TAGLN, TNC, TUBB, TUBB4B, VIM, XRC5, XRC6 | 43                  |
| Cellular assembly and organization, cellular function and maintenance      | Formation of actin cytoskeleton            | 6.71E-05         |                    | CORO1C, ERP29, FLNA, FN1, ITGB1                                           | 5                   |
| Gene expression                                                             | Transcription                              | $7.48 \times 10^{-5}$ | 0.968              | ACTR2, ACTR3, ALYREF, BASP1, BTF3, C14orf166, CIQBP, CALR, CAND1, CAV1, CBX3, CD44, CDK1, CSE1L, CYR61, DDX3X, DDX5, DDX5, ERF1D, ERF2I1, ENO1, FKBPA1, FLNA, FN1, FUBP3, GLO1, GSTD1, H2AFY, HDGE, HEXB, HINT1, H1ST1H1C, HMGBI1, HNRNPA1, HNRNPA2B1, HNRNPK, HSP90A1, IGF2, ILF2, ILF3, IQGAP1, KHDRBS1, KPN2, LGALS1, LMNA, LRPR, MAPK1, MATK, MCM7, NONO, NPM1, OTUB1, PA2G4, PARK7, PCNA, PDLIM1, PEA15, PEBP1, PEBP1, PHD2, PHD3, PICALM, PPP2CA, PRKDC, PRMT5, PTGES3, PTMA, PTFE, RHOA, RPL22, RPL6, SET, SFPRX1, STRP1, STAT5, SUPT16H1, TAGLN2, TEMPO, TRIM25, UBE2L3, VAPA, XPO1, XRC5, XRC6, YBX1, YBX3, YWHAH, YWHAM, YWHAD, YWHAC | 90                  |
| Cell-to-cell signaling and interaction, connective tissue development and function, tissue development | Adhesion of fibroblasts                   | $7.57 \times 10^{-5}$ | $-0.896$           | CD44, FN1, IGF2R, PLEC, TNC, VCL, ZXY                                     | 7                   |
| Categories                                                                 | Diseases or Functions Annotation                                                                 | p-Value       | Activation z-Score | Molecules                                                                                                                                  | Number of Molecules |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Organismal injury and abnormalities, skeletal and muscular disorders      | Neurogenic muscular atrophy                                                                  | 7.57 x 10^-5 |                    | AARS, DYN1C1H1, GARS, HINT1, HSPB1, LMNA, RAB7A                                                                                             | 7                   |
| DNA replication, recombination, and repair                                | DNA replication                                                                                | 7.63 x 10^-5 | -1.248             | CACYBP, CALR, CAV1, CDK1, HMG1, MAPK1, MCM7, NAP1L1, NASP, NCL, NPM1, PC1M, PCNA, PEA15, SET, SSRP1, SUPT16H, TMPO, XRCC5                  | 19                  |
| Molecular transport                                                      | Nuclear export of molecule                                                                     | 8.10 x 10^-5 |                    | ALYREF, CALR, CSE1L, DDX3B, EIF8A, HSPA9, KHDRBS1, RAN, XPO1                                                                               | 9                   |
| Organismal injury and abnormalities, renal and urological disease        | Chronic kidney disease                                                                        | 8.13 x 10^-5 |                    | CDV3, D8, EEF1B2, FDP, FKBP1A, HSF3A/HSF3B, HMG1, HSP90AA1, IMPDH2, MYH9, NPM1, PSMB1, PSMD2, RPL23, RPL7, TUBB, TUBB4B                 | 17                  |
| Cellular movement                                                        | Cell movement of melanoma cell lines                                                           | 8.37 x 10^-5 | -0.364             | ARF1, BSG, CAPN1, FLNA, ITGB1, KHDRBS1, KRT8, MSN, PEBP1, PRDX2, RHOA                                                                       | 11                  |
| Cell death and survival                                                  | Cytolysis                                                                                     | 8.37 x 10^-5 | 0.280              | ALDOA, ANXA1, B2M, CALR, CAV1, CD44, CD59, G6PD, GPI, HLA-A, IMPDH2, KRT18, LGALS1, PRDX1, PRDX2, PSMB2, PTMA, SHBGRL3, STAT1, STMN1   | 20                  |
| Cell morphology, cellular function and maintenance                       | Transmembrane potential                                                                        | 8.37 x 10^-5 | -0.508             | ANXA6, B2M, CLIC1, CLIC4, HSPA4, HSPB1, HSPD1, IMM, KIF5B, LDHA, LGALS1, LONP1, PARK7, PB2, SLC25A6, SODI, STOML2, VCP, VDAC1, YWHAE | 20                  |
| Protein synthesis                                                        | Initiation of translation of protein                                                           | 8.60E-05     |                    | EIF2S1, EIF3B, EIF3C, EIF3I, EIF4G1, EIF4H, HSPB1, RPS3A                                                                                     | 8                   |
| Hematological disease, infectious disease                                | Infection by Zaire ebolavirus                                                                 | 8.77 x 10^-5 | -2.216             | CTSB, HSPA5, RPL18, RPL3, RPL5                                                                                                           | 5                   |
| Cellular assembly and organization                                        | Formation of nucleus                                                                            | 8.78 x 10^-5 | -2.364             | CDK1, FLNA, FN1, GNA12, LMNA, LMNB1, RAN                                                                                                      | 7                   |
| Cellular assembly and organization, cellular function and maintenance, tissue development | Polymerization of microtubules                                                                | 8.78 x 10^-5 | 1.141              | CAPZB, CAV1, FKBP4, MAP1B, MAPRE1, STMN1, TUBB                                                                                              | 7                   |
| Inflammatory response                                                    | Immune response of cells                                                                        | 9.25 x 10^-5 | -1.018             | ANXA1, ANXA5, CALR, CAPG, CAV1, CD44, CD59, CLIC4, CLIC5, CORO1C, CTSB, DNM1L, EHD1, FN1, GNB2L1, HLA-A, HMG1, HSP90AA1, HSPB1, ITGB1, LGALS1, MAPK1,  | 34                  |
| Cell-to-cell signaling and interaction, tissue development               | Adhesion of myeloma cell lines                                                                 | 9.28 x 10^-5 |                    | ANXA2, CD44, FN1, ITGB1                                                                                                                     | 4                   |
Table 5. Cont.

| Categories                                      | Diseases or Functions Annotation                                      | p-Value        | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-------------------------------------------------|------------------------------------------------------------------------|----------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cell morphology, embryonic development           | Cell spreading of embryonic cell lines                                 | $9.28 \times 10^{-5}$ | $-1.067$           | FLNA, FN1, ITGB1, VIM                                                    | 4                   |
| Gene expression                                  | Replication of RNA                                                     | $9.28 \times 10^{-5}$ | 0.152              | G3BP1, NPM1, VAPA, YBX1                                                  | 4                   |
| Cardiovascular system development and function   | Angiogenesis                                                           | $9.48 \times 10^{-5}$ | $-1.134$           | AKR1B1, ANXA2, ARHGDBA, ATP5B, CALR, CAPZB, CAV1, CD44, CLIC4, CTSP, CYR61, FKBP1A, FLNA, FLNB, FN1, GSDP, HADHA, HMG1B, HSP90B1, HSPB1, HSPD1, IGF2R, LDHA, LGALS1, MAPK1, MYH10, MYH9, NCL, PDCD6, PK1, PKM, PLEC, RHOA, RNH1, RPSA, RTN4, SPTBN1, STAT1, TNC, VCL, VIM, WARS, YWHAE, YWHAZ | 44                  |
| Cancer, organismal injury and abnormalities, reproductive system disease | Metastatic cervical cancer                                             | $9.62 \times 10^{-5}$ |                      | ATIC, HSP90AA1, HSP90B1, HSP90B1, TUBB, TUBB4B                             | 6                   |
| Molecular transport, protein trafficking         | Nuclear export of protein                                              | $9.62 \times 10^{-5}$ |                      | CALR, CSE1L, EIF5A, HSPA9, RAN, XPO1                                    | 6                   |
| Cancer, organismal injury and abnormalities, reproductive system disease | Recurrent cervical cancer                                             | $9.62 \times 10^{-5}$ |                      | ATIC, HSP90AA1, HSP90B1, HSP90B1, TUBB, TUBB4B                             | 6                   |
| Cell morphology, renal and urological system development and function | Shape change of kidney Cell lines                                     | $9.70 \times 10^{-5}$ | 0.050              | ANXA2, FLNA, FLNC, FN1, ITGB1, MAPK1, RHOA, VIM                           | 8                   |
| Cellular development, cellular growth and proliferation | Proliferation of lung cancer cell lines                               | $1.00 \times 10^{-4}$ | $-1.422$           | ACLY, ANXA1, ANXA2, CIQBP, CAV1, CYR61, GAPDH, H2AFY, HRNRPA2B1, ITGB1, MAPK1, NASP, PKM, PTBP1, SET, SLC25A6, SOD1, STMN1, TRIM28 | 19                  |
| Cancer                                          | Mucoepidermoid carcinoma                                              | $1.01 \times 10^{-4}$ |                      | ATIC, FN1, HRNRPAK, KRT18, SFN, SLC25A5, TNC                            | 7                   |
| DNA replication, recombination, and repair       | Degradation of DNA                                                    | $1.09 \times 10^{-4}$ | $-0.941$           | APEX1, BSG, CAPN2, CAST, DHX9, ENO1, HRNRPA1, HSD17B10, HSPB1, KRT8, LMNA, NPM1, PPIA, RHOA, SOD1, STAT1 | 16                  |
| Cellular development                            | Branching of cells                                                    | $1.12 \times 10^{-4}$ | $-1.379$           | ACTR3, ANXA2, BASP1, CAPN1, CAPZB, CAV1, CSRPM1, CYR61, DBN1, DNM1, DPYS2, EZR, FN1, HMG1B, HRNRPAK, ITGB1, MAPK1, NNMT, PDLA3, PN1, RHOA, RTN4, SOD1, TNC | 24                  |
| Cell morphology, embryonic development          | Shape change of embryonic cell lines                                   | $1.13 \times 10^{-4}$ | $-0.555$           | FLNA, FN1, ITGB1, MAPK1, VIM                                           | 5                   |
| Categories | Diseases or Functions Annotation                        | p-Value        | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------|---------------------------------------------------------|----------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cardiovascular system development and function, organismal development | Vasculogenesis | $1.15 \times 10^{-4}$ | $-1.808$         | AKR1B1, ANXA2, ARHGDA, ATP5A1, CALR, CAPNS1, CAPZB, CAV1, CD44, CLIC4, CTSL, CYR61, FBX1, FLNA, FN1, GPD1, HADHA, HMGBI, HSP90BI, ICF2R, ITGB1, KRT1, LDHA, LGA1S1, MAPK1, MYH10, PDCD6, PKM, PLEC, PPIA, PRKDC, RAD23B, RHOA, SEPT9, SERPINH1, SODI, SPTBN1, STAT1, TNC, VCL, VIM, WARS, YWHAE, YWHAG, YWHAZ | 45                   |
| Cancer, cellular movement, organismal injury and abnormalities, reproductive system disease, tumor morphology | Invasion of mammary tumor cells | $1.17 \times 10^{-4}$ | $0.156$          | CD44, CTTN, FLNA, FN1, HDLBP, ITGB1, RHOA | 7                   |

Table 5. Cont.
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation                        | p-Value        | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|----------------------------------------------------------|----------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cancer, cellular movement, tumor morphology                               | Invasion of tumor cells                                  | 1.29 × 10⁻⁴    | −1.865            | AHCC, CAPN2, CD44, CTSB, CTNN, EZR, FKBP1A, FLNA, FN1, HDLBP, ITGB1, LGALS1, MAPK1, PARK2, RHOA | 15                  |
| Embryonic development, organ development, organonal development, skeletal and muscular system development and function, tissue development | Formation of muscle                                      | 1.29 × 10⁻⁴    | −0.543            | ACTA1, ACTG1, ACTN4, ANXA1, ANXA5, CALR, CAPN2, CAPZB, CAV1, FKBP1A, FLNB, FLNC, FN1, HMGB1, HS90B1, ITGB1, KRT8, MAPK1, MYH10, MYH9, PLEC, RHOA, STIP1, UCHL1, VCL, VIM | 26                  |
| Cell-to-cell signaling and interaction, embryonic development             | Binding of embryonic cells                               | 1.31 × 10⁻⁴    |                   | C1QB1, ITGB1, TNL1                                                        | 3                   |
| Cell death and survival, connective tissue disorders, developmental disorder, hematological disease, hereditary disorder | Hereditary nonspherocytic hemolytic anemia                | 1.31 × 10⁻⁴    |                   | ALDOA, G6PD, GPI                                                          | 3                   |
| Cell morphology, endocrine system development and function, organ morphology, organonal development | Morphology of thyroid cells                              | 1.31 × 10⁻⁴    |                   | CAV1, CTSB, FN1                                                            | 3                   |
| Cellular assembly and organization, cellular function and maintenance     | Quantity of filopodia-like projection                     | 1.31 × 10⁻⁴    |                   | ACTR2, ARPC2, CAPZB                                                       | 3                   |
| Amino acid metabolism, small molecule biochemistry                        | Synthesis of l-serine                                    | 1.31 × 10⁻⁴    |                   | PHGDH, PKM, SHMT2                                                         | 3                   |
| Cellular assembly and organization, cellular function and maintenance     | Formation of actin filaments                             | 1.34 × 10⁻⁴    | −1.689            | ACTR3, ARF1, ARPC2, CAPN1, CAV1, CD44, CFL1, CTTN, FN1, GNAI2, GPI, ITGB1, MAPK1, NPM1, PPN1, RHOA, TNC, TPM2, TWIF1, TWIF2, ZYX | 21                  |
| Categories                                      | Diseases or Functions Annotation                          | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------------|----------------------------------------------------------|---------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cell cycle, cellular movement                  | Cytokinesis of cervical cancer cell lines                 | $1.34 \times 10^{-4}$ | 0.218             | GNAI2, LMNA, NPM1, RH0A, SEPT7, SEPT9, SSRP1                               | 7                   |
| Cancer, respiratory disease                    | Metastatic non-small-cell lung cancer                    | $1.34 \times 10^{-4}$ |                    | ATIC, EIF4A1, HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                   | 7                   |
| Cell-to-cell signaling and interaction, tissue development | Adhesion of hepatoma cell lines                          | $1.37 \times 10^{-4}$ |                    | BSG, C1QBP, ITGB1, RH0A                                                   | 4                   |
| Cardiovascular system development and function, cell morphology, cell-to-cell signaling and interaction, organ morphology, organismal development, skeletal and muscular system development and function, tissue morphology | Morphology of intercalated disks                      | $1.37 \times 10^{-4}$ |                    | CALR, CAPZB, PLEC, VCL                                                    | 4                   |
| Cellular compromise                            | Stress response of cervical cancer cell lines             | $1.37 \times 10^{-4}$ |                    | CALR, HNRNPA1, HSP90B1, HSPA5                                           | 4                   |
| Cancer                                         | Metastatic occult primary cancer of head and neck        | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                 | 5                   |
| Cancer, connective tissue disorders, respiratory disease, skeletal and muscular disorders | Metastatic squamous cell cancer of the ethmoid sinus    | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                 | 5                   |
| Cancer, respiratory disease                    | Metastatic squamous cell cancer of the glottis           | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                 | 5                   |
| Cancer, gastrointestinal disease               | Metastatic squamous cell cancer of the lip               | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                 | 5                   |
| Categories                                      | Diseases or Functions Annotation                              | p-Value           | Activation z-Score | Molecules                                       | Number of Molecules |
|------------------------------------------------|-------------------------------------------------------------|-------------------|-------------------|------------------------------------------------|---------------------|
| Cancer, respiratory disease                    | Metastatic squamous cell cancer of the maxillary sinus       | $1.43 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B      | 5                   |
| Cancer, gastrointestinal disease, respiratory disease | Metastatic squamous cell cancer of the oropharynx          | $1.43 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B      | 5                   |
| Cancer, respiratory disease                    | Metastatic squamous cell cancer of the supraglottis         | $1.43 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B      | 5                   |
| Cellular movement, connective tissue development and function, hepatic system development and function | Migration of hepatic stellate cells | $1.43 \times 10^{-4}$ | $-0.218$          | CD44, GNB2L1, HMGB1, LGALS1, MYH10             | 5                   |
| Cancer                                          | Recurrent occult primary cancer of head and neck           | $1.43 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B      | 5                   |
| Cancer, connective tissue disorders, respiratory disease, skeletal and muscular disorders | Recurrent squamous cell cancer of the ethmoid sinus | $1.43 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B      | 5                   |
| Cancer, respiratory disease                    | Recurrent squamous cell cancer of the glottis              | $1.43 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B      | 5                   |
| Cancer, gastrointestinal disease               | Recurrent squamous cell cancer of the lip                  | $1.43 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B      | 5                   |
| Cancer, respiratory disease                    | Recurrent squamous cell cancer of the maxillary sinus      | $1.43 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B      | 5                   |
| Categories                                           | Diseases or Functions Annotation                                                                 | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cancer, respiratory disease                          | Recurrent squamous cell cancer of the supraglottis                                             | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Cancer                                               | Unresectable occult primary cancer of head and neck                                             | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Cancer, connective tissue disorders, respiratory disease, skeletal and muscular disorders | Unresectable squamous Cell cancer of the ethmoid sinus                                           | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Cancer, respiratory disease                          | Unresectable squamous Cell cancer of the glottis                                                | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Cancer, gastrointestinal disease, respiratory disease | Unresectable squamous Cell cancer of the hypopharynx                                             | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Cancer, gastrointestinal disease                     | Unresectable squamous Cell cancer of the lip                                                   | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Cancer, respiratory disease                          | Unresectable squamous Cell cancer of the maxillary sinus                                         | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Cancer, gastrointestinal disease, respiratory disease | Unresectable squamous Cell cancer of the oropharynx                                             | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Cancer, respiratory disease                          | Unresectable squamous Cell cancer of the supraglottis                                           | $1.43 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                  | 5                   |
| Categories                                                                 | Diseases or Functions Annotation | p-Value       | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|----------------------------------|---------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cellular movement                                                         | Cell movement of carcinoma Cell lines | $1.48 \times 10^{-4}$ | 0.447             | C1QBP, CAV1, CD44, CTN, CYR61, HNRNPA2B1, ITGB1, LGALS1, STMN1, TAGLN2, VIM, ZYX | 12                  |
| Cellular development, cellular growth and proliferation                  | Proliferation of colon cancer cell lines | $1.48 \times 10^{-4}$ | 1.556             | AHSA1, CACYBP, CALR, CDK1, CSE1L, DDX5, EIF3C, FN1, HSP90AA1, IGF2R, IPO7, NCL, PKM, RHOA, SFN, SFPQ, UBA1, XRCC5 | 18                  |
| Cardiovascular disease, organismal injury and abnormalities               | Dilated cardiomyopathy           | $1.50 \times 10^{-4}$ | -0.192            | CAST, DNM1L, FKBP1A, LMNA, MYH9, PGK1, PPP1CA, SDHA, TLN1, TMPO, TP11, VCL, VDAC1, VDAC2 | 14                  |
| Cardiovascular system development and function, organ morphology, organismal development, skeletal and muscular system development and function, tissue morphology | Morphology of cardiac muscle     | $1.50 \times 10^{-4}$ | -1.953            | CALR, CAPZB, CAV1, FKBP1A, FN1, HADHA, HSP90B1, IGF2R, MAPK1, MYH10, PLEC, SPTBN1, VCL, YWHAE | 14                  |
| Infectious disease                                                        | Infection by dengue virus 2      | $1.53 \times 10^{-4}$ | 0.896             | ACTR2, AP1B1, AP2B1, ARPC1B, CLTC, JFTM3, STAT1                           | 7                   |
| Cell morphology, cellular assembly and organization, cellular function and maintenance | Reorganization of cytoskeleton   | $1.59 \times 10^{-4}$ | -1.953            | ARHGDI1A, CD44, CFL1, DPYSL2, EZR, FLNA, FLNC, FN1, HMGB1, MARCKS, MSN, MYH9, PL53, RHOA, SPTAN1 | 15                  |
| Cell-to-cell signaling and interaction, tissue development                | Cell-cell adhesion of tumor Cell lines | $1.62 \times 10^{-4}$ | 0.128             | C1QBP, ERP2B, GNB2L1, ITGB1, MAPK1, ZYX                                 | 6                   |
| Cellular assembly and organization                                        | Formation of cytoplasmic aggregates | $1.62 \times 10^{-4}$ | -1.131            | CAV1, DDX6, LMNA, RHOA, SOD1, YWHAZ                                      | 6                   |
| Tissue development                                                        | Aggregation of cells             | $1.65 \times 10^{-4}$ | -0.939            | ACTG1, AKR1B1, BSG, CAPN1, CAST, CD44, CLIC1, CSRIP1, FLNA, FN1, GNAI2, HNRNPA2B1, HSPB1, ITGB1, LGALS1, MAPK1, MYH9, MYL12A, P4HB, PDIA3, TLN1, VCL | 22                  |
| Cell death and survival                                                   | Apoptosis of fibroblast Cell lines | $1.65 \times 10^{-4}$ | -0.651            | CAPNS1, CDK1, CLIC4, CYR61, DDX3X, DNM1L, EEF1A1, EEF2S1, EEF3B, EEF3C, EEF3I, EEF6, FN1, FUS, GPI, HSPA5, HSPD1, ITGB1, RHOA, RPL10, STAT1, VIM | 22                  |
### Table 5. Cont.

| Categories                                      | Diseases or Functions Annotation | $p$-Value   | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-------------------------------------------------|----------------------------------|-------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Infectious disease, reproductive system disease | Infection of cervical cancer cell lines | $1.69 \times 10^{-4}$ | $-2.295$          | ARF1, ATP5B, CCT2, COPA, COPB1, COPB2, COPG1, DDX3X, DNAJA2, EIF3I, GML, H3F3A/H3F3B, HNRNPK, HNRNPu, HSPA9, MAP4, PDLA3, PDLA6, PSME2, RAB1B, RANBP1, SPTAN1, SPTBN1, STIP1, TWIF1, UAP1, UQCRCl1, XPO1 | 28                  |
| Cell cycle                                      | Mitosis                          | $1.76 \times 10^{-4}$ | $-1.833$          | BUB3, CAPN2, CCT4, CDK1, CLTC, CSE1L, CYR61, DBI, DHX9, DYNClH1, EIF6, KPNB1, KRT18, MAPK1, MARCKS, MYH10, NUMA1, PEBP1, PPP1CA, PRMT5, PTMA, RAN, RPS24, SEPT9, STAT1, STMN1, TCP1, TNC, TUBB, YWHAE | 30                  |
| Cellular movement                               | Migration of tumor cells         | $1.76 \times 10^{-4}$ | $-0.843$          | ACTN4, AHCY, CAV1, CD44, CDK1, CSE1L, CTSB, CTTN, EZR, FN1, HMGB1, IQGAP1, ITGB1, RHOA, S100A6, TNC, VIM | 17                  |
| Cell morphology, cellular function and maintenance | Autophagy of cells               | $1.77 \times 10^{-4}$ | $0.609$           | CAPN1, CAPNS1, CAST, DNM1L, EIF2S1, EIF4G1, FKBP1A, HMGB1, HSPA5, KRT18, PAFAH1B2, PRKDC, RAB7A, SERPINH1, SOD1, SQSTM1, STAT1, TFEM | 18                  |
| Cardiovascular system development and function, | Development of blood vessel      | $1.78 \times 10^{-4}$ | $-1.788$          | AKR1B1, ANXA2, ARHDIA, ATP5A1, CALR, CAPN51, CAPZB, CAV1, CD44, CLIC4, CTSB, CYR61, FKBP1A, FLNA, FN1, G6PD, HADHA, HMGB1, HSP90B1, HSPB1, IGF2R, ITGB1, KRT1, LDLA, LGALS1, MAPK1, MYH10, PDCD6, PGK1, PKM, PLEC, PPIA, PRKDC, RAD23B, RHOA, RNHI, SEPT9, SERPINH1, SOD1, SPTBN1, STAT1, TNC, VCL, VIM, WARS, YWHAE, YWHAF, YWHAD | 48                  |
| Cardiovascular system development and function, cell morphology | Cell spreading of endothelial cells | $1.79 \times 10^{-4}$ | $-1.000$          | FLNA, FN1, ITGB1, VIM, YWHAZ | 5                  |
| Cell morphology, renal and urological system development and function | Cell spreading of kidney Cell lines | $1.79 \times 10^{-4}$ | $-0.678$          | FLNA, FLNC, FN1, ITGB1, VIM | 5                  |
| Cell death and survival, DNA replication, recombination, and repair | Fragmentation of DNA             | $1.88 \times 10^{-4}$ | $-0.910$          | APEX1, BSG, CAPN2, CAST, ENO1, HSD17B10, HSPB1, KRT8, LMNA, NPM1, PPIA, RHOA, SOD1, STAT1 | 14                  |
| Cancer, gastrointestinal disease, respiratory disease | Nasopharyngeal cancer            | $1.91 \times 10^{-4}$ | $0.068$           | HSP90AA1, HSP90AB1, HSP90B1, SFN, TUBB, TUBB4B | 6                  |
| Energy production, nucleic acid metabolism, small molecule biochemistry | Binding of ATP                   | $1.94 \times 10^{-4}$ | $-0.710$          | MAPK1, PCNA, PTGES3, STIP1 | 4                  |
| Free radical scavenging                         | Modification of hydrogen peroxide | $1.94 \times 10^{-4}$ | $-1.710$          | PRDX1, PRDX2, PRDX5, SOD1 | 4                  |
| Categories                                                                 | Diseases or Functions Annotation                     | p-Value    | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|------------------------------------------------------|------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cell-to-cell signaling and interaction, cellular assembly and organization, tissue development | Turnover of focal adhesions                         | $1.94 \times 10^{-4}$ | $-0.254$          | CAV1, ITGB1, PLEC, VCL                                                    | 4                   |
| Cancer, cell death and survival, tumor morphology                         | Cell death of tumor cells                           | $1.95 \times 10^{-4}$ | 0.142             | ACLY, ANXA1, ANXA2, B2M, BSG, CAV1, CD44, CD59, CDK1, CT5B, CYR61, EIF5C, ENO1, FASN, GNB2L1, HMGB1, HSP90A1, HSP90B1, LGA11, MAPK1, PPP2CA, RHOA, RPS3A, RTN4, SODI | 24                  |
| Cellular function and maintenance, tissue development                      | Organization of muscle cells                         | $1.98 \times 10^{-4}$ |                   | ACTG1, CALR, CAV1, CTNNA1, FN1, ITGB1, KRT8                               | 7                   |
| RNA post-transcriptional modification                                      | Processing of rRNA                                   | $1.98 \times 10^{-4}$ |                   | DDX5, NPM1, RPL5, RPL7, RPS15, RPS24, RPS7                                | 7                   |
| Cancer, gastrointestinal disease                                           | Oral cavity carcinoma                               | $2.06 \times 10^{-4}$ |                   | ATIC, EZR, FASN, FN1, HSP90A1, HSP90B1, HSP90B1, LGA11, NPM1, PLOD2, RPL10, TAGL1, TNC, TUBB, TUBBu | 15                  |
| Inflammatory response                                                      | Inflammation of body cavity                          | $2.07 \times 10^{-4}$ | 0.920             | ACTN4, ALDOA, ANXA1, ANXA5, ARHGDIA, B2M, BSG, CAV1, CD44, CYR61, DDX5, ENO1, FKBP1A, GAPDH, GSTP1, HLA-A, HMGB1, HSP90A1, HSP90B1, LGA11, NPM1, PLOD2, RPL10, TAGL1, TNC, TUBB, TUBBu | 38                  |
| Cancer                                                                     | Malignant solid tumor                                | $2.08 \times 10^{-4}$ | 0.397             | AARS, ACAT1, ACAT2, ACLY, ACTG1, ACTN1, ACTN4, ACTR2, ACTR3, AHHCY, AHNAK, AKR1B1, ALDOA, ALDOC, ANXA1, ANXA2, ANXA5, AP1B1, APEX1, ARF1, ARHGDIA, ARPC2, ATIC, ATP5A1, ATP5B, B2M, BASP1, BSG, C1orf166, C1QBP, CACYBP, CAND1, CAX1, CAP1, CAPG, CAPN1, CAPN2, PRUN1, PRUN2, PRUN3, CAST, CAV1, CBX3, CCT, CCT2, CCT4, CCT5, CCT6A, CCT7, CCT8, CD44, CD59, CDK1, CFL1, CIL1, CLC1, CLTC, CN3, COPA, COPB1, COPB2, COPE, COPI, COPII, COPII, COTL1, CRIP2, CSEF1, CTNNA1, CTPS1, CTSA, CTSP, CTTN, CUTA, CYB5R3, CYC1, CYR61, DB1, DBN1, DDX1, DDX39B, DDX39, DDX3X, DDX5, DDX9, DLAT, DNAJ1, DNAJ2, DNAJ8, DNM1L, DYS1L2, DYN1L1, DYN2L1, ECH51, EIF1A1, EIF1B2,{EIF1D, EIF2, EHD1, EIF2S1, EIF2S2, EIF3B, EIF4C, EIF4F3, EIF4M, EIF4A1, EIF4G1, EIF4H1, ENAR, ENO1, ENO2, EPRS, ESY1, ETFA, EZR, FASN, FDS, FKBP1A, FLNA, FLNB, FLNC, FN1, FUBP3, FUS, G3BP1, G3BP2, GANAB, GARS, GCN1L1, GDH1, GD2, GD2L, GLUD1, GML, GMPS, GNA12, GNB2L1, GPR1, GSP1, H2AFY, H3F3A/H3F3B, HADHA, HARS, HDGF, HDLBP, HEXB, HINT1, HIST1H1C | 383                 |
Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|-----------------------------------|---------|-------------------|-----------|-------------------|
| Cell cycle | M phase of cervical cancer Cell lines | 2.10 × 10^{-4} | 0.218 | GNAI2, LMNA, MCM7, NPM1, RHOA, SEPT7, SEPT9, SRRP1 | 8 |
| Cardiovascular system development and function, organismal development, tissue morphology | Morphology of cardiovascular tissue | 2.11 × 10^{-4} | | ARHGDI1, CALR, CAPZB, CAV1, CD44, CLIC4, FKBP1A, FN1, HADHA, HSP90B1, IGF2R, MAPK1, MYH10, PLEC, SPTBN1, VCL, YWHAE | 17 |
| Cell cycle | Interphase of tumor cell lines | 2.11 × 10^{-4} | 1.067 | ANXA2, CDK1, CSE1L, CYR61, FASN, ITGB1, LGALS1, MCM7, NAP1L1, NAP1L4, NPM1, PDCD6, PTGES, RHOA, RPL23, RPL5, RPL7A, SFN, SPTAN1, STAT1, TCPI, TFRC, YWHAQ, YWHAH, YWHAQ, YWHAQ, YWHAQ | 23 |
| Infectious disease | Replication of retroviridae | 2.19 × 10^{-4} | 0.989 | ANXA5, BTF3, CAV1, DD5, DHX9, IFTM3, PLIN3, PIAA, PRDX1, PRDX2, RAB11A, TMPo | 12 |
| Categories                                      | Diseases or Functions Annotation                        | p-Value   | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------------|--------------------------------------------------------|-----------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cell morphology                                | Sprouting                                              | $2.22 \times 10^{-4}$ | $-1.379$          | ACTR3, ANXA2, BASPI, CAPNS1, CAPZB, CAV1, CSRP1, CYR61, DBN1, DNM1L,      | 24                  |
|                                                |                                                        |           |                   | DPYS1L2, EZR, FN1, HMGB1, HNRNPK, ITGB1, MAP1B, NNMT, PDLA3, PFN1, RHOA, |                      |
|                                                |                                                        |           |                   | RTN4, SOD1, TNC                                                           |                      |
| Connective tissue disorders, developmental disorder, hereditary disorder | Marfan’s syndrome                                      | $2.22 \times 10^{-4}$ |                   | ALDOC, FLNA, MYH10, TAGLN, VCL                                          | 5                   |
| Cancer, gastrointestinal disease, respiratory disease | Metastatic squamous cell cancer of the hypopharynx      | $2.22 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                | 5                   |
| Cellular function and maintenance              | Pinocytosis                                            | $2.22 \times 10^{-4}$ | $-1.000$          | ACTN4, CAV1, EZR, NCL, RHOA                                              | 5                   |
| Cancer, gastrointestinal disease, respiratory disease | Recurrent squamous cell cancer of the hypopharynx      | $2.22 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                | 5                   |
| Cancer, gastrointestinal disease, respiratory disease | Recurrent squamous cell cancer of the oropharynx       | $2.22 \times 10^{-4}$ |                   | HSP90AA1, HSP90AB1, HSP90B1, TUBB, TUBB4B                                | 5                   |
| Embryonic development, tissue morphology       | Morphology of visceral endoderm                        | $2.23 \times 10^{-4}$ |                   | DHX9, ITGB1, MAPK1, MYH9, RAB7A, SERPINH1                                 | 6                   |
| Cellular movement                              | Cell movement of lung cancer cell lines                | $2.26 \times 10^{-4}$ | $0.276$           | C1QBP, CAV1, CD44, FN1, HNRNPA2B1, ITGB1, STMP1, VIM, YBX1, ZYX         | 10                  |
| Cellular movement                              | Migration of cancer cells                              | $2.28 \times 10^{-4}$ | $-0.743$          | AHCY, CAV1, CD44, CDK1, CSE1L, CTSB, EZR, FN1, HMGB1, IQGAP1, ITGB1, RHOA, S100A6, TNC, VIM | 15                  |
| Cell cycle                                     | Arrest in interphase of tumor cell lines               | $2.29 \times 10^{-4}$ |                   | ANXA2, CDK1, CSE1L, CYR61, FASN, ITGB1, LGALS1, PDCD6, PTGES3, RHOA, RPL23, RPL5, RPL7A, SFN, SPTAN1, TCP1, TFRC, YWHAG | 18                  |
| Cellular function and maintenance              | Engulfment of tumor cell lines                         | $2.48 \times 10^{-4}$ | $0.222$           | ANXA1, CAV1, CD44, CLTC, EZR, GNB2L1, ITGB1, NCL, PFN1, RHOA, SFPQ, VIM | 12                  |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|----------------------------------------------------------------------------|-----------------------------------|------------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cell-to-cell signaling and interaction, tissue development                 | Detachment of cells                | $2.52 \times 10^{-4}$ | 0.851              | ANXA1, ANXA5, CAPN2, FLNA, FN1, ITGB1, MAPK1, RHOA, TLN1                  | 9                   |
| Cell morphology, cell-to-Cell signaling and interaction                    | Morphology of intercellular junctions | $2.52 \times 10^{-4}$ |                    | B2M, CALR, CAPRIN1, CAPZB, CAV1, LGALS1, PLEC, VCL, YWHAG               | 9                   |
| Gene expression, protein synthesis                                         | Initiation of translation of mRNA  | $2.53 \times 10^{-4}$ |                    | EIF3B, EIF3C, EIF3I, EIF4G1, EIF4H, HSPB1, RPS3A                          | 7                   |
| Cell-to-cell signaling and interaction, connective tissue development and function, tissue development | Attachment of fibroblast Cell lines | $2.57 \times 10^{-4}$ |                    | FN1, IPO9, ITGB1                                                         | 3                   |
| Cell morphology                                                            | Cell spreading of fibrosarcoma cell lines | $2.57 \times 10^{-4}$ |                    | FLNA, FLNB, ITGB1                                                       | 3                   |
| Organ morphology, skeletal and muscular system development and function     | Contraction of airway smooth muscle | $2.57 \times 10^{-4}$ |                    | CAV1, GNAI2, RHOA                                                       | 3                   |
| Cellular assembly and organization, DNA replication, recombination, and repair | Formation of nuclear envelope      | $2.57 \times 10^{-4}$ |                    | CDK1, LMNA, RAN                                                          | 3                   |
| Carbohydrate metabolism                                                    | Metabolism of fructose-1, 6-diphosphate | $2.57 \times 10^{-4}$ |                    | ALDOA, ALDOC, PFKP                                                      | 3                   |
| Cancer, endocrine system disorders, organismal injury and abnormalities, reproductive system disease | Metastatic ovarian tumor | $2.57 \times 10^{-4}$ |                    | HSP90AA1, HSP90AB1, HSP90B1                                            | 3                   |
| Cellular development, cellular growth and proliferation                     | Outgrowth of breast cancer Cell lines | $2.57 \times 10^{-4}$ |                    | CYR61, FN1, ITGB1                                                       | 3                   |
| Cellular assembly and organization, cellular function and maintenance, protein trafficking | Sequestration of g-actin         | $2.57 \times 10^{-4}$ |                    | PFN1, TWF1, TWF2                                                       | 3                   |
| Categories                                                                 | Diseases or Functions Annotation                              | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|---------------------------------------------------------------------------|---------------------------------------------------------------|------------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cell cycle                                                                | Abnormal cell cycle                                          | $2.58 \times 10^{-4}$ |                   | CAV1, H3F3A/H3F3B, HSPB1, PRDX1, RBM3, STAT1, TMPO, YWHAE                | 8                   |
| Cell death and survival                                                   | Apoptosis of cerebral cortex cells                           | $2.84 \times 10^{-4}$ | 0.080             | CAPN1, CAST, CDK1, HSPA5, MAP1B, P4H8, PEA15, RPS3, SOD1, YWHAB          | 10                  |
| Cell death and survival, renal and urological system development and function | Cell viability of kidney cell lines                          | $2.85 \times 10^{-4}$ | $-0.378$          | ANXA5, CAV1, EZR, HNRNPU, HSP90B1, HYOU1, PPIA, VDAC1                   | 8                   |
| Cell-to-cell signaling and interaction, renal and urological system development and function | Binding of kidney cell lines                                | $2.85 \times 10^{-4}$ | 0.055             | ANXA2, BSG, CAV1, ITGB1, PPP2CA, PRMT5, RPSA                             | 7                   |
| Molecular transport, RNA trafficking                                      | Transport of mRNA                                             | $2.85 \times 10^{-4}$ |                   | ALYREF, DDX39B, EIF5A, FUS, KHDBRS1, U2AF2, XPO1                       | 7                   |
Table 5. Cont.

| Categories | Diseases or Functions Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|----------------------------------|---------|-------------------|-----------|---------------------|
| Gene expression | Transcription of RNA | $2.90 \times 10^{-4}$ | 1.084 | ACTR2, ACTR3, ALYREF, BASP1, BTF3, C14orf166, CIQBP, CALR, CAND1, CAV1, CBX3, CD44, CDK1, CSE1L, CYB61, DDX3X, DDX5, EEF1D, EIF2S1, ENO1, FBXO5, FN1, FUBP3, GLO1, GSTP1, H2AFY, HDGE, HEXB, HINT1, HIST1H1C, HMGB1, HNRPNA1, HNRPNA2B1, HNRPNAK, HSPA8, ILF2, ILF3, IQGAP1, KHDRBS1, KPNNA2, LGALS1, LMNA, LRPPRC, MAPK1, MATR3, MCM7, NONO, NPM1, OTUB1, PA2G4, PARK7, PCNA, PDLIM1, PEA15, PEBP1, PHAS1, PHGDH, PICALM, PPP2CA, PRKDC, PRMT5, PTGES3, PTMA, PTEF, RHOA, RPL6, SET, SF3B1, SOSTM1, SSTR1, STAT1, TMO2, TRIM25, UBE2L3, VAPA, XPO1, XRC5, XRC6, YBX1, YBX3, YWHAB, YWHHA, YWHAD, YWHAE |
| Cancer, endocrine system disorders, respiratory disease | Small cell lung cancer | $2.99 \times 10^{-4}$ | | ENO2, HSP90AA1, HSP90AB1, HSP90B1, HSPD1, PDCD6, TUBB, TUBB4B, YWHAE |
| Cellular development, cellular growth and proliferation, embryonic development, organ development, organismal development, skeletal and muscular system development and function, tissue development | Formation of muscle cells | $3.04 \times 10^{-4}$ | −1.408 | ACTA1, ACTG1, ACTN4, CALR, CAPZB, FLNC, FN1, HMGB1, HSP90B1, ITGB1, KRT8, MYH10, PLEC, UCHL1 |
| Cellular assembly and organization | Quantity of actin filaments | $3.14 \times 10^{-4}$ | −0.570 | CFL1, FN1, GNB2L1, MARCKS, PLEC, RHOA, SPTAN1, TMOD3 |
| DNA replication, recombination, and repair | Repair of DNA | $3.18 \times 10^{-4}$ | −0.335 | APEX1, CDK1, DDX1, FUS, HMGB1, HNRPNA, KPNNA2, NPM1, OTUB1, PCNA, PRKDC, PRPF19, RAD23B, TRIM25, UBE2N, VCP, XRC5, XRC6, YBX1 |
| Cell-to-cell signaling and interaction | Binding of leukemia cell lines | $3.20 \times 10^{-4}$ | 0.415 | ANXA2, ANXA5, CD44, HLA-A, ITGB1, NCL, TNC |
| Molecular transport, RNA trafficking | Export of RNA | $3.20 \times 10^{-4}$ | −1.974 | ALYREF, DDX39B, EIF5A, KHDRBS1, RAN, U2AF2, XPO1 |
| Cancer, hematological disease, immunological disease, organismal injury and abnormalities | Large-cell Ki-1 lymphoma | $3.20 \times 10^{-4}$ | | HMGB1, PSMB1, PSMD2, TUBB, TUBB4B, TUBB6, TUBB8 |
| Cellular assembly and organization, cellular function and maintenance | Organization of microtubules | $3.20 \times 10^{-4}$ | −1.000 | DPYSL2, GAPDH, MAPRE1, NUMA1, PCM1, RRBP1, TUBB |
Table 5. Cont.

| Categories                                                                 | Diseases or Functions Annotation                          | p-Value         | Activation z-Score | Molecules                                                                 | Number of Molecules |
|----------------------------------------------------------------------------|-----------------------------------------------------------|-----------------|-------------------|---------------------------------------------------------------------------|---------------------|
| Cancer, organismal injury and abnormalities, reproductive system disease   | Metastatic breast cancer                                   | $3.25 \times 10^{-4}$ |                   | FDP5, FKBP1A, FLNA, HSP90AA1, HSP90AB1, HSP90B1, STAT1, TUBB, TUBB4B     | 9                   |
| Immunological disease, inflammatory disease, inflammatory response, organismal injury and abnormalities, renal and urological disease | IGA nephropathy                                            | $3.31 \times 10^{-4}$ |                   | ACTN4, IMPDH2, PDLIM1, PSMB1, PSMD2                                       | 5                   |
| Cellular movement, hematological system development and function, immune cell trafficking | Cell rolling of granulocytes                               | $3.47 \times 10^{-4}$ | 0.000             | ANXA1, CD44, CTTN, GNAI2, ITGB1, TLN1                                      | 6                   |
| DNA replication, recombination, and repair                                  | Conformational modification of DNA                         | $3.47 \times 10^{-4}$ |                   | HMGB1, MCM4, MCM6, MCM7, NCL, SSRP1                                      | 6                   |
| Cancer                                                                     | Locally advanced malignant tumor                           | $3.47 \times 10^{-4}$ |                   | ATIC, FKBP1A, HSP90AA1, HSP90AB1, HSP90B1, TUBB4B                         | 6                   |
| Organismal survival                                                         | Viability                                                  | $3.53 \times 10^{-4}$ | $-1.671$          | B2M, GNAI2, MAP1B, PFN1, PRKDC, RAN, TKT, VCL, XRCC3                      | 9                   |
| Cell-to-cell signaling and interaction, skeletal and muscular system development and function, tissue development | Adhesion of smooth muscle cells                            | $3.56 \times 10^{-4}$ |                   | CYR61, FN1, ITGB1, RHOA                                                  | 4                   |
| Cellular assembly and organization, cellular function and maintenance       | Quantity of lamellipodia                                    | $3.56 \times 10^{-4}$ | 0.000             | ACTR2, ARPC2, ENAH, TPM3                                                 | 4                   |
| Cell morphology                                                             | Shape change of leukemia Cell lines                        | $3.56 \times 10^{-4}$ |                   | FN1, ITGB1, MAPK1, TNC                                                   | 4                   |
| Cardiovascular disease, organismal injury and abnormalities                 | Primary cardiomyopathy                                     | $3.58 \times 10^{-4}$ |                   | LMNA, PGK1, SDHA, TPII, VCL, VDAC1, VDAC2                               | 7                   |
Table 5. Cont.

| Categories                                                | Diseases or Functions Annotation | p-Value      | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-----------------------------------------------------------|----------------------------------|--------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cellular growth and proliferation                         | Formation of cells               | $3.63 \times 10^{-4}$ | $-2.209$           | ACTA1, ACTG1, ACTN4, ANXA2, ARHGDIA, B2M, BSG, CALR, CAPZB, CD44, CTTN, DNAJA1, EEF1D, EHDL, ENAH, EZR, FLNA, FLNB, FLNC, FN1, HEXB, HMGB1, HSP90B1, HSPA4, ITGB1, KRT18, KRT8, LGALS1, MAP1K1, MYH10, MYH9, NPEPPS, PAFAH1B2, PEBP1, Plec, PL53, PRDX4, RAD23B, RANBP1, RHOA, RPL22, SFN, SOD1, SQSTM1, STAT1, STIP1, STMN1, TCP1, UCHL1, XRCC6, YBX3 | 51                  |
| Cancer, organismal injury and abnormalities, reproductive system disease | Uterine leiomyoma                | $3.74 \times 10^{-4}$ |                    | ALDOA, CYB61, DDX6, HSD17B10, HSP90AB1, IQGAP1, KPNA3, MDH1, MYH10, NPEPPS, PCNA, RPL27, RPS15, SF3A1, TNC, TWF1, VCP, ZYX | 18                  |
| Cell morphology, cellular assembly and organization, cellular function and maintenance | Reorganization of actin cytoskeleton | $3.78 \times 10^{-4}$ | $-2.219$           | ARHGDIA, CFL1, DPYSL2, EZR, FLNA, FLNC, FN1, MYH9, PLS3, RHoa, SPTAN1      | 11                  |
| Cancer                                                   | Stage 3 cancer                   | $3.78 \times 10^{-4}$ |                    | ATIC, CAV1, CBX3, CCT3, FKBP1A, FN1, KRT8, MAP1K1, PCNA, TUB4B1, TUB86     | 11                  |
| Cancer, tumor morphology                                | Progression of tumor             | $3.83 \times 10^{-4}$ | $-0.342$           | ANXA1, ANXA2, BSG, CAV1, CD44, EZR, FASN, FUS, GSTP1, HMGB1, STAT1, TNC, YWHAZ | 13                  |
Table 6. 187 categories of vancomycin-associated toxicity analyzed using IPA.

| Categories                                | Disease or Function | Annotation                  | p-Value   | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-------------------------------------------|---------------------|------------------------------|-----------|--------------------|---------------------------------------------------------------------------|---------------------|
| Liver hyperplasia/hyperproliferation      |                     | Cholangiocarcinoma           | 7.33 x 10^{-7} | ANXA1, ANXA2, GNB2L1, HSP90AA1, HSP90AB1, PKG1, PKM, RPL4, RPL9, VIM | 10                  |
| Renal damage, renal tubule injury         |                     | Proximal tubular toxicity    | 2.17 x 10^{-6} | ACAT1, FASN, FN1, G6PD, GSTP1, HADH, HADHA, HSP90AA1, HSP90AB1, LGALS1, YBX1, YWHAH | 12                  |
| Nephrrosis                                |                     | Nephrosis                   | 1.35 x 10^{-5} | ACTN4, ANXA1, ARHGDI, CLTC, FKBPIA, IMPDH2, ITGB1, LAMBI, PDLIM1         | 9                   |
| Liver fibrosis                            |                     | Migration of hepatic stellate cells | 1.43 x 10^{-4} | −0.218 | CD44, GNB2L1, HMGB1, LGALS1, MYH10 | 5                   |
| Nephrrosis                                |                     | Minimal change nephrotic syndrome | 2.66 x 10^{-4} | ACTN4, FKBPIA, IMPDH2, PDLIM1 | 4 |
| Renal necrosis/cell death                 |                     | Cell viability of kidney cell lines | 2.85 x 10^{-4} | −0.378 | ANXA5, CAV1, EZR, HNRNP1, HSP90AB1, HYOU1, PPIA, VDAC1 | 8 |
| Renal inflammation, renal nephritis      |                     | IgA nephropathy              | 3.31 x 10^{-4} | ACTN4, IMPDH2, PDLIM1, PSMB1, PSMD2 | 5 |
| Renal inflammation, renal nephritis      |                     | Fechtner syndrome            | 5.69 x 10^{-4} | MYH10, MYH9 | 2 |
| Liver cirrhosis                           |                     | Cryptogenic cirrhosis        | 5.69 x 10^{-4} | KRT18, KRT8 | 2 |
| Renal inflammation, renal nephritis      |                     | Diffuse proliferative lupus nephritis | 5.69 x 10^{-4} | ACTN4, PDLIM1 | 2 |
| Renal inflammation, renal nephritis      |                     | Epstein syndrome             | 5.69 x 10^{-4} | MYH10, MYH9 | 2 |
| Liver cirrhosis                           |                     | Susceptibility to noncryptogenic cirrhosis | 5.69 x 10^{-4} | KRT18, KRT8 | 2 |
| Liver hyperplasia/hyperproliferation      |                     | Liver cancer                 | 1.13 x 10^{-3} | ACLY, ACTC1, ACTR2, ACTR3, AHNAK, ANXA1, ANXA2, AP1B1, APEX1, ARF1, ARHGDI, ARHGDIA, ARHSG, ATIC, ATP5A1, ATP5B, B2M, BSG, CACYBP, CARG, CAST, CBX3, CCT6A, CCT8, CD44, CLIC1, CLIC3, COPS, COPG1, COTI1, CRIP2, CSE1H, CTNNA1, CTPS1, CTSA, CTTN, CUBA, CYR61, DBI, DDX39, DLAT, DNAJ1, DNM1L, DYNCE1H1, EEF1A1, EEF2, EF1A1, ENAH, ENO2, EPRS, FASN, FKBPIA, FLNA, FLNB, FLNC, FN1, GARS, GCNII, GD2, GLUI, GMP5, GNB2L1, GPI, GSTP1, H2AFY, HEP3A/H3F3B, HADHA, HADHB, HDLP1, HEXB, HMGB1, HNRNA1, HNRNA2, HNRNA2B1, HNRNF1, HNRNF2K, HNRPPM, HSP90AA1, HSP90AB1, HSP90AB2, HSPA5, HSPA6, HSPDH1, LARS, IFTM3, IGF2R, ILF2, ILF3, IMPDH2, IP05, IP07, IQGAP1, ITGB1, KHSRP, KIF5B, KPNBI, KRT9, LAMBI, LDHA, LMNA, LOC102724594/U2AF1, LONP1, LRP3P, LRRCC, MAP1B, MAP2K1, MARS, MCM3, MCM4, MCM6, MCM7, MDH1, MIP, MYH10, NACA, NAP1L4, NASP, NMITE, NPEPPS, NPLCG4, NPM1, NUMA1, P4B1, PAG4, PAKCS, PCP2, PDIA4, PKF, PKG1, PKM, PHKC3H, PKM, PLEC, PMM1G, PPI2CA, PPP2R1A, PRDX1, PRKCSH, PRKDC, PSMC1, PSMD2, PTRE, PUF60, PYGL, QARS, RAN, RPL12, RPL4, RPL7A, RPL90, RPN1, RPS2, RPS24, RPS4X, RRBP1, RTN4, SDHA, SF3A1, SF3B1, SFPQ, SFRBIR, SLC38A2, SN1, SOD1, SPTBN1, SQSTM1, STAT1, TIP1, TUBB4B, TWF2, UAPI, UBE2N, UBXN4, UCHL1, VARS, VCL, VCP, VIM, WARS, XIRC6, YB3, YWHAH, YWHAH | 180 |

| Liver hyperplasia/hyperproliferation |                     | Liver cancer                 | 1.13 x 10^{-3} | 1.133 | ACLY, ACTC1, ACTR2, ACTR3, AHNAK, ANXA1, ANXA2, AP1B1, APEX1, ARF1, ARHGDI, ARHGDIA, ATIC, ATP5A1, ATP5B, B2M, BSG, CACYBP, CARG, CAST, CBX3, CCT6A, CCT8, CD44, CLIC1, CLIC3, COPS, COPG1, COTI1, CRIP2, CSE1H, CTNNA1, CTPS1, CTSA, CTTN, CUBA, CYR61, DBI, DDX39, DLAT, DNAJ1, DNM1L, DYNCE1H1, EEF1A1, EEF2, EF1A1, ENAH, ENO2, EPRS, FASN, FKBPIA, FLNA, FLNB, FLNC, FN1, GARS, GCNII, GD2, GLUI, GMP5, GNB2L1, GPI, GSTP1, H2AFY, HEP3A/H3F3B, HADHA, HADHB, HDLP1, HEXB, HMGB1, HNRNA1, HNRNA2, HNRNA2B1, HNRNF1, HNRNF2K, HNRPPM, HSP90AA1, HSP90AB1, HSP90AB2, HSPA5, HSPA6, HSPDH1, LARS, IFTM3, IGF2R, ILF2, ILF3, IMPDH2, IP05, IP07, IQGAP1, ITGB1, KHSRP, KIF5B, KPNBI, KRT9, LAMBI, LDHA, LMNA, LOC102724594/U2AF1, LONP1, LRP3P, LRRCC, MAP1B, MAP2K1, MARS, MCM3, MCM4, MCM6, MCM7, MDH1, MIP, MYH10, NACA, NAP1L4, NASP, NMITE, NPEPPS, NPLCG4, NPM1, NUMA1, P4B1, PAG4, PAKCS, PCP2, PDIA4, PKF, PKG1, PKM, PHKC3H, PKM, PLEC, PMM1G, PPI2CA, PPP2R1A, PRDX1, PRKCSH, PRKDC, PSMC1, PSMD2, PTRE, PUF60, PYGL, QARS, RAN, RPL12, RPL4, RPL7A, RPL90, RPN1, RPS2, RPS24, RPS4X, RRBP1, RTN4, SDHA, SF3A1, SF3B1, SFPQ, SFRBIR, SLC38A2, SN1, SOD1, SPTBN1, SQSTM1, STAT1, TIP1, TUBB4B, TWF2, UAPI, UBE2N, UBXN4, UCHL1, VARS, VCL, VCP, VIM, WARS, XIRC6, YB3, YWHAH, YWHAH | 180 |
| Categories                                   | Disease or Function Annotation                  | p-Value  | Activation z-Score | Molecules                                                                 | Number of Molecules |
|----------------------------------------------|------------------------------------------------|----------|--------------------|----------------------------------------------------------------------------|---------------------|
| Liver hyperplasia/hyperproliferation         | Liver tumor                                    | $1.16 \times 10^{-3}$ | 0.590              | ACYL, ACTG1, ACTR2, ACTR3, AHNAK, ANXA1, ANXA2, API1, APEX1, ARF1, ARHGDA, ATIC, ATP5A1, ATP5B, B2M, BRG, CAC4B, CAF, CAST, CBX3, CCHS, CCHS, CD44, CLC1, CLTC, COPG1, CDTL1, CRIP2, CSEIL, CTNN1A1, CTPSI, CTSA, CTTN, CUTA, CYR61, D8B, DDX3X, DLAT, DNAJ1A1, DNM1L, DYNCH1H1, EEF1A1, EEF2, EIF3, EIF4A1, ENAH, ENO2, EPRS, FASN, FKBP1A, FLNA, FLNB, FLNC, FN1, GARS, GCN11L1, GD2, GLUD1, GMP5, GRN21L1, GPR1, GTP1, H2AFY, H3F3A/H3F3B, HADHA, HDBP, HEXB, HMGBI, HNRNPA1, HNRNP4B1, HNRNP4B2, HNRNP4H, HNRNP4PM, HSP90AA1, HSP90AB1, HSP5, HSP90B, HSPD1, IARS, IFTM3, IGF2R, ILF2, ILF3, IMDPDH2, IPO5, IPO7, IQGAP1, ITGB1, KHSRP, KIF5B, KPNB1, KRT9 | 181                 |
| Liver damage, liver inflammation/hepatitis   | Susceptibility to hepatitis c virus             | $1.6 \times 10^{-3}$ | 0.515              | LAMBI, LDHA, LMNA, LOC10272494/U2AF1, LONP1, LRPPRC, LRRC39, MAP1B, MAPRE1, MARS, MCM3, MCM4, MCM4, MCM7, MDH1, MYP, MYH10, NACA, NAP1L4, NAF, NNM, NPEPS, NPLOC4, NPM1, NUMA1, P4HB, PAX2, PAX4, PACS, PCBP2, PDXA, PFK, PFKP, PKIN, PCK1, PGMI, PHGDH, PKM, PLEC, PMAL1G, PPP2CA, PPP2RA, PRDX1, PRKCSH, PRKDC, PSMB1, PSMB2, PSMB4, Psf60, PYGL, QARS, RAN, RPL12, RPL4, RPL7A, RPLP0, RP11, RP2, RPS2, RPS24, RPS4X, RRBP1, RTN4, S100A6, SDHA, SFA1, SFB1, SFPQ, SIFBGRAYL3, SLC38A2, SMD, SOD1, SODI, SPTBN1, SSTD4, STAT1, TPI1, TUBB4B, TUBF, TUBF, TUBP1, UAPI, UBE2N, UBXN1, UCHL1, VARS, VCL, VCP, VM, WARS, XCC6, YBX3, YWHAG, YWHAG | 2                   |
| Renal necrosis/cell death                    | Cell death of kidney cell lines                | 2.01 $\times 10^{-3}$ | 0.222              | CD44, CDK1, EZR, GAPDH, GSTP1, HSP5, HSPB1, HYOU1, ITGB1, LDHA, PE1A5, PRKDC, SODI, SRRP1, TFC, VCP, VDAC1, YWHAQ | 18                  |
| Cardiac necrosis/cell death                  | Cell death of cardiomyocytes                   | 2.22 $\times 10^{-3}$ | 1.920              | CALR, CYR61, GAPDH, GNAI2, HADHA, HSPB1, HSPD1, MAPK1, NCL, PARK7, RHOA, RPSA, STAT1, ZYX | 14                  |
| Renal necrosis/cell death                    | Cell death of kidney cells                     | 2.29 $\times 10^{-3}$ | 0.515              | ATP1A1, CD44, CDK1, EZR, GAPDH, GSTP1, HSP5, HSPB1, HYOU1, ITGB1, LDHA, PE1A5, PRKDC, SODI, SRRP1, STMP1, TFC, VCP, VDAC1, YWHAQ | 20                  |
| Renal proliferation                          | Proliferation of kidney cell lines             | 4.64 $\times 10^{-3}$ | $-2.423$           | HSP90AA1, HSP90AB1, HSP4, HSPD1, ITGB1, LMNA, NCL, PPP2RA, RHOA, VDAC1, YBX3 | 11                  |
| Cardiac damage, cardiac degeneration         | Degeneration of cardiomyocytes                 | 4.98 $\times 10^{-3}$ | $-2.423$           | CAV1, HADHA, MAPK1 | 3                   |
| Nephrosis                                    | Autosomal recessive steroid-resistant nephrotic syndrome | 5.43 $\times 10^{-3}$ | 0.515              | ARHGDA, IMFPH2 | 2                   |
| Decreased levels of albumin                  | Increased uptake of albumin                    | 5.43 $\times 10^{-3}$ | 0.243              | CAV1, CTSA, EEF1D, FN1, HMCGI1, IGF2R, MAPK1, PPIA, RHOA, S100A6 | 10                  |
| Cardiac hypertrophy                          | Hypertrophy of heart cells                     | 5.90 $\times 10^{-3}$ | $-0.243$           | CAV1, CTSA, EEF1D, FN1, HMCGI1, IGF2R, MAPK1, PPIA, RHOA, S100A6 | 2                   |
| Hepatocellular carcinoma, liver hyperplasia/hyperproliferation | Hepatocellular carcinoma                      | 5.96 $\times 10^{-3}$ | 1.133              | ACTG1, ARF1, B2M, BRG, CAC4B, CAF, CAST, CTNS, FKBP1A, GLUD1, GNB2L1, H2AFY, HMCGI1, HNRNPA1, HSP5, ITIM3, IGF2R, IPO7, IQGAP1, MAPRE1, NNM, PFC, PPH1, PRDXI, SODI, SPTBN1, TPI1, TUBB4B, YWHAG | 27                  |
| Cardiac necrosis/cell death                  | Cell viability of cardiomyocytes               | 6.07 $\times 10^{-3}$ | 0.515              | CALR, HSPDI, IQGAP1, RHOA | 4                   |
| Categories | Disease or Function Annotation | \(p\)-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|--------------------------------|-------------|------------------|-----------|--------------------|
| Liver fibrosis, liver proliferation | Proliferation of hepatic stellate cells | \(6.67 \times 10^{-3}\) | \(-0.847\) | CTSB, ITGB1, LGALS1, SERPINH1, STAT1 | 5 |
| Cardiac arrythmia | Chronic atrial fibrillation | \(8.01 \times 10^{-3}\) | | PPP1CA, PPP2CA | 2 |
| Renal dilation | Dilation of collecting tube | \(8.01 \times 10^{-3}\) | | ARHGDDIA, PRKCSh | 2 |
| Kidney failure | Acute renal failure | \(9.94 \times 10^{-3}\) | | ATP1A1, CYR61, GSTP1, HEXB, STMN1 | 5 |
| Liver damage, liver inflammation/hepatitis | Hepatitis c | \(1.51 \times 10^{-2}\) | | DDX5, FKBP1A, IMPDH2, KRT18, KRT8 | 5 |
| Liver damage | Damage of liver | \(1.67 \times 10^{-2}\) | \(0.513\) | BSG, CD44, CTSB, DDX5, FKBP1A, GSTP1, HLA-B, HMGB1, IMPDH2, KRT18, KRT8, SOD1, STAT1 | 13 |
| Cardiac inflammation | Inflammation of heart | \(1.76 \times 10^{-2}\) | \(0.686\) | B2M, CAV1, HMGB1, PPIA | 4 |
| Glomerular injury | Focal segmental glomerulosclerosis | \(1.89 \times 10^{-2}\) | | ACTN4, MYH9, PDLIM1 | 3 |
| Cardiac dilation | Dilation of left ventricle | \(1.90 \times 10^{-2}\) | \(-1.000\) | CAPNS1, CAV1, LMNA, RHOA | 4 |
| Glomerular injury | Autosomal dominant focal segmental glomerulosclerosis | \(2.39 \times 10^{-2}\) | | ACTN4 | 1 |
| Liver inflammation/hepatitis | Chronic phase hepatitis | \(2.39 \times 10^{-2}\) | | HLA-A | 1 |
| Decreased levels of albumin | Decreased accumulation of albumin | \(2.39 \times 10^{-2}\) | | CAV1 | 1 |
| Renal degeneration | Degeneration of renal tubular epithelial cells | \(2.39 \times 10^{-2}\) | | ARHGDDIA | 1 |
| Cardiac dysplasia | Dysplasia of right ventricle | \(2.39 \times 10^{-2}\) | | RPSA | 1 |
| Cardiac arrythmia, tachycardia | Familial ventricular tachycardia | \(2.39 \times 10^{-2}\) | | GNAI2 | 1 |
| Cardiac fibrosis | Fibrosis of right ventricle | \(2.39 \times 10^{-2}\) | | CTNNA1 | 1 |
| Kidney failure | Gentamicin-induced renal injury | \(2.39 \times 10^{-2}\) | | HEXB | 1 |
| Glomerular injury | Glomerulopathy with fibronectin deposits type 2 | \(2.39 \times 10^{-2}\) | | FN1 | 1 |
| Pulmonary hypertension | Hypertension of pulmonary artery | \(2.39 \times 10^{-2}\) | | CAV1 | 1 |
| Increased levels of albumin | Increased export of albumin | \(2.39 \times 10^{-2}\) | | RAN | 1 |
| Liver failure | Infantile liver failure syndrome type 2 | \(2.39 \times 10^{-2}\) | | MARS | 1 |
Table 6. Cont.

| Categories                                      | Disease or Function Annotation                               | p-Value   | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-------------------------------------------------|-------------------------------------------------------------|-----------|-------------------|---------------------------------------------------------------------------|---------------------|
| Liver hyperplasia/hyperproliferation             | Nodular hyperplasia of liver                                | 2.39 × 10^{-2} | SOD1             |                                                                           | 1                   |
| Pulmonary hypertension                          | Primary pulmonary hypertension 3                            | 2.39 × 10^{-2} | CAV1             |                                                                           | 1                   |
| Cardiac damage                                  | Rupture of ventricular septum                               | 2.39 × 10^{-2} | CTNNA1           |                                                                           | 1                   |
| Bradycardia, cardiac arrhythmia                 | Severe bradycardia                                          | 2.39 × 10^{-2} | RHOA             |                                                                           | 1                   |
| Kidney failure                                  | Failure of kidney                                           | 2.48 × 10^{-2} |                 | ACTN4, ARHGDA, ATP1A1, CYR61, FDPS, FKBPIA, GSTP1, HEXB, IMPDH2, MYH9, STMN1 | 11                  |
| Renal inflammation, renal nephritis             | Autoimmune glomerulonephritis                               | 2.85 × 10^{-2} |                 | ACTN4, PDLIM1, PPP2CA                                                     | 3                   |
| Liver cirrhosis                                 | Cirrhosis                                                  | 3.11 × 10^{-2} |                 | B2M, BSG, FN1, GSTP1, HRNRNK, KRT18, KRT8, PCNA, TXLNA                   | 9                   |
| Liver necrosis/cell death                       | Necrosis of liver                                           | 3.18 × 10^{-2} | 0.791            | CTSB, FKBPIA, FLNA, HMGB1, HSPD1, KRT8, NCL, SERPINH1, SLC25A5, SOD1, SPTBN1, STAT1 | 12                  |
| Cardiac damage                                  | Damage of heart                                            | 3.20 × 10^{-2} | 0.156            | ANXA1, CAV1, CTNNA1, HADHA, MAPK1                                         | 5                   |
| Liver inflammation/hepatitis                    | Inflammation of liver                                       | 3.24 × 10^{-2} | 1.231            | CD44, CYR61, DDX5, FKBPIA, GSTP1, HLA-A, HMGB1, IMPDH2, KRT8, KRT8, PPIA, SOD1, STAT1 | 13                  |
| Renal inflammation, renal nephritis             | Lupus nephritis                                            | 3.28 × 10^{-2} |                 | ACTN4, FKBPIA, IMPDH2, PDLIM1, PSMB1, PSMD2                               | 6                   |
| Cardiac arrhythmia                              | Arrhythmia                                                 | 3.34 × 10^{-2} | -1.103           | ATP1A1, CALR, GNA12, HMGB1, PPI1CA, PPP2CA, RHOA, TUBB, TUBB4B, VCL       | 10                  |
| Liver damage                                    | Injury of liver                                            | 3.41 × 10^{-2} | -0.447           | BSG, CTSB, HLA-B, HMGB1, KRT8, SOD1, STAT1                                | 7                   |
| Hepatocellular carcinoma, liver hyperplasia/hyperproliferation | Incidence of hepatocellular carcinoma | 3.54 × 10^{-2} | 1.718            | IQGAP1, PRDX1, SOD1, SPTBN1                                               | 4                   |
| Glomerular injury, renal hypertrophy            | Hypertrophy of mesangial cells                             | 3.73 × 10^{-2} |                 | MAPK1, PARK7                                                              | 2                   |
| Liver hepatomegaly                              | Hepatomegaly                                               | 4.07 × 10^{-2} |                 | CTSB, HADHA, IGF2R, KRT18, STAT1                                         | 5                   |
| Cardiac hypertrophy                             | Hypertrophy of cardiomyocytes                              | 4.35 × 10^{-2} | -0.243           | CAV1, FN1, HMGB1, IGF2R, MAPK1, PPIA, RHOA                                 | 7                   |
| Cardiac arrhythmia                              | Supraventricular arrhythmia                                | 4.35 × 10^{-2} |                 | ATP1A1, CALR, PPI1CA, PPP2CA, RHOA, TUBB, TUBB4B                          | 7                   |
| Congenital heart anomaly                        | Ventricular septal defect                                  | 4.67 × 10^{-2} | 0.128            | AIP, FKBPIA, FLNA, MYH10, MYH9, YYHAE                                     | 6                   |
| Liver degeneration                              | Degeneration of hepatocytes                                 | 4.72 × 10^{-2} |                 | XRCC5                                                                    | 1                   |
| Increased levels of potassium                  | Increased efflux of k+                                      | 4.72 × 10^{-2} |                 | MAPK1                                                                    | 1                   |
| Liver fibrosis, liver proliferation             | Proliferation of hepatic stellate cells/myofibroblasts      | 4.72 × 10^{-2} |                 | CTSB                                                                     | 1                   |
Table 6. Cont.

| Categories                        | Disease or Function Annotation          | p-Value     | Activation z-Score | Molecules                                                                 | Number of Molecules |
|-----------------------------------|----------------------------------------|-------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Cardiac regeneration              | Regeneration of cardiomyocytes          | 4.72 × 10⁻² | HMGB1              |                                                                           | 1                   |
| Cardiac regeneration              | Regeneration of myocardium              | 4.72 × 10⁻² | HMGB1              |                                                                           | 1                   |
| Liver hyperplasia/hyperproliferation | Hyperplasia of liver                    | 4.87 × 10⁻² | IGF2R, SOD1        |                                                                           | 2                   |
| Renal inflammation, renal nephritis | Membranous glomerulonephritis          | 4.87 × 10⁻² | ACTN4, PDLIM1      |                                                                           | 2                   |
| Renal necrosis/cell death          | Apoptosis of kidney cell lines          | 5.43 × 10⁻² | −0.777             | CD44, CDK1, EZR, HSPA5, HSPB1, HYOU1, ITGB1, PEA15, TFRC, VDAC1, YWHAQ | 11                  |
| Cardiac necrosis/cell death        | Apoptosis of cardiomyocytes             | 5.55 × 10⁻² | 1.348              | CALR, CYR61, GAPDH1, GNAI2, HSPD1, MAPK1, PARK7, RHOA, STAT1              | 9                   |
| Cardiac hypertrophy                | Hypertrophy of heart                    | 5.62 × 10⁻² | −0.859             | CAV1, CT5B, EEF1D, FNI, GNAI2, HMGB1, IGF2R, MAPK1, MYH10, PARK7, PPN1, PPIA, RHOA, S100A6, TLN1 | 15                  |
| Liver cirrhosis                    | Cirrhosis of liver                      | 6.13 × 10⁻² |                    | B2M, BSG, FNI, HNRNPK, KRT18, KRT8, TXLNA                                | 7                   |
| Cardiac arrhythmia                 | Atrial fibrillation                     | 6.18 × 10⁻² |                    | ATP1A1, PPP1CA, PPP2CA, RHOA, TUBB, TUBB4B                                | 6                   |
| Cardiac inflammation               | Pericarditis                            | 6.77 × 10⁻² |                    | TUBB, TUBB4B                                                             | 2                   |
| Liver steatosis                    | Advanced stage hepatic steatosis        | 7.00 × 10⁻² |                    | CD44                                                                     | 1                   |
| Cardiac arteriopathy, cardiac hypertrophy | Hypertrophy of coronary artery           | 7.00 × 10⁻² |                    | RHOA                                                                     | 1                   |
| Glomerular injury, renal hypertrophy | Hypoplasia of mesangial cells          | 7.00 × 10⁻² |                    | ARHGDAI                                                                  | 1                   |
| Cardiac inflammation               | Rheumatic cardiitis                     | 7.00 × 10⁻² |                    | ANXA1                                                                    | 1                   |
| Cardiac arteriopathy               | Vasospasm of coronary artery            | 7.00 × 10⁻² |                    | SOD1                                                                     | 1                   |
| Liver fibrosis                     | Fibrosis of liver                       | 8.42 × 10⁻² | 0.391              | CT5B, GNB2L1, GSTP1, HDGF, HSPB1, STAT1                                  | 6                   |
| Cardiac fibrosis                   | Fibrosis of heart                       | 9.03 × 10⁻² | −0.956             | CAPNS1, CAV1, CTNN1, FNI, ITGB1, LMNA, RHOA, TLN1                       | 8                   |
| Liver hypoplasia                   | Hypoplasia of liver                     | 9.21 × 10⁻² |                    | EIF6, SPTBN1, YBX1                                                      | 3                   |
| Renal damage, renal tubule injury  | Damage of tubular cells                 | 9.22 × 10⁻² |                    | YBX1                                                                     | 1                   |
| Glomerular injury, renal fibrosis  | Fibrosis of renal tubule                | 9.22 × 10⁻² |                    | STMN1                                                                    | 1                   |
| Renal inflammation, renal nephritis | Progressive crescentic glomerulonephritis | 9.22 × 10⁻² |                    | ACTN4                                                                    | 1                   |
| Renal inflammation, renal nephritis | Nephritis                               | 1.12 × 10⁻¹ |                    | ACTN4, ARHGDA1, FKBP1A, IMPDH2, MYH10, MYH9, PDLIM1, PPP2CA, PSMB1, PSMD2, YBX1 | 11                  |
Table 6. Cont.

| Categories | Disease or Function Annotation | p-Value | Activation z-Score | Molecules | Number of Molecules |
|------------|--------------------------------|---------|-------------------|-----------|---------------------|
| Renal damage | Damage of kidney | $1.13 \times 10^{-1}$ | $-0.447$ | ARHGDLA, B2M, CD44, FN1, ITGB1, YBX1 | 6 |
| Renal proliferation | Arrest in growth of kidney cell lines | $1.14 \times 10^{-1}$ | | LMNA | 1 |
| Cardiac enlargement | Enlargement of atrium | $1.14 \times 10^{-1}$ | | RHOA | 1 |
| Cardiac artherosclerosis, cardiac fibrosis | Fibrosis of coronary artery | $1.14 \times 10^{-1}$ | | RHOA | 1 |
| Cardiac damage, cardiac degeneration | Injury of cardiomyocytes | $1.14 \times 10^{-1}$ | | MAPK1 | 1 |
| Liver steatosis | Nonalcoholic fatty liver disease | $1.22 \times 10^{-1}$ | | FASN, HADHA, SOD1 | 3 |
| Liver damage | Hepatotoxicity | $1.27 \times 10^{-1}$ | | AIP, HLA-B | 2 |
| Heart failure | Failure of heart | $1.31 \times 10^{-1}$ | $-0.798$ | ATP1A1, CAPNS1, CAV1, FKBP1A, HMGBI, IGF2R, MAPK1, MYH10, PARK7, PPP2R1A | 10 |
| Liver proliferation | Proliferation of liver cells | $1.34 \times 10^{-1}$ | $-1.461$ | CAV1, CTSB, ITGB1, LGALS1, MAPK1, SERPINH1, SPTBN1, STAT1 | 8 |
| Kidney failure | Acute tubular necrosis | $1.35 \times 10^{-1}$ | | STMN1 | 1 |
| Liver adhesion | Adhesion of hepatocytes | $1.35 \times 10^{-1}$ | | KRT8 | 1 |
| Heart failure | End stage heart failure | $1.35 \times 10^{-1}$ | | PARK7 | 1 |
| Liver enlargement | Enlargement of liver | $1.35 \times 10^{-1}$ | | LMNA | 1 |
| Liver hyperplasia/hyperproliferation | Polycystic liver disease | $1.35 \times 10^{-1}$ | | PRKCSH | 1 |
| Cardiac necrosis/cell death | Survival of ventricular myocytes | $1.35 \times 10^{-1}$ | | CALR | 1 |
| Renal transformation | Transformation of kidney cells | $1.35 \times 10^{-1}$ | | EIF2S1 | 1 |
| Cardiac dysfunction | Systolic dysfunction | $1.52 \times 10^{-1}$ | | ANXA5, FKBP1A | 2 |
| Liver necrosis/cell death | Cell death of liver cells | $1.52 \times 10^{-1}$ | $0.256$ | CTSB, HMGBI, HSPD1, KRT8, NCL, SERPINH1, SLC25A5, SPTBN1 | 8 |
| Renal proliferation | Proliferation of renal tubular epithelial cells | $1.56 \times 10^{-1}$ | | STMN1 | 1 |
| Cardiac arrhythmia, tachycardia | Ventricular tachycardia | $1.61 \times 10^{-1}$ | | ATP1A1, GNAI2, VCL | 3 |
| Liver hemorrhaging | Bleeding of liver | $1.69 \times 10^{-1}$ | | FKBP1A, KRT8 | 2 |
| Renal inflammation, renal nephritis | Acute phase crescentic glomerulonephritis | $1.76 \times 10^{-1}$ | | ACTN4 | 1 |
| Liver fibrosis | Chemotaxis of hepatic stellate cells | $1.76 \times 10^{-1}$ | | MAPK1 | 1 |
| Increased levels of albumin | Increased localization of albumin | $1.76 \times 10^{-1}$ | | B2M | 1 |
### Table 6. Cont.

| Categories                                | Disease or Function Annotation | p-Value      | Activation z-Score | Molecules                             | Number of Molecules |
|-------------------------------------------|--------------------------------|--------------|--------------------|---------------------------------------|---------------------|
| Hepatocellular peroxisome proliferation   | Quantity of peroxisomes        | $1.76 \times 10^{-1}$ | DNM1L              |                                       | 1                   |
| Bradycardia, cardiac arrhythmia           | Sinus bradycardia              | $1.76 \times 10^{-1}$ | CALR               |                                       | 1                   |
| Cardiac inflammation                      | Carditis                       | $1.85 \times 10^{-1}$ | ANXA1, TUBB, TUBB4B |                                       | 3                   |
| Bradycardia, cardiac arrhythmia           | Bradycardia                    | $1.86 \times 10^{-1}$ | CALR, RHOA         |                                       | 2                   |
| Renal dilation                            | Dilation of kidney             | $1.96 \times 10^{-1}$ | PRKCSH             |                                       | 1                   |
| Hepatocellular carcinoma, liver hyperplasia/hyperproliferation | Size of hepatocellular carcinoma | $1.96 \times 10^{-1}$ | IQGAP1              |                                       | 1                   |
| Liver cirrhosis                           | Primary biliary cirrhosis      | $1.97 \times 10^{-1}$ | B2M, BSG, HNRNPK, TXLNA |                                       | 4                   |
| Liver necrosis/cell death                 | Cell death of hepatocytes      | $2.11 \times 10^{-1}$ | −0.537 CT5B, HMGB1, KRT8, NCL, SLC25A5, SPTBN1 |                                       | 6                   |
| Glomerular injury                         | Glomerulosclerosis             | $2.13 \times 10^{-1}$ | ACTN4, ARHGDIA, MYH9, PDLIM1, STMN1 |                                       | 5                   |
| Renal necrosis/cell death                 | Apoptosis of proximal tubule cells | $2.15 \times 10^{-1}$ | ATP1A1              |                                       | 1                   |
| Cardiac infarction                        | Infarction of heart            | $2.15 \times 10^{-1}$ | CAV1                |                                       | 1                   |
| Kidney failure                            | Ischemic acute renal failure   | $2.15 \times 10^{-1}$ | ATP1A1              |                                       | 1                   |
| Renal necrosis/cell death                 | Apoptosis of tubular cells     | $2.21 \times 10^{-1}$ | ATP1A1, STMN1       |                                       | 2                   |
| Liver necrosis/cell death                 | Apoptosis of liver cells       | $2.22 \times 10^{-1}$ | 0.000 CT5B, HMGB1, KRT8, NCL, SERPINH1, SPTBN1 |                                       | 6                   |
| Increased levels of creatinine            | Increased quantity of creatinine | $2.30 \times 10^{-1}$ | AKR1B1, CD44        |                                       | 2                   |
| Glomerular injury                         | Cortical renal glomerulopathies | $2.34 \times 10^{-1}$ | ACTN4               |                                       | 1                   |
| Cardiac hyperplasia/hyperproliferation    | Hyperplasia of heart           | $2.34 \times 10^{-1}$ | IGF2R               |                                       | 1                   |
| Liver necrosis/cell death                 | Apoptosis of hepatocytes       | $2.48 \times 10^{-1}$ | −0.492 CT5B, HMGB1, KRT8, NCL, SPTBN1 |                                       | 5                   |
| Decreased levels of albumin               | Decreased excretion of albumin | $2.52 \times 10^{-1}$ | LAMB1               |                                       | 1                   |
| Cardiac proliferation                     | Proliferation of cardiac fibroblasts | $2.52 \times 10^{-1}$ | STAT1               |                                       | 1                   |
| Cardiac congestive cardiac failure, heart failure | Congestive heart failure    | $2.58 \times 10^{-1}$ | −1.103 CAV1, FKBPI1A, IGF2R, MYH10 |                                       | 4                   |
| Cardiac damage                            | Injury of heart                | $2.65 \times 10^{-1}$ | ANXA1, MAPK1        |                                       | 2                   |
Table 6. Cont.

| Categories                               | Disease or Function Annotation | p-Value          | Activation z-Score | Molecules                                                                 | Number of Molecules |
|------------------------------------------|--------------------------------|------------------|--------------------|---------------------------------------------------------------------------|---------------------|
| Renal damage, renal tubule injury        | Damage of tubulointerstitium   | 2.70 × 10⁻¹       | FN1                |                                                                           | 1                   |
| Increased levels of creatinine           | Increased clearance of creatinine | 2.70 × 10⁻¹       | ARHGDIA            |                                                                           | 1                   |
| Renal damage, renal tubule injury        | Damage of renal tubule         | 2.74 × 10⁻¹       | FN1, YBX1          |                                                                           | 2                   |
| Liver steatosis                          | Hepatic steatosis              | 2.75 × 10⁻¹       | 1.715              | CAV1, CD44, FASN, GSTP1, H2AFY, HADHA, KRT8, LMNA, SOD1                   | 9                   |
| Congenital heart anomaly                 | Congenital heart disease       | 2.85 × 10⁻¹       | 0.294              | AIP, ENO2, FKBP1A, FLNA, MYH10, MYH9, YWHAE                                | 7                   |
| Liver inflammation/hepatitis             | Acute hepatitis                | 3.04 × 10⁻¹       | CD44               |                                                                           | 1                   |
| Increased levels of blood urea nitrogen  | Increased quantity of blood urea nitrogen | 3.04 × 10⁻¹     | CD44               |                                                                           | 1                   |
| Liver fibrosis                           | Activation of hepatic stellate cells | 3.10 × 10⁻¹   | FN1, STAT1         |                                                                           | 2                   |
| Liver damage, liver inflammation/hepatitis | Chronic hepatitis c          | 3.10 × 10⁻¹       | DDX5, IMPDH2       |                                                                           | 2                   |
| Kidney failure                           | End stage renal disease        | 3.12 × 10⁻¹       | FDPS, FKBP1A, IMPDH2, MYH9 |                                                                       | 4                   |
| Liver necrosis/cell death                | Focal necrosis of liver        | 3.21 × 10⁻¹       | STAT1              |                                                                           | 1                   |
| Increased levels of potassium            | Increased excretion of k⁺      | 3.21 × 10⁻¹       | AKR1B1             |                                                                           | 1                   |
| Renal inflammation, renal nephritis      | Glomerulonephritis             | 3.23 × 10⁻¹       | ACTN4, FKBP1A, IMPDH2, PDLIM1, PPP2CA, PSMB1, PSMD2 |                           | 7                   |
| Cardiac arteriopathy                     | Coronary artery disease        | 3.23 × 10⁻¹       | ACAT2, EIF4H, FKBP1A, NMN1, RHOA, SOD1, TK1, TUBB, TUBB4B |                         | 9                   |
| Cardiac infarction                       | Myocardial infarction          | 3.27 × 10⁻¹       | 2.000              | ACTA1, CC17, CD44, MAPK1, SOD1, STAT1 |                           | 6                   |
| Renal damage                             | Injury of kidney               | 3.32 × 10⁻¹       | ARHGDIA, B2M, CD44 |                                                                           | 3                   |
| Renal inflammation, renal nephritis      | Interstitial nephritis         | 3.37 × 10⁻¹       | ARHGDIA            |                                                                           | 1                   |
| Renal necrosis/cell death                | Apoptosis of kidney cells      | 3.51 × 10⁻¹       | ATP1A1, ITGB1, STMN1 |                                                                       | 3                   |
| Cardiac hypoplasia                       | Hypoplasia of heart ventricle  | 3.62 × 10⁻¹       | CALR, MYH10        |                                                                           | 2                   |
| Liver necrosis/cell death                | Apoptosis of hepatic stellate cells | 3.68 × 10⁻¹   | SERPINH1           |                                                                           | 1                   |
| Liver hyperbilirubinemia                 | Hyperbilirubinemia             | 3.68 × 10⁻¹       | GSTP1              |                                                                           | 1                   |
| Renal damage                             | Injury of renal glomerulus     | 3.68 × 10⁻¹       | B2M                |                                                                           | 1                   |
| Glutathione depletion in liver           | Conjugation of glutathione     | 3.84 × 10⁻¹       | GSTP1              |                                                                           | 1                   |
Table 6. Cont.

| Categories                      | Disease or Function Annotation                        | p-Value         | Activation z-Score | Molecules                  | Number of Molecules |
|---------------------------------|------------------------------------------------------|-----------------|-------------------|----------------------------|---------------------|
| Cardiac fibrosis                | Fibrosis of myocardium                              | $3.84 \times 10^{-1}$ | ITGB1             |                            | 1                   |
| Increased levels of hematocrit  | Increased hematocrit of organism                     | $4.03 \times 10^{-1}$ | CD59, PRDX1, PRDX2 |                            | 3                   |
| Cardiac hypertrophy             | Hypertrophy of ventricular myocytes                 | $4.13 \times 10^{-1}$ | RHOA              |                            | 1                   |
| Liver cholestasis               | Progressive familial intrahepatic cholestasis type 1 | $4.13 \times 10^{-1}$ | HDLBP, SLC25A6    |                            | 2                   |
| Increased levels of red blood cells | Increased quantity of red blood cells              | $4.22 \times 10^{-1}$ | CD59, PICALM, SOD1 |                            | 3                   |
| Renal necrosis/cell death       | Apoptosis of mesangial cells                        | $4.27 \times 10^{-1}$ | ITGB1             |                            | 1                   |
| Renal dysfunction               | Dysfunction of kidney                               | $4.40 \times 10^{-1}$ | BSG               |                            | 1                   |
| Congenital heart anomaly        | Perimembranous ventricular septal defect            | $4.40 \times 10^{-1}$ | MYH10             |                            | 1                   |
| Cardiac hypertrophy             | Hypertrophy of right ventricle                      | $4.54 \times 10^{-1}$ | CAV1              |                            | 1                   |
| Cardiac necrosis/cell death     | Apoptosis of ventricular myocytes                   | $4.67 \times 10^{-1}$ | RHOA              |                            | 1                   |
| Cardiac dilation                | Dilation of heart                                   | $4.67 \times 10^{-1}$ | PPP2CA            |                            | 1                   |
| Cardiac fibrosis                | Interstitial fibrosis of heart                      | $4.67 \times 10^{-1}$ | CAPNS1            |                            | 1                   |
| Cardiac arrythmia               | Ventricular fibrillation                            | $4.67 \times 10^{-1}$ | ATP1A1            |                            | 1                   |
| Cardiac arrythmia               | Arrhythmia of heart ventricle                       | $4.78 \times 10^{-1}$ | ATP1A1, GNA2      |                            | 2                   |
| Liver hyperplasia/hyperproliferation | Proliferation of liver cancer cells             | $4.80 \times 10^{-1}$ | S100A6            |                            | 1                   |
| Increased levels of alkaline phosphatase | Increased activation of alkaline phosphatase | $4.93 \times 10^{-1}$ | ANXA6, ITGB1      |                            | 2                   |
| Categories                  | Disease or Function Annotation                      | p-Value          | Activation z-Score | Molecules                  | Number of Molecules |
|-----------------------------|-----------------------------------------------------|------------------|-------------------|-----------------------------|---------------------|
| Renal damage                | Reperfusion injury of kidney                       | 5.04 × 10^{-1}   |                   | CD44                        |                     |
| Cardiac arrhythmia, tachycardia | Supraventricular tachycardia                   | 5.28 × 10^{-1}   |                   | ATP1A1                      | 1                   |
| Liver inflammation/hepatitis | Alcoholic hepatitis                               | 5.39 × 10^{-1}   |                   | GSTP1                       | 1                   |
| Renal proliferation         | Proliferation of kidney cells                     | 5.45 × 10^{-1}   |                   | AKR1B1, STMN1                | 2                   |
| Congenital heart anomaly    | Conotruncal heart malformations                   | 5.59 × 10^{-1}   |                   | AIP, FLNA                   | 2                   |
| Congenital heart anomaly    | Persistent truncus arteriosus                     | 5.61 × 10^{-1}   |                   | FLNA                        | 1                   |
| Cardiac hypoplasia          | Hypoplasia of trabeculae carne                    | 5.92 × 10^{-1}   |                   | CALR                        | 1                   |
| Cardiac output              | Cardiac output                                    | 6.01 × 10^{-1}   |                   | MAPK1                       | 1                   |
| Liver inflammation/hepatitis, liver steatosis | Steatohepatitis                                  | 6.29 × 10^{-1}   |                   | SOD1                        | 1                   |
| Cardiac hypertrophy         | Hypertrophy of left ventricle                     | 1.00E00          |                   | CAV1                        | 1                   |
| Liver proliferation         | Proliferation of hepatocytes                      | 1.00E00          |                   | CAV1, MAPK1, SPTBN1         | 3                   |
| Cardiac hypertrophy         | Ventricular hypertrophy                           | 1.00E00          |                   | CAV1, RHOA                  | 2                   |
Figure 1. Proteomic analysis revealed molecular interactome regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. There were 290 related pathways regulated by vancomycin in HK-2 cells. Red indicates an up-regulation; green indicates a down-regulation.
**Figure 2.** Intergrated signaling pathways regulated by vancomycin in HK-2 cells.

**Figure 3.** Vancomycin regulated RNA post-transcriptional modification, carbohydrate metabolism, and small molecule biochemistry. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
**Figure 4.** Vancomycin regulated protein trafficking, cell death and survival, and nucleic acid metabolism. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

**Figure 5.** Vancomycin regulated hematological disease, organismal injury and abnormalities, and RNA post-transcriptional modification. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 6. Vancomycin regulated cellular assembly and organization, cell-to-cell signaling and interaction, and reproductive system development and function. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 7. Vancomycin regulated infectious disease, small molecule biochemistry, and reproductive system disease. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 8. Vancomycin regulated infectious disease, organismal injury and abnormalities, and immunological disease. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 9. Vancomycin regulated protein synthesis, cellular movement, and gene expression. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
**Figure 10.** Vancomycin regulated cellular growth and proliferation, infectious disease, and cellular development. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

**Figure 11.** Vancomycin regulated molecular transport, protein trafficking, and RNA post-transcriptional modification. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 12. Vancomycin regulated post-translational modification, protein folding, and drug metabolism. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 13. Vancomycin regulated post-translational modification, protein folding, and cell morphology. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 14. Vancomycin regulated cellular compromise, cellular assembly and organization, and cellular function and maintenance. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 15. Vancomycin regulated cellular assembly and organization, cellular function and maintenance, and cell morphology. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 16. Vancomycin regulated endocrine system development and function, lipid metabolism, and small molecule biochemistry. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 17. Vancomycin regulated post-translational modification, protein folding, and dermatological diseases and conditions. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 18. Vancomycin regulated DNA replication, recombination, and repair, cell morphology, and cellular function and maintenance. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 19. Vancomycin regulated cellular movement, connective tissue disorders, and hematological disease. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 20. Vancomycin regulated molecular transport, RNA trafficking, and cell death and survival. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 21. Vancomycin regulated developmental disorder, hereditary disorder, and metabolic disease. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 22. Vancomycin regulated cancer, endocrine system disorders, and organismal injury and abnormalities. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 23. Vancomycin regulated RNA post-transcriptional modification, dermatological diseases and conditions, cell death and survival. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 24. Vancomycin regulated carbohydrate metabolism, small molecule biochemistry, and cell morphology. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 25. Vancomycin regulated cell-to-cell signaling and interaction, tissue development, and cardiovascular system development and function. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
2.3. Vancomycin Induces Toxicity in HK-2 Cells

After we observed the effect of vancomycin on cellular functions and disease development, we also analysed the toxic effect of vancomycin in HK-2 cells. As shown in Table 6, there were 187 different toxic effects of vancomycin which were predicted in HK-2 cells. The proteomic results showed that treatment of vancomycin induced renal, heart, and liver toxicity, with cell necrosis and cell death. Moreover, toxic function analysis showed that there were 500 different diseases and functions which were regulated by vancomycin in HK-2 cells (Table 5). Notably, the analysis showed that vancomycin primarily induced renal toxicity, to a lesser extent, liver and heart toxicity. Vancomycin-induced renal toxicity included renal degradation, renal inflammation, renal nephritis, renal atrophy, renal hydronephrosis, kidney failure, renal hypoplasia, glomerular injury, renal fibrosis, renal necrosis/cell death, renal damage, and renal tubule injury. These are all observed in clinical studies.

Following the analysis of the effect of vancomycin on the cellular function and toxicity in HK-2 cells, we analyzed the effect of vancomycin on cellular signaling pathways, including the G\textsubscript{2}/M DNA damage check point signaling pathway, apoptosis signaling pathway, autophagy signaling pathway, endoplasmic reticulum (ER) stress signaling pathway, unfolded protein response (UPR) signaling pathway, ERK-MAPK signaling pathway, and tight junction signaling pathway.

2.4. Vancomycin Regulates G\textsubscript{2}/M DNA Damage Check Point Signaling Pathway in HK-2 Cells

The proteomic results showed that treatment of HK-2 cells with 50 µg/mL vancomycin regulated G\textsubscript{2}/M DNA damage check point signaling pathway (Table 3). Vancomycin reduced the expression level of CDK1, PRKDC, SFN, YWHAE, YWHAG, YWHAH, and YWHAZ by 1.1-, 1.3-, 1.6-, 1.2-, 1.1-, 1.6-, and 1.1-fold, respectively (Figure 27). However, treatment of vancomycin induced the expression level of YWHAB and YWHAQ by 1.1- and 1.2-fold, respectively. Taken together, the results suggest that vancomycin affects the G\textsubscript{2}/M DNA damage check point signaling pathway in HK-2 cells.
Figure 27. G2/M DNA damage check point signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Green indicates a down-regulation. The intensity of green color indicates the degree of down-regulation. Solid arrow indicates direct interaction.

2.5. Vancomycin Regulates Apoptosis and Autophagy in HK-2 Cells

Apoptosis and autophagy are two predominant programmed cell death pathways, being promising targets for the treatment of cancer via regulating mitochondria-dependent or independent or PI3K/Akt/mTOR-mediated signaling pathways. Furthermore, apoptosis and autophagy have been implicated in the pathogenesis of various diseases, including cancer [12–16]. In order to examine the effect of vancomycin on apoptosis and autophagy in HK-2 cells, the identified protein targets were subject to IPA pathway analysis. The results showed that vancomycin regulated apoptosis signaling pathway via the down-regulation of CAPN1, CDK1, and MAPK1 by 1.3-, 1.1-, and 1.7-fold, respectively (Tables 1 and 2 and Figure 28). In addition, vancomycin regulated apoptotic signaling pathway via increasing the expression level of CAPN2, CAPNS1, LMNA, and SPTAN1 by 1.4-, 1.2-, 1.1-, and 1.21-fold, respectively. Moreover, Akt/mTOR signaling pathway plays a central role in the regulation of cell metabolism, growth, proliferation and survival through the integration of both intracellular and extracellular signals [17]. mTOR complexes 1 and 2 (mTORC1 and mTORC2) are two distinct complexes in mTOR signaling pathway transducing a variety of signals to downstream targets, including Akt, p70S6K, Atgs, eIF4G, PPAR-α, and PPAR-γ, to modulate cell growth, cell proliferation, energy metabolism, and autophagy [17]. Aberrant mTOR signaling pathway has been implicated in the pathogenesis of many diseases including cancer and targeting mTOR signaling pathway may be a promising strategy for cancer therapy [18]. As showed in Table 3, vancomycin exhibited a capability of modulating PI3K/Akt/mTOR signaling pathway in HK-2 cells (Figures 29 and 30). The results showed that vancomycin decreased the expression level of a number of key proteins, such as HSP90B1, ITGB1, MAPK1, PPP2R1A, SFN, YWHAE, YWHAG, YWHAH, and YWHAZ by 1.1-, 1.2-, 1.7-, 1.2-, 1.6-, 1.2-, 1.1-, 1.6-, and 1.1-fold, respectively; but increased the expression level of EIF3C, EIF3M, EIF4A1, EIF4G1, FKBP1A, PPP2CA, RPS2, RPS3, RPS8, RPS11, RPS15, RPS24, RPS27A, RPS3A, RPS4X, and RPSA. Moreover, treatment of HK-2 cells with vancomycin induced mitochondrial dysfunction with alterations in the expression level of a number of proteins, including ATP5A1, ATP5B, ATP5H, CYB5R3, CYC1, HSD17B10, PARK7, PRDX5, SDHA, UQCRCL, VDAC1, and VDAC2 (Figure 31). Taken together, the results suggest that the regulatory effects of vancomycin on apoptosis signaling pathway, PI3K/Akt/mTOR signaling pathway, and mitochondrial dysfunction contribute to the toxicity of vancomycin in HK-2 cells.
Figure 28. Apoptosis signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 29. PI3K/Akt signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 30. mTOR signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 31. Mitochondrial dysfunction was induced by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/ml vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
2.6. Vancomycin Regulates EMT Pathways in HK-2 cells

EMT has a close association with cell migration and invasion and it plays an important role in fibrosis and cancer development [19]. Suppressing the progress of EMT may represent a useful approach for the treatment of fibrosis and cancer. We analyzed the effect of vancomycin on EMT-related proteins and signaling pathways using SILAC-based proteomic approach. The proteomic data showed that vancomycin regulated the epithelial adherent junction signaling pathway (Figure 32), tight junction signaling pathway (Figure 33), and remodeling of epithelial adherent junction signaling pathway (Figure 34) in HK-2 cells involving a number of functional proteins, including ACTA1, ACTG1, ACTN1, ACTN4, ACTR2, ACTR3, ARPC2, ARPC1B, CTNNA1, DNM1L, IQGAP1, MYH9, MAPRE1, MYH10, PPP2CA, PPP2R1A, RAB7A, RHOA, TUBA1B, TUBB, TUBB6, TUBB8, TUBB4B, VCL, ZYX, SPTAN1, VAPA, VCL, and YBX3. Taken together, the proteomic data show that vancomycin markedly induces EMT in HK-2.

![Figure 32](image-url). Epithelial adherent junction signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
Figure 33. Tight junction signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.

Figure 34. Remodeling of epithelial adherent junction signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction.
2.7. Vancomycin Regulates ER Stress Pathways in HK-2 cells

The unfolded protein response (UPR) is a cellular stress response related to the ER [20]. It is a stress response that has been found to be conserved between all mammalian species, as well as yeast and worm organisms [21]. The UPR is activated in response to an accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum [20,21]. The proteomic data showed that vancomycin regulated UPR signaling pathway (Figure 35) and ER stress (Figure 36) in HK-2 cells. Incubation of HK-2 cells with vancomycin altered the expression level of several key proteins involved in UPR signaling pathway, including CALR, CANX, DNAJA2, HSP90B1, HSPA4, HSPA5, HSPA8, HSPA9, P4HB, UBXN4, and VCP. Furthermore, vancomycin altered the expression level of CALR, EIF2S1, HSP90B1, and HSPA5. Collectively, the regulatory effect of vancomycin on UPR and ER stress may contribute to vancomycin-associated nephropathy.

2.8. Vancomycin Regulates ERK-MAPK Signaling Pathway in HK-2 Cells

Additionally, treatment of HK-2 cells with vancomycin induced the ERK-MAPK signaling response (Figure 37). There were a number of important proteins which were regulated by vancomycin in HK-2 cells. There was an increase in the expression level of H3F3A/H3F3B, PPP2CA, YWHAB, and YWHAQ, whereas there was a reduction in the expression level of HSPB1, ITGB1, MAPK1, PPP1CA, PPP2R1A, STAT1, TLN1, YWHAH, and YWHAZ. Taken together, the modulating effect of vancomycin on ERK-MAPK signaling pathway may contribute, at least in part, to vancomycin-induced nephrotoxicity.

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**Figure 35.** UPR signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Green indicates a down-regulation. The intensity of green color indicates the degree of down-regulation. Solid arrow indicates direct interaction.
Figure 36. ER stress signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Green indicates a down-regulation. The intensity of green color indicates the degree of down-regulation. Solid arrow indicates direct interaction.

Figure 37. ERK-MAPK signaling pathway was regulated by vancomycin in HK-2 cells. HK-2 cells were treated with 50 µg/mL vancomycin for 24 h and the protein samples were subject to quantitative proteomic analysis. Red indicates an up-regulation; green indicates a down-regulation. The intensity of green and red colors indicates the degree of down- or up-regulation. Solid arrow indicates direct interaction and dashed arrow indicates indirect interaction.
3. Discussion

In the present study, we evaluated the global proteomic responses to vancomycin treatment with regard to cell cycle, programmed cell death, EMT and related molecular targets and signaling pathways in HK-2 cells using SILAC-based quantitative proteomic approach. The quantitative proteomic study showed that a large number of important proteins regulating cell proliferation, growth, cell death, and migration in HK-2 cells, with the involvement of a number of function proteins, such as CDK1, CDK2, E-cadherin, PI3K, Akt, mTOR, cytochrome c, caspase 9, caspase 3, Bcl-2, Bax, p53, PPAR, HSP, Erk1/2, Ras, and Rho.

This proteomic study also showed that vancomycin regulated mitochondrial function and cell death. Mitochondrial disruption and the subsequent release of cytochrome c initiate the process of apoptosis, with the latter being initiated by pro-apoptotic members of the Bcl-2 family but antagonized by anti-apoptotic members of this family [22,23]. Anti-apoptotic members of Bcl-2 can be inhibited by post-translational modification and/or by increased expression of PUMA, which is an essential regulator of p53-mediated cell apoptosis [24]. In addition, cytochrome c released from mitochondria can activate caspase 9, which then activates caspase 3 and caspase 7 [25]. In our study, we observed that vancomycin regulated expression level of a number of proteins, such as CAPN1, CDK1, and MAPK1. Furthermore, vancomycin regulated apoptotic signaling pathway via increasing the expression level of CAPN2, CAPNS1, LMNA, and SPTAN1 in HK-2 cells.

Furthermore, the proteomic results show that vancomycin exhibits a modulating effect on PI3K/Akt/mTOR signaling pathway. Under optimal growth conditions, activated mTORC1 inhibits autophagy by direct phosphorylation of Atg13 and ULK1 at Ser757 [26–28]. This phosphorylation inhibits ULK1 kinase activity and subsequent autophagosome formation. When the kinase activity of mTORC1 is suppressed, the autophagic machinery is initiated. In the present study, vancomycin regulated autophagy in HK-2 cells as indicated by the alteration in the expression of HSP90B1, ITGB1, MAPK1, PPP2R1A, SFN, YWHAE, YWHAG, YWHAH, and YWHAZ. Taken together, the autophagy-modulating effect of vancomycin may contribute to its nephrotoxic effect via the regulation of PI3k/Akt/mTOR signaling pathway.

EMT is characterized as epithelial cells to lose their polarization and specialized junction structures, undergoing cytoskeleton reorganization and acquiring morphological and functional features of mesenchymal-like cells [19,29]. In our proteomic study, we observed marked regulatory effects of vancomycin on the expression of a number of functional proteins that modulate epithelial adherent junction signaling pathway in HK-2 cells. Again, the SILAC-based quantitative proteomic analysis can discriminate the role of EMT modulation in vancomycin-associated nephrotoxicity.

Our data have provided new insights into the molecular mechanisms of vancomycin-induced nephrotoxicity that is often observed in clinical practice. Our data are consistent with previously observed biochemical changes at cellular levels induced by vancomycin in renal epithelial cells. Our data may help identify new targets that are useful for discovery of new therapeutic approaches for vancomycin-induced nephrotoxicity. Further functional studies are warranted to validate our proteomic data.

4. Materials and Methods

4.1. Chemicals and Reagents

Vancomycin, $^{13}$C$_6$-L-lysine, L-lysine, $^{13}$C$_6^{15}$N$_4$-L-arginine, L-arginine, Dulbecco’s phosphate buffered saline (PBS), heat inactivate fetal bovine serum (FBS), and dialyzed FBS were purchased from Sigma-Aldrich (St. Louis, MO, USA). DEME/F12 medium was bought from Invitrogen Inc. (Carlsbad, CA, USA). FASP™ protein digestion kit was purchased from Protein Discovery Inc. (Knoxville, TN, USA). The proteomic quantitation kits for acidification, desalting, and digestion, Ionic Detergent Compatibility Reagent (IDCR), DMEM/F12 medium for SILAC, Pierce bicinchoninic acid protein
molecules kit, and Western blotting substrate were obtained from Thermo Fisher Scientific Inc. (Hudson, NH, USA).

4.2. Cell Culture and Treatment

The human proximal tubule epithelial cell line HK-2 was purchased from the American Type Culture Collection (Manassas, VA, USA) and maintained in regular DMEM/F12 (1:1) medium supplemented with 10% heat-inactivated FBS at 37 °C in a 5% CO2/95% air humidified incubator. Cells were seeded into the plates for 24 h to achieve a confluence of ~80% prior to vancomycin treatment. Vancomycin was dissolved in DMSO with a stock concentration of 50 mM, and was freshly diluted to the pre-determined concentrations with culture medium with 0.05% (v/v) final concentration of DMSO.

For proteomic analysis, HK-2 cells were cultured in DMEM/F12 medium (for SILAC) with (heavy) or without (light) stable isotope labeled amino acids (13C6-L-lysine and 13C615N4-L-arginine) and 10% dialyzed FBS. HK-2 cells cultured in SILAC medium for six cell doubling times to achieve a high level (>98%) of labeled amino acid incorporation. Then the cells grown in “light” media were treated with 0.5% DMSO for 24 h to serve as the negative control; cells grown in “heavy” media were treated with pre-determined vancomycin for 24 h. All the experiments were performed three times independently. After vancomycin treatment, HK-2 cell samples were harvested, lysated with hot lysis buffer (100 mM Tris base, 4% SDS, and 100 mM dithiothreitol), and denatured for 5 min at 95 °C. Then, the samples were stored at −80 °C till further analysis.

4.3. Digestion and Desalting SILAC Protein Samples

Prior to the quantitative proteomic analysis, the protein samples were subject to digestion and desalting which were performed using SILAC-based approach as described previously [8,10,30]. Briefly, the thermal denatured cell lysate was subject to a brief sonication at 20% AMPL for 3 s with 6 pulses. The sonicated samples were centrifuged at 15,000 × g for 20 min at room temperature and the supernatant was collected. The protein concentration was determined using IDCR. Subsequently, equal amount of heavy and light protein sample was combined to reach a total volume of 30–60 µL containing 300–600 µg protein. The combined protein sample was digested using FASP™ protein digestion kit. A quota of 40 µL of combined lysate was added to a spin column prewetted with 8 M urea. The lysate buffer was exchanged to 8 M urea using centrifugation prior to iodoacetamide alkylation and then exchanged to 50 mM ammonium bicarbonate for trypsin digestion at a ratio of 1:100 (w/w). Digestion was carried out overnight in a humidified incubator at 37 °C and terminated with the addition of 5% formic acid. After the digestion, the resultant sample was acidified to pH of 3 and desalted using a C18 solid-phase extraction column. Samples were loaded and washed in 0.1% formic acid and eluted using 90% acetonitrile/10% formic acid. Samples were concentrated in a vacuum concentrator at 45 °C for 120 min and resuspended in 0.1% formic acid prior to LC-MS/MS analysis.

4.4. Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) and Statistical Analysis

The concentrated samples (5 µL) were subject to the hybrid linear ion trap-Orbitrap (LTQ Orbitrap XL, Thermo Scientific Inc.). LC-MS/MS was performed using a 10 cm-long 75 µm (inner diameter) reversed-phase column packed with 5 µm-diameter C18 material with 300 Å pore size (New Objective, Woburn, MA, USA) with a gradient mobile phase of 2%–40% acetonitrile in 0.1% formic acid at 200 µL/min for 125 min. The Orbitrap full MS scanning was performed at a mass (m/z) resolving power of 60,000, with positive polarity in profile mode [M + H]+. Raw data files were submitted for simultaneous search using standard SILAC settings for LTQ Orbitrap XL instruments. Proteins for which at least two fully trypsin-digested L and H peptides were detected at >99% confidence were used for subsequent comparative quantitative analysis. Peptide SILAC ratio was calculated using MaxQuant version 1.2.0.13. The SILAC ratio was determined by averaging all peptide SILAC ratios from peptides identified of the same protein. Differential regulation within each experimental data set was determined by normalization of each data set. Briefly, the L/H ratio was converted into log2 space.
to determine geometric means and facilitate normalization. The average log\textsubscript{2} L/H ratios and standard deviation of the log\textsubscript{2} L/H ratios were determined for each data set, both before and after computational removal of the few significant outliers found in a few data sets. Every protein’s log\textsubscript{2} L/H ratio was then converted into a z-score that is the measure of how many standard deviation units (expressed as “σ”) that protein’s log\textsubscript{2} L/H ratio is away from its population mean. Therefore, a protein with a z-score of >1.645σ indicates that that protein’s differential expression lies outside the 90% confidence level, >1.960σ indicates that it is outside the 95% confidence level, 2.576σ indicates 99% confidence, and 3.291σ indicates 99.9% confidence. z-Scores of >1.960 were considered significant.

4.5. Pathway Analysis and Bioinformatics

The protein IDs were identified using Scaffold 4.3.2 from Proteome Software Inc. (Portland, OR, USA) and the pathway was analyzed using Ingenuity Pathway Analysis (IPA) from QIAGEN (Redwood City, CA, USA). Geometric means for total protein expression ratios across biological samples were calculated respective to intensity. Geometric means and Uniprot Protein identification numbers were uploaded to Ingenuity Pathway Analysis (IPA) to determine localization, molecular function, and protein interactions. Upstream regulator analysis was also performed within IPA where activity of potential upstream regulators is predicted based on the expression profile of known down-stream targets in relation to known upstream regulator mediated expression changes reported in the literature. This analysis determines the significance of overlap of the detected targets with the upstream regulator through a Fisher’s exact test in addition to implementation of a z-score algorithm to make prediction of the direction of upstream regulator activity change. Description of the z-score algorithm is available on the IPA Web site (www.ingenuity.com).

4.6. Statistical Analysis

Data are expressed as the mean ± standard deviation (SD). Multiple comparisons were evaluated by one-way analysis of variance (ANOVA) followed by Tukey’s multiple comparison. A value of \( p < 0.05 \) was considered statistically significant.

5. Conclusions

In summary, the quantitative SILAC-based proteomic approach showed that vancomycin regulated cell proliferation, mitochondria-dependent apoptotic pathway and autophagy, and EMT in HK-2 cells, involving a number of key functional proteins and related molecular signaling pathways. This study may provide a clue to fully identify the molecular targets and elucidate the underlying mechanism of vancomycin-associated nephrotoxicity, resulting in an improved therapeutic effect and reduced side effect in clinical settings.

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References

1. Camacho-Gonzalez, A.; Spearman, P.W.; Stoll, B.J. Neonatal infectious diseases: Evaluation of neonatal sepsis. Pediatr. Clin. N. Am. 2013, 60, 367–389. [CrossRef] [PubMed]
2. Vandecasteele, S.J.; de Vriese, A.S. Recent changes in vancomycin use in renal failure. Kidney Int. 2010, 77, 760–764. [CrossRef] [PubMed]
3. Pacifici, G.M.; Allegaert, K. Clinical pharmacokinetics of vancomycin in the neonate: A review. Clinics 2012, 67, 831–837. [CrossRef]
4. Rostas, S.E.; Kubiak, D.W.; Calderwood, M.S. High-dose intravenous vancomycin therapy and the risk of nephrotoxicity. *Clin. Ther.* 2014, 36, 1098–1101. [CrossRef] [PubMed]

5. Mergenhagen, K.A.; Borton, A.R. Vancomycin Nephrotoxicity: A Review. *J. Pharm. Pract.* 2014. [CrossRef]

6. Elyasi, S.; Khalili, H.; Dashti-Khavidaki, S.; Mohammadpour, A. Vancomycin-induced nephrotoxicity: Mechanism, incidence, risk factors and special populations. A literature review. *Eur. J. Clin. Pharmacol.* 2012, 68, 1243–1255. [CrossRef] [PubMed]

7. Moh’d, H.; Kheir, F.; Kong, L.; Du, P.; Farag, H.; Mohamad, A.; Zurlo, J.J. Incidence and predictors of vancomycin-associated nephrotoxicity. *South. Med. J.* 2014, 107, 383–388. [CrossRef] [PubMed]

8. Ong, S.E.; Mann, M. Stable isotope labeling by amino acids in cell culture for quantitative proteomics. *Methods Mol. Biol.* 2007, 359, 37–52. [PubMed]

9. Gruhler, S.; Kratchmarova, I. Stable isotope labeling by amino acids in cell culture (SILAC). *Methods Mol. Biol.* 2008, 424, 101–111. [PubMed]

10. Mann, M. Functional and quantitative proteomics using SILAC. *Nat. Rev. Mol. Cell Biol.* 2006, 7, 952–968. [CrossRef] [PubMed]

11. Ong, S.E. The expanding field of SILAC. *Anal. Bioanal. Chem.* 2012, 404, 967–976. [CrossRef] [PubMed]

12. Shanware, N.P.; Bray, K.; Abraham, R.T. The PI3K, metabolic, and autophagy networks: Interactive partners in cellular health and disease. *Annu. Rev. Pharmacol. Toxicol.* 2013, 53, 89–106. [CrossRef] [PubMed]

13. Morgensztern, D.; McLeod, H.L. PI3K/Akt/mTOR pathway as a target for cancer therapy. *Anticancer Drugs* 2005, 16, 797–803. [CrossRef] [PubMed]

14. Wu, W.K.; Coffelt, S.B.; Cho, C.H.; Wang, X.J.; Lee, C.W.; Chan, F.K.; Yu, J.; Sung, J.J. The autophagic paradox in cancer therapy. *Onco gene* 2012, 31, 939–953. [CrossRef] [PubMed]

15. Ferreira, C.G.; Epping, M.; Kruyt, F.A.; Giaccone, G. Apoptosis: Target of cancer therapy. *Clin. Cancer Res.* 2005, 11, 797–803. [PubMed]

16. Jeffers, J.R.; Parganas, E.; Lee, Y.; Yang, C.; Wang, J.; Brennan, J.; MacLean, K.H.; Han, J.; Chittenden, T.; Ihle, J.N.; et al. Puma is an essential mediator of p53-dependent and -independent apoptotic pathways. *Cancer Cell* 2003, 4, 321–328. [CrossRef] [PubMed]

17. Chen, Y.; Yu, L. Autophagic lysosome reformation. *Exp. Cell Res.* 2013, 319, 142–146. [CrossRef] [PubMed]

18. Denton, D.; Nicolson, S.; Kumar, S. Cell death by autophagy: Facts and apparent artefacts. *Cell Death Differ.* 2012, 19, 87–95. [CrossRef] [PubMed]
29. Zheng, H.; Kang, Y. Multilayer control of the EMT master regulators. *Oncogene* **2014**, *33*, 1755–1763. [CrossRef] [PubMed]

30. Ong, S.E.; Mann, M. A practical recipe for stable isotope labeling by amino acids in cell culture (SILAC). *Nat. Protoc.* **2006**, *1*, 2650–2660. [CrossRef] [PubMed]

**Sample Availability:** Samples of vancomycin-treated HK-2 cells are available from the authors.