OBJECTIVE. The importance of signal transduction in cell activities has been generally accepted. The purpose of this study was to analyze the regulatory effect of intracellular signaling cascade-associated genes on rat liver regeneration (LR) at transcriptional level. **Material and methods.** The associated genes were originally obtained through a search of the databases and related scientific publications; their expression profiles were then checked in rat LR using the Rat Genome 230 2.0 array. The LR-associated genes were identified by comparing the discrepancy in gene expression changes between the partial hepatectomy (PH) group and the sham operation (SO) group. **Results.** A total of 566 genes associated with the intracellular signaling cascade were LR related. The genes involved in nine signaling pathways including intracellular receptor-, second messenger-, nitric oxide-, hormone-, carbohydrate-mediated, protein kinase, small GTPase, ER-nuclear and target of rapamycin (TOR) signaling pathways were detected to be enriched in a cluster characterized by up-regulated expression in LR. According to their expression similarity and time relevance, they were separately classified into 5 and 5 groups. **Conclusions.** It is presumed that following PH, the second messenger-mediated signaling pathway inhibits the inflammatory response, while the protein kinase cascade and small GTPase-mediated signal transduction stimulate the immune response; the intracellular receptor-, second messenger-, small GTPase-mediated signal transduction and protein kinase cascade coordinately control cell replication; the intracellular receptor-, second messenger-mediated and ER-nuclear signaling pathways facilitate cell differentiation; the MAPK cascade and small GTPase-mediated signal transduction play a role in cytoskeletal reconstruction and cell migration; the second messenger-, small GTPase-mediated and IκB kinase/NFκB cascades take care of protein transport, etc., in LR.

**Key Words:** Genes associated with liver regeneration, intracellular signaling cascade, partial hepatectomy (PH), Rat Genome 230 2.0 array

**Introduction**

Liver is unique in its ability to regenerate rapidly even in adulthood [1]. Liver regeneration (LR) is a process during which the liver recovers its mass and function after damage due to various causes such as partial hepatectomy (PH), virus infection and intoxication [1]. This regenerative process is divided into four phases including the forepart (0.5–4 h after PH), prophase (6–12 h after PH), metaphase (16–66 h after PH) and the anaphase (72–168 h after PH) according to time-course [2], and involves a series of complex physiological and biochemical activities which include cell activation, de-differentiation, proliferation and its regulation, and re-differentiation [3]. All these activities can be modulated by the actions of various signaling pathways [4,5]. These multiple signaling pathways can be roughly categorized as extracellular and intracellular signaling pathways, based on the location of signaling molecules on the cell, the latter comprising nine pathways, i.e. the intracellular receptor-, second messenger-, nitric oxide-, hormone-, carbohydrate-mediated, protein kinase, small GTPase, ER-nuclear and target of rapamycin (TOR) signaling pathways. These nine signaling pathways are not independent of each other, but are woven into a complex network
by crosstalk among them, corporately governing a variety of biological processes such as cytokinesis, proliferation, differentiation, movement, apoptosis and immunity, etc [6,7]. We have previously discussed the regulatory action of cell surface receptor-mediated signal transduction pathways in rat LR [8]. To further comprehensively study the role of all the signaling pathways in LR, we investigated the expression patterns of intracellular signaling cascade-related genes in the regenerating liver following a partial (2/3) hepatectomy using the Rat Genome 230 2.0 array containing 1507 intracellular signaling cascade-related genes, confirming that 566 genes are LR associated. Based on the above data, their expression dynamics, interactions and actions during hepatic regeneration were further analyzed.

Material and methods

Regenerating liver preparation

The study included 276 healthy Sprague-Dawley rats (200–250 g) obtained from the Experimental Animal Center of Henan Normal University. The animals were randomly divided into 23 partial hepatectomy (PH) groups and 23 sham operation (SO) groups, with 6 rats in each group. The rats in the PH groups were subjected to an operation to remove the left lateral and median lobes of their livers, as described by Higgins & Anderson [9]. The rats were killed by cervical dislocation at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 96, 120, 144 and 168 h post-PHx, respectively, and their livers were instantly removed. The procured livers were immediately washed three times in phosphate buffered saline (PBS) at 4°C. For each tissue of six rats for each group (total liver mass: 0.6–1.2 g) were gathered and mixed, and then stored at –80°C until use. The SO group was subjected to the same procedure as the PH group, but without liver removal. The control for both groups was normal rat liver. In the above experiments, the animal protection laws of China were strictly enforced.

RNA isolation and purification

Total RNA was isolated according to the Trizol reagent manual (Invitrogen Corporation, Carlsbad, Calif., USA) and then purified following the RNase free water for 35 min at 94°C and digested into 35–200 bp cRNA fragments. The hybridization buffer was prepared according to the Affymetrix protocol and the prehybridized Rat Genome 230 2.0 microarray was added to it. Hybridization was then carried out in a rotating chamber (60 rpm, 16 h, 45°C). After the superfluous hybridization buffer had been absorbed, the arrays were washed and stained using the GeneChip fluidics station 450 (Affymetrix Inc., Santa Clara, Calif, USA). Subsequently, they were scanned with a GeneChip Scanner 3000 (Affymetrix Inc.) and images were obtained [14].

Microarray data analysis

The images were converted to signal value using Affymetrix GCOS 1.4 software. The probe signal values were scaled to evaluate gene expression (p-value < 0.05), marginal expression (0.05 < p-value < 0.065) and no expression (p-value > 0.065). Signal values of each chip were then normalized and it was evaluated whether gene expression changed according to the ratios comparing the normalized p-value of the PH groups with that of the control groups, e.g. ratios ≥ 2, up-regulated expression genes; ratios ≤ 0.33, down-regulated expression genes. To minimize the technical error derived from the microarray analysis, regenerating liver for each time-point was measured three times with the Rat Genome 230 2.0
microarray. Their average value was calculated for corrective value use. Finally, these values were analyzed using GeneMath, GeneSpring (Silicon Genetics, San Carlos, Calif., USA) and Microsoft Excel Software (Microsoft, Redmond, Wash., USA) [14–16].

Identification of genes associated with liver regeneration

First, the nomenclatures of nine intracellular signaling pathways were adopted from the GENONTOLOGY database (www.geneontology.org), and were input into the databases at NCBI (www.ncbi.nlm.nih.gov) and RGD (rgd.mcw.edu) to identify the rat, mouse and human genes associated with the intracellular signaling cascade. In addition, according to maps of biological pathways embodied by GENMAPP (www.genmapp.org), BIOCARTA (www.biocarta.com/genes/index.asp) and KEGG (www.genome.jp/kegg/pathway.html), the genes associated with the above pathways were collated and reconfirmed by a search of the literature for the pertinent articles. The genes that exhibited a greater than 3-fold change in the rat regenerating liver were referred to as meaningfully expressed genes. Besides the rat genes, the above genes that were now known only to exist in mouse and/or humans were considered as rat homologous genes. Finally, the genes that displayed the same or similar results using the three independent analyses showed meaningful expression changes in at least one time-point, and displayed a significant difference (0.01 ≤ p < 0.05) or an extremely significant difference (p ≤ 0.01) between PO and SO by F-test, were included as being associated with rat liver regeneration.

Results

Expression changes of intracellular signaling cascade-associated genes in rat LR

According to the information from databases such as NCBI, AMIGO, BIOCARTA, KEGG, RGD and MGI, etc., 2417 genes were involved in the intracellular signaling cascade. Among them, 110, 426, 15, 9, 2, 738, 369, 26 and 3 genes related to intracellular receptor-, second messenger-, nitric oxide-, hormone-, carbohydrate-mediated, protein kinase, small GTPase, ER-nuclear and TOR signaling pathways were found in the Rat Genome 230 2.0 array. Correspondingly, 41, 169, 6, 4, 2, 271, 138, 7 and 1 genes revealed meaningful expression changes in at least single time-points after PH, and showed significant or extremely significant differences between PH and SO, and displayed reproducible results in three independent analyses using the Rat Genome 230 2.0 array, suggesting that these genes were associated with LR. Among a total of 566 genes, 309 genes were up-expressed, 183 were down-expressed, while 74 were up-expressed at some time-points and down-expressed at others during LR (up/down-regulated for short). The range of up-regulation was 3- to 128-fold compared with the control, and that of down-regulation was 3- to 32-fold (Table I available online at the journal website www.informa.com/gastro). Different genes varied greatly at the time-points when the expression was initiated and terminated, as well as during the persistence period of expression. In this case, the original time-point at which genes were meaningfully expressed is considered as the initially expressed time-point, thus the genes significantly altered in expression at this time-point are called initially expressed genes; we added together the numbers of genes with a 3-fold change or more at any time-point and obtained the total number of expressed genes during the whole regenerative period. The results demonstrated that initially up-regulated and down-regulated genes were 347 and 219, respectively, in LR. Specifically, the number of initially up- and down-regulated genes, orderly, involved in the above nine pathways was in the sequence 22 and 19, 97 and 71, 4 and 2, 4 and 0, 1 and 1, 173 and 98, 88 and 50, 5 and 2, 1 and 0 (Figure 1A). The total frequencies of up-regulation and down-regulation of the genes in LR were 1575 and 693, respectively, and in these nine pathways, the sequence was 92 and 63, 495 and 217, 21 and 2, 21 and 0, 2 and 1, 766 and 305, 356 and 168, 29 and 7, 2 and 0, respectively (Figure 1B).

Expression similarity and time relevance of intracellular signaling cascade-associated genes in LR

Based on the similarity in expression, the above 556 genes were classified into the following five clusters by H-clustering analysis: only up-, predominantly up-, only down-, predominantly down-, up/down-regulation, involving 309, 19, 183, 13 and 42 genes, respectively. According to time relevance, they were categorized into 5 groups (0.5–12 h, 6 h, 16–96 h, 18–24 h and 72–144 h) and the frequencies of up-regulation and down-regulation were 407 and 89, 74 and 24, 269 and 108, 521 and 339, 304 and 133, respectively (Figure 2A). Among 58 genes up-regulated by 10-fold or more and 26 genes down-regulated by 10-fold or more, the number of up- and down-regulated genes was 3 and 2, 21 and 7, 1 and 0, 26 and 15, 12 and 5, 0 and 1, 1 and 1, in parallel, in intracellular receptor-, second messenger-, nitric oxide-mediated, protein kinase, small GTPase, ER-nuclear and general intracellular signaling pathways (Figure 2B).
Interaction relationship among intracellular signaling cascade-associated genes in four different periods in rat LR

To answer the question of what are the interactions among the intracellular signaling cascade-related genes in the four different phases, we took advantage of the ResnetCore1.2 software database attached in pathway studio 5.0 and constructed a network map of direct physical and transcriptional interactions between these genes. The resulting network contains 1183 genes and 3793 interactions, in which genes are depicted as greater colored spheres, and molecular relationships are represented as the physical spacing between the nodes. For convenience, here 54 representative LR-related genes were selected because of the higher level of connectivity (that is, individual genes have more than 10 interaction partners on average) and were then networked. Among the genes involved in intracellular receptor-mediated, second messenger-mediated, protein kinase cascade, small GTPase-mediated signal transduction and ER-nuclear signaling pathways, the number of up- and down-regulated genes was 3 and 3, 2 and 2, 24 and 18, 6 and 2, 1 and 1, respectively (Figure 3A). On this basis, the expression kinetics was subject to analysis. The results showed that at the forepart (0.5–4 h after PH) of LR, 14 genes were up-regulated and 8 down-regulated; at prophase (6–12 h after PH), 14 genes were up- and 3 down-regulated; at metaphase (16–66 h after PH), 25 genes were up- and 19 down-regulated; at anaphase (72–168 h after PH), 14 genes were up-regulated, 6 down-regulated and 1 up/down-regulated (Figure 3B).

Discussion

The importance of signal transduction in cell activities has been generally accepted [17]. Our study demonstrated that five intracellular receptor-mediated signaling pathway-associated genes, including *ccne1* which promotes cell proliferation [18], were up-expressed during LR; while *gpr30*, which blocks cell growth and proliferation [19], was down-regulated. It was learned by a search of the peer-reviewed scientific publications that 5 genes including *sos1* involved in the small GTPase-mediated pathway, 25 genes including *igfbp1* in the second messenger-mediated pathway, 9 genes including *e2f1*, *hsbp1* and *camkk2* in the MAPK pathway promote cell growth and division [20–22]. They were all elevated at mRNA level during LR. Notably, *sos1* was predominant at 4, 54–60 and 168 h, reaching its peak at 168 h with 15-fold of control. *igfbp1* increased in expression almost for the whole LR, and showed the expression with a marked high level of 65-fold at 1 h, basically consistent with the results reported by Crissey et al. [23]. Five genes including *rfc4* related to phosphoinositide-mediated signaling and gene *brca1* in the intracellular receptor-mediated signaling pathway are required for DNA replication and repair [24]. These genes were up-regulated mainly at metaphase; *ccnd1*, increased in expression at middle phase, has a role in cell growth and proliferation via the IκB kinase/NFκB cascade [25]. Conversely, 8 IκB kinase/NFκB cascade-related up-expressed genes including *ect2*, 2 protein kinase cascade-associated genes *gps2* and *fos* negatively control proliferation [26,27]. All 4 genes including *cnr1*, participating in the second messenger-mediated signaling pathway, and 2 MAPK
Figure 2. Cluster analysis of genes associated with the intracellular signaling cascade during rat liver regeneration (LR). A total of 556 genes whose intensities varied from 3-fold or over at least at one time-point in LR were subjected to H-clustering analysis. Red, black and green represent the higher, indistinctively altered and lower mRNA levels, respectively, in relation to that of control liver. The left tree and upper tree show function and time series clusters, respectively. A. Cluster assay of a total of 556 genes. B. Cluster analysis of genes with expression levels that changed 10-fold or more during LR.
cascade-involved genes (nrtn and p2ry12) stimulate neuron growth [28,29] showed significant down-regulation at the middle phase of LR. Based on the above results, it can be inferred that regenerating hepatocyte multiplication might be controlled by the above signaling pathways.

This study indicates that differentiation-promoting gene xbp1 [30], associated with the ER-nuclear signaling pathway, was elevated in expression at 4 and 54 h post-PH, while being reduced at 144 h. In the intracellular receptor-mediated signaling pathway, 6 cell differentiation-enhancing genes containing fhl2 and rxra [31] rose significantly at the middle and late stage of LR. In the second messenger-mediated signaling pathway, 6 neurogenesis and differentiation-promoting genes including drd1a and ang1 were up-regulated in LR [32,33]. It is worth mentioning that ang1 had the highest

Figure 3. Expression dynamics and interaction of 54 intracellular signaling cascade-associated genes during rat liver regeneration (LR). The interactions of intracellular signaling cascade-associated genes were assayed by pathway studio 5.0 software. Red, green, gray and white shapes denote the up-regulated, the down-regulated, the up/down-regulated and the meaninglessly expressed genes, respectively. A. The interactions of 54 genes with closer relationships. B. Expression changes at each phase during LR.
showed the observable rise in expression in LR. Fourteen small GTPase Rab family-associated proteins (including RAB11B, RAB12 and RAB34, etc.), which are needed for vesicular traffic and protein transport [49], were significantly up-regulated at middle and late phases of LR. Three small GTPase-mediated signal transduction-related genes including limk1, and IκB kinase/NFκB cascade-participating gene vapa were able to stimulate endocytosis [50,51] and were elevated in expression mainly at the middle phase of LR. In addition, in the retinoic acid receptor signaling pathway, the retinoic acid-catabolizing gene cyp26b1 [52] displayed high expression abundance at 8 and 18 h. Almost in the whole LR, the down-regulated gene prlr inhibiting lipoprotein lipase activity [53] depending on the protein kinase cascade, fell to the lowest level of 23-fold at 0.5 h.

Taken together, the treatment of experimental material in this study is characterized by comparatively long-time and multiple time-points, and a high-throughput gene expression technique is used to investigate the expression changes and regulatory effect of genes involved in the above nine signaling pathways, post-rat PH. This facilitates investigation of the molecular mechanism of LR and gene function. After analysis, genes igfbp1, mapk8, esr, akt and crk can be preliminarily confirmed as therapeutic target candidates for liver disease. Meanwhile, this work provides a theoretical basis for studying gene therapy, selecting target genes and time-points, etc. Therefore, the above results need to be further analyzed by techniques such as protein chip, gene transfer, RNA interference, protein-interaction, and so on.

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Table I. Expression abundance of 566 intracellular signaling cascade-associated genes during rat liver regeneration.

| Name                                      | Gene Abbr. | Associated to others | Fold difference |
|-------------------------------------------|------------|----------------------|-----------------|
| **1 Intracellular receptor mediated signaling pathway** |            |                      |                 |
| **1 General**                             |            |                      |                 |
| aryl hydrocarbon receptor nuclear translocator 2 | *Arnt2     |                      | 6.8             |
| mediator complex subunit 1               | *Pparbp    |                      | 5.0             |
| low density lipoprotein receptor adaptor protein 1 | LdLRap1    |                      | 4.3             |
| discoidin, CUB and LCCL domain containing 2 | *Dcbld2    |                      | 4.3             |
| myeloid/lymphoid or mixed-lineage leukemia 3 | *Mil3      |                      | 3.2             |
| aryl hydrocarbon receptor nuclear translocator | *Arnt     |                      | 0.2             |
| thyroid hormone receptor associated protein 4 | *Thrap4    |                      | 0.2             |
| aryl-hydrocarbon receptor repressor       | *Ahrr      |                      | 0.1             |
| **2 Androgen receptor mediated signaling pathway** |            |                      |                 |
| cyclin E                                 | *Ccne1     |                      | 18.5            |
| breast cancer 1, early onset              | *Brcal     |                      | 13.8            |
| four and a half LIM domains 2             | Fh12       |                      | 9.0             |
| nuclear receptor coactivator 3            | *Ncoa3     |                      | 4.3             |
| DnaJ (Hsp40) homolog, subfamily A, member 1 | DnaJ1a     |                      | 0.3             |
| peroxisome proliferative activated receptor, gamma, coactivator 1 alph | *Pparc1a   |                      | 0.2             |
| **3 Glucocorticoid receptor mediated signaling pathway** |            |                      |                 |
| RNA binding motif protein 14             | *Rbm14     |                      | 5               |
| nuclear receptor subfamily 3, group C, member 1 | *Nr3c1  |                      | 4.7             |
| **4 Mineralocorticoid receptor mediated signaling pathway** |            |                      |                 |
| nuclear receptor subfamily 3, group C, member 2 | Nr3c2  |                      | 0.3             |
| **5 Estrogen receptor mediated signaling pathway** |            |                      |                 |
| estrogen receptor 2 beta                 | *Esrl      |                      | 6.1             |
| estrogen receptor 1                      | *Esrl2     |                      | 3.5             |
| G protein-coupled receptor 30            | Esrb       |                      | 0.3             |
| estrogen related receptor, alpha          | *Safb      |                      | 0.2             |
| estrogen-related receptor beta            | Gpr30      |                      | 0.1             |
| scaffold attachment factor B             | *Esrra     |                      | 0.1             |
| **6 Progesterone receptor mediated signaling pathway** |            |                      |                 |
| progesterone receptor membrane component 2 | Pgrmc2     |                      | 0.3             |
| **7 Thyroid Hormone receptor mediated signaling pathway** |            |                      |                 |
| jumonji domain containing 1C             | Jmjd1c     |                      | 3.7             |
| nuclear receptor subfamily 1, group I, member 3 | Nrl13     |                      | 3.2             |
| thyroid hormone receptor beta             | *Thrb      |                      | 16              |
| nuclear receptor binding SET domain protein 1 | Nsd1 |                      | 0.1             |
| **8 Prostaglandin E receptor mediated signaling pathway** |            |                      |                 |
| prostaglandin E receptor 3               | *Ptger3    |                      | 13-14           |
| **9 Retinoic acid receptor mediated signaling pathway** |            |                      |                 |
| retinoid X receptor alpha                | *Rxra      |                      | 11.3            |
| cytochrome P450, family 26, subfamily B, polypeptide 1 | Cyp26b1 |                      | 8.3             |
| retinoid X receptor gamma                | Rxrg       |                      | 5.6             |
| cAMP responsive element modulator        | Crem       |                      | 4.1             |
| pancreas specific transcription factor, 1a retinoic acid receptor, alpha | Ptd1a  | *Rara                | 0.2             |
| cytochrome P450, family 26, subfamily A, polypeptide 1 | Cyp26a1 |                      | 0.1             |
| aldehyde dehydrogenase family 1, subfamily A2 | Aldh1a2 |                      | 0.1             |
| **10 Vitamin D receptor mediated signaling pathway** |            |                      |                 |
| thyroid hormone receptor associated protein 3 | Thrap3   |                      | 2.7             |
| hairless homolog                        | Hr         |                      | 7               |
| **II Second-messenger mediated signaling pathway** |            |                      |                 |
| **11 General**                           |            |                      |                 |
| protein phosphatase 2a, catalytic subunit, alpha isoform stathmin 1 | *Ppp2ca |                      | 16              |
|                                                                 *Stm1 |                      | 17 15.9,0.2     |
| **12 Calcium mediated signaling pathway** |            |                      |                 |
| alpha-2-macroglobulin                    | *A2m       |                      | 46.2            |
| dopamine receptor 1A                     | *Drd1a     |                      | 13-14           |
| AHNAK nucleoprotein                     | Ahnak      |                      | 13.6            |
| ring finger and KH domain containing 3   | Rhkd3      |                      | 8.6             |
| Name                                                                 | Gene Abbr. | Associated to others | Fold difference |
|----------------------------------------------------------------------|------------|----------------------|-----------------|
| calcium/calmodulin-dependent protein kinase kinase 2, beta          | *Camkk2    | 17                   | 7.6             |
| ryanodine receptor 1, skeletal muscle                               | *Ryr1      | 13                   | 6.0             |
| myosin, light polypeptide kinase                                    | *Mylk      | 13                   | 5.3 4.7         |
| dopamine receptor 4                                                 | Drd4       |                      | 4.4             |
| Calcium/calmodulin-dependent serine protein kinase                  | *Cask      |                      |                 |
| neuromedin U receptor 2                                             | Nmur2      | 13-14                | 3.7             |
| ATPase, Ca + + transporting, plasma membrane 4                      | Arp2b4     |                      | 3.6             |
| tumor necrosis factor                                               | *Tnf       | 15,17                | 3.2             |
| double cortin and calcium/calmodulin-dependent protein kinase-like 1 | Dcamk1     | 17                   | 0.3             |
| immunoglobulin heavy chain (epsilon polypeptide)                    | *Ighe      | 13,17                | 0.2             |
| visinin-like 1                                                      | Vsnl1      |                      | 0.2             |
| cartilage oligomeric matrix protein                                 | *Comp      |                      | 0.2             |
| calpain 3                                                           | *Capn3     |                      | 0.2             |
| presenilin 2                                                        | *Psen2     |                      | 0.2             |
| EF hand calcium binding protein 1                                   | Eefbp1     |                      | 0.2             |
| T-cell receptor beta chain                                           | *Tcrb      | 13                   | 0.2             |
| G protein-coupled receptor 66                                       | Gpr66      | 13-14                | 0.1             |
| casein beta                                                         | Csn2       | 16                   | 0.1             |
| growth factor receptor bound protein 7                              | *Grb7      | 17                   | 0.1             |
| PDZ domain containing 11                                             | Pdzk11     |                      | 0.1             |
| down syndrome critical region homolog 1                             | Dscr1      |                      | 4.8 0.2         |

**13 Cyclic-nucleotide mediated signaling pathway**

| Name                                                                 | Gene Abbr. | Associated to others | Fold difference |
|----------------------------------------------------------------------|------------|----------------------|-----------------|
| chemokine (C-C motif) ligand 2                                       | *Ccl2      | 16-17                | 128.0           |
| chemokine (C-C motif) receptor 1                                     | *Ccr1      | 14,18                | 27.9            |
| regulator of G-protein signaling 1                                   | *Rgs1      |                      | 24.3            |
| guanine nucleotide binding protein, alpha transducing 1              | *Gnat1     |                      | 18.5            |
| glutamate receptor, metabotropic 3                                   | Grm3       |                      | 14.0            |
| parathyroid hormone                                                  | Pth        |                      | 10.8            |
| histamine receptor H 1                                               | *Hrh1      | 18                   | 9.9             |
| guanylate cyclase 2C                                                 | *Gucy2c    | 14                   | 9.8             |
| 5-hydroxytryptamine (serotonin) receptor 6                           | *Htr6      |                      | 9.2             |
| neuropeptide Y receptor Y1                                           | Npy1r      |                      | 8.6             |
| dopamine receptor 2                                                  | *Drd2      | 14,17                | 8.6             |
| cAMP responsive element binding protein 3                            | *Creb3     |                      | 8.4             |
| arrestin, beta 1                                                     | Arrb1      | 17                   | 8.0             |
| adrenomedullin                                                      | *Adm       |                      | 8.0             |
| adrenergic receptor, alpha 1d                                         | Adra1d     | 14                   | 7.5             |
| guanylate cyclase 2g                                                 | Gucy2g     |                      | 6.5             |
| endothelial differentiation sphingolipid G-protein-coupled receptor 1| Edg1       | 14,18                | 6.3             |
| regulator of G-protein signaling 2                                   | *Rgs2      |                      | 6.0             |
| somatostatin receptor 4                                              | Sstr4      |                      | 5.9             |
| phosphodiesterase 8B                                                 | Pde8b      |                      | 5.9             |
| cAMP responsive element binding protein 3-like 4                     | *Creb3l4   |                      | 5.7             |
| regulator of G-protein signaling 9                                   | Rgs9       |                      | 5.5             |
| guanylate cyclase 2d                                                 | *Gucy2d    |                      | 5.3             |
| PDZ domain containing 3                                               | Pdzk3      |                      | 5.3             |
| G protein-coupled receptpr kinase 1                                  | *Grk1      | 20                   | 5.2             |
| adrenergic receptor, alpha 2a                                         | Adra2a     | 17                   | 5.2             |
| somatostatin receptor 2                                              | *Sstr2     | 17                   | 4.9             |
| solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulator 1 | Sloc9a3r1 |                      | 4.8             |
| brain and kidney protein                                             | Bk         |                      | 4.5             |
| cholinergic receptor, muscarinic 5                                   | Chrm5      |                      | 4.3             |
| endothelial differentiation, sphingolipid G-protein-coupled receptor, 3 | *Edg3     | 14                   | 4.0             |
| corticotropin releasing hormone receptor 1                           | *Cnr1      |                      | 3.8             |
| protein phosphatase 1, regulatory (inhibitor) subunit 1B             | Ppp1r1b    |                      | 3.6             |
| calcitonin receptor-like                                             | Calcrl     |                      | 3.6             |
| adenylate cyclase activating polypeptide 1                           | *Adcya1    |                      | 3.5             |
| adenylate cyclase 3                                                  | *Adc3      |                      | 3.5             |
| adrenergic receptor kinase, beta 2                                   | Adrb2k2    |                      | 3.4             |
| calcitonin receptor                                                  | Calcr      | 14                   | 3.4             |
| phosphodiesterase 6A, cGMP-specific, rod, alpha                      | Pde6a      |                      | 3.2             |
| phosphodiesterase 9A                                                 | Pde9a      |                      | 0.3             |
| Name                                                                 | Gene Abbr. | Associated to others | Fold difference |
|---------------------------------------------------------------------|------------|-----------------------|-----------------|
| piccolo                                                             | Pclo       |                       | 0.3             |
| 5-hydroxytryptamine (serotonin) receptor 4                         | Htr4       |                       | 0.3             |
| cAMP responsive element binding protein-like 2                     | Crebl2     |                       | 0.3             |
| CD52 antigen                                                        | Cd52       |                       | 0.3             |
| phosphodiesterase 8A                                               | Pde8a      |                       | 0.3             |
| Iroquois related homeobox 4                                        | Irox6      |                       | 0.3             |
| gastric inhibitory polypeptide receptor                            | *Gipr      |                       | 0.3             |
| frizzled homolog 2                                                 | Fzd2       |                       | 0.3             |
| phosphodiesterase 6G, cGMP-specific, rod, gamma                    | *Pde6g     |                       | 0.2             |
| WAS protein family, member 2                                        | *Wasf2     |                       | 0.2             |
| histamine receptor H3                                               | *Hrh3      |                       | 0.2             |
| guanine nucleotide binding protein, alpha stimulating, olfactory type | Gna         |                       | 0.2             |
| cyclic nucleotide-gated cation channel                             | Cnga1      |                       | 0.2             |
| tubulin, beta 3                                                    | *Tubb3     |                       | 0.2             |
| glutamate receptor, metabotropic 7                                  | Grm7       |                       | 0.2             |
| adenylyl cyclase 6                                                  | *Adcy6     |                       | 0.2             |
| 5-hydroxytryptamine (serotonin) receptor 1B PDZ domain containing 3 | Htr1b Pdzk2 |                       | 0.2             |
| adenylyl cyclase 4                                                  | *Adcy4     |                       | 0.1             |
| trace-amine-associated receptor 1                                   | Taar1      |                       | 0.1             |
| phosphodiesterase 6H, cGMP-specific, cone, gamma                   | Pde6h      |                       | 0.1             |
| 5-hydroxytryptamine (serotonin) receptor 1F                        | Htr1f      |                       | 0.1             |
| regulator of G-protein signaling 7                                 | Rgs7       |                       | 0.1             |
| cannabinoid receptor 1                                              | *Cnr1      |                       | 0.1             |
| melanocortin 4 receptor                                            | *Mc4r      |                       | 0.1             |
| doublesex and mab-3 related transcription factor 1                 | *Dmrt1     |                       | 0.1             |
| purinergic receptor P2Y, G-protein coupled 12                       | *P2ry12    |                       | 0.1             |
| adenylyl cyclase 8                                                  | *Adcy8     |                       | 0.04            |
| G protein-coupled receptor kinase 5                                 | *Gprk5     |                       | 9.1,0.3         |
| regulator of G-protein signaling 16                                 | *Rgs16     |                       | 8.6,0.1         |
| histamine receptor H 2                                              | Hrh2       |                       | 8.6,0.1         |
| G protein-coupled receptor 24                                       | Gpr24      |                       | 6.1,0.3         |
| protein kinase, cGMP-dependent, type II                            | *Prkg2     |                       | 5.7,0,2         |
| melanocortin 5 receptor                                            | Mc5r       |                       | 5.5,0.1         |
| galanin receptor 1                                                  | Ga1r1      |                       | 4.3,0.3         |
| glucagon-like peptide 1 receptor                                   | Glp1r      |                       | 3.7,0.2         |
| Soluble adenylyl cyclase                                           | *Sac       |                       | 3.5,0,3         |
| neurofibrinomatosis 1                                              | *Nfl       |                       | 18-19           |
| **14 Phosphoinositide mediated signaling pathway**                 |            |                       |                 |
| insulin-like growth factor binding protein 1                       | *Igf2bp1   |                       | 64.7            |
| angiogenin, ribonuclease A family, member 1                         | *Ang1      |                       | 58.2            |
| pleckstrin 2                                                        | Pk2        |                       | 33.4            |
| sperm associated antigen 5                                          | *Spag5     |                       | 31.9            |
| high-mobility group box 2                                           | Hmgb2      |                       | 19.6            |
| FK506 binding protein 1b                                            | Fkbp1b     |                       | 18.4            |
| endothelin 2                                                        | Edn2       |                       | 16.0            |
| thymidylate synthase                                               | Tys         |                       | 15.0            |
| topoisomerase (DNA) 2 alpha                                         | Top2a      |                       | 11.0            |
| proliferating cell nuclear antigen                                  | *PcnA      |                       | 10.6            |
| leukotriene B4 receptor                                             | *Ltb4r     |                       | 8.7             |
| prokineticin 2                                                      | *Prok2     |                       | 8.6             |
| phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1    | *Pik3r1    |                       | 7.6             |
| platelet-activating factor receptor                                 | *Ptafr     |                       | 7.1             |
| similar to phosphatidylinositol-3-phosphate/phosphatidylinositol 5-kinase type III | Loc316457 |                       | 6.5             |
| isoform 2                                                           |             |                       |                 |
| Sorting nexin 5                                                     | Snx5       |                       | 5.7             |
| membrane-spanning 4-domains, subfamily A, member 2                 | *Ms4a2     |                       | 5.3             |
| endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2 | *Edg2 | 15,17 | 5.2 |
| angiotensinogen                                                    | *Agt       |                       | 5.0             |
| protein kinase C, alpha binding protein                             | Prkcbp     |                       | 4.6             |
| Centaurin-alpha2 protein                                            | Centa2     |                       | 4.3             |
| pleckstrin homology domain containing, family A (phosphoinositide binding specific) member 4 | Plekha4 | | 4.3 |
| Name | Gene Abbr. | Associated to others | Fold difference |
|------|------------|----------------------|-----------------|
| homer homolog 1 | Homer1 | 17 | 4.1 |
| unc-13 homolog A | Unc13a | 17 | 4.0 |
| G protein-coupled receptor 2 | *Gpr2 | 17 | 3.3 |
| sorting nexin 11 | Snx11 | 3.5 |
| insulin-like growth factor binding protein 5 | Igfbp5 | 17 | 3.3 |
| phosphatidylinositol 3-kinase, catalytic, alpha polypeptide | *Pik3ca | 17 | 3.3 |
| carbonic anhydrase 8 | Car8 | 3.3 |
| glutamate receptor, metabotropic 5 | *Grm5 | 17 | 3.2 |
| Phospholipase C, delta 4 | Plcd4 | 3.2 |
| sorting nexin 16 | Snx16 | 3.1 |
| sorting nexin 1 | Snx1 | 3.0 |
| phosphatidylinositol 3-kinase catalytic delta polypeptide | *Pik3cd | 0.3 |
| phosphoinositol-3-kinase, class 2, beta polypeptide | Pik3c2b | 0.3 |
| growth associated protein 43 | *Gap43 | 0.3 |
| cholecystokinin B receptor | Cckbr | 0.3 |
| complement component 3a receptor 1 | *C3ar1 | 0.3 |
| pyrimidinergic receptor P2Y, G-protein coupled, 4 | P2ry4 | 0.2 |
| thromboxane A2 receptor | *Tbxa2r | 0.2 |
| flap structure-specific endonuclease 1 | *Fen1 | 0.2 |
| hippocalcin | Hpcal | 0.2 |
| multiple PDZ domain protein | *Mpdz | 0.2 |
| phospholipase C, delta 3 | Plcd3 | 0.2 |
| sorting nexin 4 | Snx4 | 0.2 |
| low density lipoprotein receptor-related protein 1 | Lrp1 | 0.1 |
| RAS guanyl releasing protein 4 | Rasgrp4 | 17,19 | 0.1 |
| diacylglycerol kinase, theta | Dgkq | 0.1 |
| Junctophilin 2 | Jph2 | 0.1 |
| -erb-b2 erythoblastic leukemia viral oncogene homolog 2, neuro/glioblastoma | *Erbb2 | 17-18 | 0.1 |
| derived oncogene homolog (avian) | Cystr1 | 0.1 |
| cysteinyi leukotriene receptor 1 | *Htr2b | 15 | 0.1 |
| 5-hydroxytryptamine (serotonin) receptor 2B | *Rfc4 | 27.7,0.3 |
| ubiquitin-conjugating enzyme E2C | *Ube2c | 12.1,0.2 |
| sorting nexin 8 | Snx8 | 4.6,0.1 |
| chemokine (C-C motif) receptor 6 | *Ccr6 | 4.3,0.3 |
| phospholipase C, beta 2 | *Plch2 | 4.0,0.3 |
| pyrimidinergic receptor P2Y, G-protein coupled, 6 | P2ry6 | 3.6,0.1 |
| phosphatidylinositol 3 kinase, regulatory subunit, polypeptide 3 | *Pik3r3 | 3.5,0.3 |
| interleukin 2 | Il2 | 16 | 3.5,0.3 |
| cholecystokinin A receptor | *Cckar | 3.2,0.3 |
| unc-13 homolog B | Unc13b | 17 | 3.0,0.3 |

### III Nitric oxide mediated signal transduction
- nitric oxide synthase interacting protein | *Nosip | 10.6 |
- nitric oxide synthase trafficking | *Nostrin | 8 |
- metallothionein 1a | Mt1a | 4.9 |
- N-myristoyltransferase 2 | Nmt2 | 4.1 |
- guanylate cyclase 1, soluble, alpha 3 | *Gucy1a3 | 0.3 |
- nitric oxide synthase 3, endothelial cell | *Nos3 | 15 | 0.2 |

### IV Hormone mediated signaling pathway
- nucleoporin 62kDa | Nup62 | 7,15 | 6.6 |
- growth hormone secretagogue receptor | *Ghsr | 5.3 |
- endothelin converting enzyme-like 1 | Ecel1 | 5.0 |
- ghrelin precursor | *Ghr | 4.0 |

### V Carbohydrate mediated signaling pathway
- collectin sub-family member 12 | *Colec12 | 3.9 |
- C-type lectin domain family 7, member A | *Clec7a | 0.2 |

### VI Protein kinase cascade
- 15 I-KB kinase/NF-KB cascade
  - vesicle-associated membrane protein, associated protein a | *Vapa | 28.8 |
  - pyruvate dehydrogenase kinase, isoenzyme 1 | *Pdk1 | 18.45 |
| Name                                                                 | Gene Abbr. | Associated to others | Fold difference |
|----------------------------------------------------------------------|------------|----------------------|-----------------|
| ect2 oncogene                                                        | Ect2       | 18                   | 13.0            |
| nuclear factor of kappa light chain gene enhancer in B-cells inhibitor, beta | Nfkibib    | 11.8                 |                 |
| caspase 8                                                            | Casp8      | 17                   | 10.6            |
| adipocytecomplementrelatedproteinof30kDa                            | Adc        |                      | 9.2             |
| FYN binding protein                                                  | Fyb        | 16-17                | 9.2             |
| germ cell associated 2                                               | Gsg2       | 16-17                | 9.2             |
| PTK2 protein tyrosine kinase 2                                       | Ptk2       | 8.9                  |                 |
| Nedd4 family interacting protein 1                                   | Ndfip1     | 6.9                  |                 |
| nuclear factor of kappa light chain gene enhancer in B-cells inhibitor, alpha lectin, galactose binding, soluble 9 | Nfkbia     | 17                   | 6.8             |
| tumor necrosis factor receptor superfamily, member 10b              | Lgals9     | 5.7                  |                 |
| tribbles homolog 3                                                   | Trib3      | 16-17                | 4.9             |
| carbonic anhydrate 10                                                | Car10      |                      | 4.9             |
| mitogen-activated protein kinase kinase kinase kinase 4              | Map4k4     | 17-18                | 4.5             |
| extracellular matrix protein 1                                       | Ecm1       |                      | 4.5             |
| growth factor receptor-bound protein 10                              | Grb10      |                      | 4.3             |
| toll-like receptor adaptor molecule 2                                | Ticam2     |                      | 4.3             |
| lectin, galactose binding, soluble 1                                 | Lgals1     | 17                   | 3.7             |
| Programmed cell death protein 11                                     | Pdcd11     |                      | 3.7             |
| CXXC finger 5                                                        | Cxxc5      |                      | 3.6             |
| transformed mouse 3T3 cell double minute 2 homolog                   | Mdm2       | 16-17                | 3.5             |
| MAP kinase-interacting serine/threonine kinase 2                     | Mnk2       | 16-17                | 3.5             |
| caspase recruitment domain family, member 9                          | Card9      | 17                   | 3.5             |
| G substrate                                                         | Gsbs       | 16-17                | 3.2             |
| PTEN induced putative kinase 1                                       | Pink1      | 16-17                | 3.2             |
| ADAM metallopeptidase domain 9                                       | Adam9      | 16-17                | 3.2             |
| carbonic anhydrate 14                                                | Car14      |                      | 3.2             |
| protein kinase N1                                                    | Pkn1       | 16-17                | 3.2             |
| ribosomal protein S6 kinase, polypeptide 1                           | Rps6kb1    | 18                   | 3.2             |
| 5-azacytidine induced gene 2                                         | Azi2       |                      | 3.1             |
| caspase 1                                                            | Casp1      | 17                   | 3.0             |
| inositol polyphosphate-5-phosphatase D                               | Inpp5d     | 17                   | 0.3             |
| mindbomb homolog 2                                                   | Mib2       |                      | 0.3             |
| peroxisome proliferator activated receptor dela                      | Ppard      |                      | 0.3             |
| erbb2 interacting protein                                            | Erbb2ip    | 17                   | 0.3             |
| inhibitor of kappaB kinase beta                                       | Ihk1b      | 17                   | 0.3             |
| B lymphoid kinase                                                    | Blik       | 16-17                | 0.3             |
| cell division cycle 37 homolog                                       | Cdc37      |                      | 0.3             |
| protein phosphatase 1A, magnesium dependent alpha isoform            | Ppm1a      | 17                   | 0.3             |
| CD80 antigen                                                         | Cd80       | 18                   | 0.3             |
| fibroblast growth factor 1                                            | Fgfl       | 16-17                | 0.3             |
| Ras homolog gene family, member C                                    | Rhoc       | 17,20                | 0.3             |
| centaurin, beta 1                                                    | Ccntb1     |                      | 0.2             |
| choline kinase alpha                                                 | Chka       | 18                   | 0.2             |
| homeodomain interacting protein kinase 2                             | Hipk2      | 17                   | 0.2             |
| caspase recruitment domain family, member 11                         | Card11     | 17                   | 0.2             |
| tuberous sclerosis 1                                                 | Tsc1       | 20                   | 0.1             |
| growth factor receptor bound protein 2-associated protein 2          | Gbk2       |                      | 14.9,0.3        |
| Ribosomal protein S6 kinase, polypeptide 2                           | Rps6kb2    | 16-17                | 12.1,0.3        |
| microtubule associated serine/threonine kinase 1                     | Mast1      | 16-17                | 6.1,0.2         |
| bcl2-associated death promoter                                       | Bad        | 17-18                | 5.5,0.3         |
| checkpoint kinase 1 homolog                                          | Chek1      |                      | 5.3,0.3         |
| mitogen-activated protein kinase kinase 8                             | Map3k8     |                      | 4.6,0.2         |
| secreted and transmembrane 1                                         | Sectm1     | 17                   | 4.0,0.2         |
| neutrophil cytosolic factor 1                                         | Ncf1       |                      | 3.7,0.2         |

**16 Jak-Stat cascade**

| myelocytomatosis viral oncogene homolog                             | Myc        | 17                   | 19.7            |
| Son of sevenless homolog 1                                          | Sos1       | 17,19-20             | 14.9            |
| ankyrin repeat and SOCS box-containing protein 2                    | Ash2       |                      | 9.2             |
| Janus kinase 2                                                      | Jak2       | 17                   | 6.5             |
| WD repeat and SOCS box-containing 1                                 | Wshb1      | 17                   | 4.5             |
| signal transducer and activator of transcription 4                 | Stat4      |                      | 4.0             |
| Name                                                                 | Gene Abbr.  | Associated to others | Fold difference |
|----------------------------------------------------------------------|-------------|----------------------|-----------------|
| SH2-B PH domain containing signaling mediator 1                      | Sh2bpsm1    |                      | 3.5             |
| leukemia inhibitory factor                                           | *Lif        |                      | 3.0             |
| Stam binding protein                                                 | Stambp      |                      | 0.3             |
| Signal transducer and activator of transcription 5B                 | *Stat5b     |                      | 0.3             |
| coagulation factor 2                                                 | *F2         |                      | 0.3             |
| Suppressor of cytokine signaling 2                                   | Socs2       |                      | 0.3             |
| signal transducer and activator of transcription 5A                 | *Stat5a     |                      | 0.2             |
| ankyrin repeat and SOCS box-containing protein 6                      | Asb6        |                      | 0.2             |
| tyrosine kinase 2                                                    | Tyk2        |                      | 0.2             |
| proviral integration site 1                                           | Pim1        |                      | 0.2             |
| interleukin 22 receptor, alpha 2                                     | *Il22ra2    |                      | 0.1             |
| interleukin 4                                                        | *I4         | 17                   | 0.1             |
| suppressor of cytokine signaling 3                                   | *Socs3      | 17                   | 0.1             |
| CREB binding protein                                                 | *Crebbp     |                      | 0.1             |
| prolactin receptor                                                   | Ptrl        |                      | 0.04            |
| interleukin 6                                                        | *I6         | 17                   | 6.1, 0.3        |
| hepatocyte nuclear factor 4, alpha                                   | *Hnf4a      |                      | 4.5, 0.1        |
| similar to ankyrin repeat and SOCs box-containing protein 5          | Asb5        |                      | 3.0, 0.3        |
| 17 MAPK cascade                                                       |             |                      |                 |
| growth arrest and DNA-damage-inducible 45 beta                       | *Gadd45b    |                      | 55.7            |
| FBJ murine osteosarcoma viral oncogene homolog                       | *Fos        |                      | 28.4            |
| protein tyrosine phosphatase, receptor type, R                       | Ptprr       |                      | 26.7            |
| G protein pathway suppressor 2                                        | *Gps2       |                      | 24.3            |
| E2F transcription factor 1                                            | *E2f1       | 18                   | 21.2            |
| mitogen-activated protein kinase 8                                   | *Mapk8      |                      | 19.7            |
| early growth response 1                                              | *Egr1       |                      | 18.6            |
| sema domain, immunoglobulin domain (Ig), transmembrane domain (TM)  |             |                      |                 |
| and short cytoplasmic domain, (semaforin) 4D                        | *Sema4d     |                      | 10.0            |
| connective tissue growth factor                                      | *Ctgf       |                      | 13.9            |
| plasminogen activator, urokinase receptor                            | *Plaur      |                      | 13.9            |
| mitogen-activated protein kinase-activated protein kinase 3          | Mapkapk3    |                      | 12.1            |
| heat shock 27kDa protein 1                                            | *Hspb1      |                      | 11              |
| sperm associated antigen 9                                            | Spag9       |                      | 10.8            |
| caveolin                                                             | *Cav        |                      | 10.6            |
| toll-like receptor 2                                                 | *Tlr2       |                      | 10.6            |
| matrix metalloproteinase 9                                           | *Mmp9       |                      | 9.5             |
| mitogen activated protein kinase 1                                   | *Map2k1     |                      | 9.1             |
| mitogen-activated protein kinase 8 interacting protein 2             | Mapkapk8p2  |                      | 8.6             |
| MAP3K12 binding inhibitory protein 1                                 | Mibp        |                      | 8.6             |
| ELK1, member of ETS oncogene family                                  | *Elk1       | 18                   | 8.6             |
| mitogen activated protein kinase kinase kinase kinase 1              | Mapkapk1    | 18                   | 8.5             |
| mitogen-activated protein kinase kinase 1                            | Map2k1lp1   |                      | 8.3             |
| interacting protein 1 Protein kinase C, beta 1                       | *Prkcb1     |                      | 8.2             |
| growth arrest and DNA-damage-inducible 45 gamma                      | *Gadd45g    |                      | 8.0             |
| cell division cycle 25 homolog B                                    | *Cdc25B     |                      | 8.0             |
| protein kinase, AMP-activated, alpha 1 catalytic subunit             | *Prkaa1     |                      | 7.5             |
| cerebral cavernous malformation 2                                    | Ccm2        |                      | 7.5             |
| Jun-B oncogene                                                       | *Junb       |                      | 7.0             |
| v-jun sarcoma virus 17 oncogene homolog                              | *Jun        |                      | 6.9             |
| Discs, large homolog 5                                               | *Dlk5       |                      | 6.9             |
| fibroblast growth factor 9                                           | *Fgf9       |                      | 6.6             |
| serum/glucocorticoid regulated kinase                                | *Sgg        |                      | 6.5             |
| sprouty-related, EVH1 domain containing 2                           | *Sprd2      |                      | 6.4             |
| Amyloid beta (A4) precursor protein                                  | *App        |                      | 6.4             |
| mitogen activated protein kinase 13                                  | *Mapk13     |                      | 6.1             |
| fibroblast growth factor 13                                          | Fgf13       |                      | 6.1             |
| protein phosphatase 3, regulatory subunit B, alpha isoform,type 1    | Ppp3r1      |                      | 6.0             |
| dual specificity phosphatase 1                                       | Dusp1       |                      | 6.0             |
| RAS related protein 1b                                               | Rap1b       | 19                   | 5.6             |
| ribosomal protein S6 kinase, 90kDa, polypeptide 5                    | *Rps6ka5    |                      | 5.6             |
| stathmin-like 4                                                      | Stmn4       |                      | 5.3             |
| src homology 2 domain-containing transforming protein C3              | *Shc3       |                      | 5.3             |
| Name                                                                 | Gene Abbr. | Associated to others | Fold difference |
|----------------------------------------------------------------------|------------|----------------------|-----------------|
| LIM motif-containing protein kinase 2                                 | *Limk2     | 20                   | 5.3             |
| fibroblast growth factor receptor substrate 2                        | Frs2       | 5.3                  |                 |
| mitogen-activated protein kinase 6                                    | *Mapk6     | 5.3                  |                 |
| integrin, alpha V                                                    | *Itgav     | 5.2                  |                 |
| alpha 1 microglobulin/bikunin                                        | *Ambp      | 5.1                  |                 |
| Moesin                                                               | *Msn       | 5.0                  |                 |
| leucine rich repeat protein 3                                         | Lrn3       | 4.9                  |                 |
| TAO kinase 1                                                         | Taok1      | 4.9                  |                 |
| arrestin, beta 2                                                     | Arreb2     | 4.9                  |                 |
| plasminogen activator, tissue                                        | *Plat      | 4.9                  |                 |
| RAS, guanyl releasing protein 3                                       | Rasgrp3    | 4.9                  |                 |
| Src homology 2                                                        | *Shc2      | 4.8                  |                 |
| domain-containing transforming protein C2 docking protein 2          | Dok2       | 19                   | 4.6             |
| protein kinase C, alpha                                              | *Prkca     | 4.6                  |                 |
| Amyloid beta (A4) precursor protein-binding, family A, member 1       | Atpa1      | 4.6                  |                 |
| inositol 1,4,5-trisphosphate 3-kinase B                               | Itpkb      | 18                   | 4.5             |
| Myeloid cell leukemia sequence 1                                     | *Mcl1      | 4.3                  |                 |
| activin A receptor, type IC                                          | *Acvrlc    | 4.3                  |                 |
| transforming growth factor, beta 1                                   | *Tgfb1     | 4.0                  |                 |
| RAS p21 protein activator 2                                           | Ras2a      | 19                   | 4.0             |
| TAO kinase 2                                                         | Taok2      | 4.0                  |                 |
| FYVE, RhoGEF and PH domain containing 4                              | Fgkd4      | 20                   | 4.0             |
| ATPase, H+ transporting, lysosomal accessory protein 2                | Atpp6ap2   | 20                   | 4.0             |
| V-akt murine thymoma viral oncogene homolog 1                        | *Akt1      | 3.9                  |                 |
| fibroblast growth factor 4                                            | *Fgd4      | 3.9                  |                 |
| RAS protein-specific guanine nucleotide-releasing factor 2            | Rasgrf2    | 19                   | 3.9             |
| nerve growth factor, beta                                            | *Ngbf      | 3.7                  |                 |
| Protein tyrosine kinase 2 beta                                       | *Ptck2b    | 20                   | 3.6             |
| microtubule-associated protein 2                                     | *Mtap2     | 3.6                  |                 |
| Enigma homolog                                                       | Enh        | 3.6                  |                 |
| phosphoprotein enriched in astrocytes 15                             | Pea15      | 3.6                  |                 |
| v-crk sarcoma virus CT10 oncogene homolog (avian)-like               | *Crlk      | 18                   | 3.5             |
| Src homology 2 domain containing transforming protein D              | Shd        | 3.5                  |                 |
| dual specificity phosphatase 19                                      | Dusp19     | 3.5                  |                 |
| protein phosphatase 1 (formerly 2C)-like                             | Ppm11      | 3.4                  |                 |
| Rho guanine nucleotide exchange factor 7                             | Arhgef7    | 20                   | 3.3             |
| serine/threonine kinase 38 like                                      | Stk38l     | 3.3                  |                 |
| NADPH oxidase organizer 1                                            | Noxo1      | 3.2                  |                 |
| macrophage migration inhibitory factor                               | *Mif       | 3.2                  |                 |
| protein kinase C, eta                                                | *Prkch     | 3.2                  |                 |
| sprouty protein with EVH-1 domain 1, related sequence                | Spred1     | 3.2                  |                 |
| arginine vasopressin-induced 1                                       | *Avp1      | 3.2                  |                 |
| gonadotropin-releasing hormone 1                                     | Gnrh1      | 3.1                  |                 |
| CCAAT/enhancer binding protein (C/EBP), beta                        | *Cebp      | 3.1                  |                 |
| high mobility group nucleosomal binding domain 1                     | *Hmg1      | 3.0                  |                 |
| protein kinase C, theta                                              | *Prkqc     | 3.0                  |                 |
| A kinase (PRKA) anchor protein 7                                      | Akap7      | 3.0                  |                 |
| plasminogen activator, urokinase                                     | *Plau      | 3.0                  |                 |
| ret proto-oncogene                                                   | *Ret       | 0.3                  |                 |
| SH3-domain binding protein 2                                         | Sh3bp2     | 0.3                  |                 |
| tumor necrosis factor receptor superfamily, member 19                | Tnfrsf19   | 0.3                  |                 |
| Protein phosphatase 3, catalytic subunit, gamma isoform              | Ppp3cc     | 0.3                  |                 |
| RAS p21 protein activator 3                                          | Rasa3      | 19                   | 0.3             |
| actin related protein 2/3 complex, subunit 5                         | Arcp5      | 0.3                  |                 |
| Similar to PHD finger protein 20-like 1 isoform 1                    | *Prkci     | 0.3                  |                 |
| B-cell leukemia/lymphoma 2                                          | *Bcl2      | 0.3                  |                 |
| mitogen-activated protein kinase 11                                   | Mapk11     | 0.3                  |                 |
| protein kinase C, nu                                                | Prkcn      | 0.3                  |                 |
| hypocretin (orexin) receptor 1                                       | Hcrtr1     | 0.3                  |                 |
| nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1 | *Nfatc1 | 0.3                  |                 |
| MAP-kinase activating death domain                                   | *Madd      | 0.3                  |                 |
| ataxia telangiectasia mutated homolog                               | *Atm       | 0.3                  |                 |
| Name                                                                 | Gene Abbr. | Associated to others | Fold difference |
|----------------------------------------------------------------------|------------|----------------------|-----------------|
| colony stimulating factor 2                                           | *Csf2      |                      | 0.3             |
| fibroblast growth factor 8                                            | *Fgf8      |                      | 0.2             |
| RAS protein-specific guanine nucleotide-releasing factor 1            | Rasgrf1    |                      | 19              |
| adrenergic receptor kinase, beta 1                                    | Adrbk1     |                      | 2.0             |
| integrin beta 3                                                       | *Igb3      |                      | 2.0             |
| heat shock 70kD protein 1B                                             | *Hspa1a     |                      | 0.2             |
| choleric receptor, nicotinic, alpha polypeptide 7                      | *ChrnA7     |                      | 0.2             |
| dual specificity phosphatase 16                                       | *Dusp16     |                      | 0.2             |
| muscle and microspikes RAS                                            | *Mras      |                      | 0.2             |
| mitogen-activated protein kinase 12                                    | *Mapk12     |                      | 0.2             |
| TXK tyrosine kinase                                                    | Txk        |                      | 0.2             |
| fibroblast growth factor receptor 1                                   | *Fgfr1      |                      | 0.1             |
| solute carrier family 2, member 4                                     | *Slc2a4     |                      | 0.1             |
| v-crk sarcoma virus CT10 oncogene homolog (avian)                     | *Crk       |                      | 18              |
| involucrin                                                            | Ivl        |                      | 0.1             |
| nephrosis 1 homolog                                                   | Nphs1      |                      | 0.1             |
| neurotrophin 3                                                        | *Ntr3      |                      | 0.1             |
| prostaglandin-endoperoxide synthase 2                                 | *Ptgs2      |                      | 0.1             |
| bone morphogenetic protein 4                                          | *Bmp4      |                      | 0.1             |
| coagulation factor 3                                                  | *F3        |                      | 0.1             |
| similar to KIAA0303                                                   | Rgd1310139  |                      | 0.1             |
| dual specificity phosphatase 8                                        | Dusp8      |                      | 0.1             |
| neurturin                                                             | Nrtn       |                      | 0.1             |
| 24-dehydrocholesterol reductase                                       | *Dhcr24     |                      | 18              |
| serum/glucocorticoid regulated kinase 2                                | Sgk2       |                      | 0.1             |
| CCAAT/enhancer binding protein (C/EBP), alpha                         | *CebpA     |                      | 0.1             |
| retinitis pigmentosa 1 homolog                                       | *Rp1h      |                      | 59.7, 0.2       |
| interleukin 1 receptor, type II                                       | Il1r2      |                      | 9.8, 0.2        |
| chymase 1, mast cell                                                  | Cma1       |                      | 9.8, 0.2        |
| NADPH oxidase 1                                                       | *Nox1      |                      | 8.6, 0.3        |
| adrenergic receptor, alpha 2c                                         | Adra2c     |                      | 8.6, 0.2        |
| nuclear receptor subfamily 0, group B, member 2                       | *Nrb2      |                      | 8.6, 0.2        |
| endothelial differentiation, sphingolipid G-protein-coupled receptor, 5 | Edg5       |                      | 8.4, 0.3        |
| nuclear receptor subfamily 4, group A, member 1                       | *NRA4a1    |                      | 7.5, 0.2        |
| collagen, type III, alpha 1                                           | *Col3a1    |                      | 6.5, 0.3        |
| transforming growth factor, beta 3                                    | *Tgfb3      |                      | 6.1, 0.2        |
| phospholipase C, delta 1                                              | *Pldc1     |                      | 5.5, 0.2        |
| BCL2-like 1                                                           | Bcl2l11    |                      | 5.4, 0.2        |
| ELK4, member of ETS oncogene family                                   | *Elk4      |                      | 5.3, 0.3        |
| megakaryocyte-associated tyrosine kinase                              | *Matk      |                      | 4.9, 0.3        |
| zinc finger protein 3                                                 | *Zfp36     |                      | 4.6, 0.1        |
| vascular endothelial growth factor A                                  | *Vega      |                      | 4.5, 0.1        |
| v-ets erythroblastosis virus E26 oncogene like (avian)                | *Erg       |                      | 4.3, 0.2        |
| mitogen-activated protein kinase kinase 6                             | Map3k6     |                      | 4.0, 0.3        |
| death-associated kinase 2                                             | Dapk2      |                      | 3.5, 0.1        |
| stathmin-like 2                                                       | Smm2       |                      | 3.3, 0.1        |
| v-mos moloney murine sarcoma viral oncogene homolog                   | *Mos       |                      | 3.2, 0.3        |
| DNA fragmentation factor, alpha subunit                               | *Dff4      |                      | 3.2, 0.3        |

**VII Small GTPase mediated signal transduction**

**18 General**

| Name                                                                 | Gene Abbr. | Fold difference |
|----------------------------------------------------------------------|------------|-----------------|
| hecdomain and RCC1 -like domain 1                                    | Herc1      | 7.2             |
| guanine nucleotide binding protein, gamma 2                          | Gng2       | 7.0             |
| retinal G protein coupled receptor                                    | *Rgr       | 6.1             |
| pleckstrin homology, Sec7 and coiled/coil domains 2                   | Pscd2      | 9.2             |
| membrane associated guanylate kinase, WW and PDZ domain containing 1 | *Magl1     | 5.0             |
| similar to RRP22                                                      | Rgd1306100 | 5.0             |
| regulator of G-protein signaling 19                                   | Rgs19      | 4.5             |
| deleted in polyposis 1                                               | *Dp1       | 4.0             |
| ubiquitin specific protease 8                                         | Usp8       | 3.7             |
| hecdomain and RCC1 -like domain 2                                    | *Rehn      | 0.3             |
| chromosome condensation 1-like                                       | Eif2b2     | 0.2             |
| eukaryotic translation initiation factor 2B, subunit 2 beta           | Chc11      | 0.2             |
Table 1 (Continued)

| Name                                                                 | Gene Abbr.       | Associated to others | Fold difference |
|----------------------------------------------------------------------|------------------|----------------------|-----------------|
| Reelin                                                               | Herc2            |                      | 0.1             |
| hypothetical protein LOC303515                                      | Loc303515        |                      | 3.9, 0.2        |
| Notch gene homolog 2                                                 | Pscd3            |                      | 3.5, 0.2        |
| pleckstrin homology, Sec7 and coiled/coil domains 1                  | Pscd1            |                      | 3.5, 0.1        |
| pleckstrin homology, Sec7 and coiled-coil domains 3                  | *Notch2          |                      | 3.1, 0.3        |

**19 Ras protein signal transduction**

| Ras and Rab interactor 1                                             | Rin1             | 21                   | 9.8             |
| regulatory factor X-associated ankyrin-containing protein            | Rfxank           |                      | 6.1             |
| kinase suppressor of ras 1                                           | *Ksr1            |                      | 6.1             |
| MIRO2 protein                                                        | Rhot2            |                      | 5.5             |
| Ras-related associated with diabetes                                 | Rrad             |                      | 4.9             |
| RasGEF domain family, member 1A                                       | Rasgef1a         |                      | 4.7             |
| Rap2A-like protein                                                   | Rap2a            |                      | 4.1             |
| Rap guanine nucleotide exchange factor 5                             | Rapgef5          |                      | 3.5             |
| soc-2 homolog                                                        | Shoc2            |                      | 3.2             |
| RASD family, member 2                                                | Rasd2            |                      | 3.1             |
| Ras and Rab interactor 2                                              | Cnksr1           | 20                   | 0.3             |
| HRAS-like suppressor                                                 | Rerg             |                      | 0.3             |
| GRB2-related adaptor protein                                          | *Dab2lp          |                      | 0.3             |
| Ras responsive element binding protein 1                             | Rgl1             |                      | 0.3             |
| v-ral simian leukemia viral oncogene homolog B                        | Rasgef1c         |                      | 0.2             |
| Ras-GTPase-activating protein SH3-domain binding protein             | G3Bp             |                      | 0.2             |
| RasGEF domain family, member 1C                                       | Ralb             |                      | 0.2             |
| ral guanine nucleotide dissociation stimulator,-like 1               | Rtebl            |                      | 0.2             |
| disabled homol 2 interacting protein                                 | Grap             |                      | 0.2             |
| connector enhancer of kinase suppressor of Ras 1                      | Hrasls           |                      | 0.2             |
| similar to RAS-like, estrogen-regulated, growth-inhibitor            | Rin2             | 21                   | 0.2             |
| RAP1, GTPase activating protein 1                                     | Rap1Ga1          |                      | 3.4, 0.3        |

**20 Rho/Rac/CDC42 protein signal transduction**

| IQ motif containing GTPase activating protein 3                       | Iqgap3           |                      | 27.7            |
| ras homolog gene family, member Q                                    | Rhoq             |                      | 14.0            |
| Rho, GDP dissociation inhibitor beta                                  | *Arhgdib         |                      | 13.0            |
| LIM motif-containing protein kinase 1                                 | *Limk1           |                      | 12.0            |
| ras homolog gene family, member f                                    | Rhof             |                      | 11.3            |
| B-cell leukemia/lymphoma 6                                           | *Bcl6            |                      | 8.6             |
| RhoB gene                                                            | *RhoB            |                      | 8.1             |
| Rho family GTPase 1                                                  | *Rnd1            |                      | 7.5             |
| oligophrenin 1                                                       | Ophn1            |                      | 6.9             |
| wiskott-Aldrich syndrome-like                                         | *Wasl            |                      | 6.8             |
| Rho guanine nucleotide exchange factor 5                             | Arhgef5          |                      | 6.2             |
| Cdc42-binding protein kinase beta                                     | Cdc42Bbp         |                      | 4.6             |
| engulfment and cell motility 1, ced-12 homolog                       | Elmo1            |                      | 4.2             |
| mcf.2 transforming sequence-like                                      | Mcf2L            |                      | 4.0             |
| FYVE, RhoGEF and PH domain containing 5                              | Fgd5             |                      | 3.5             |
| platelet/endothelial cell adhesion molecule 1                        | *Pecam1          |                      | 3.5             |
| synaptotagmin 2 binding protein                                       | Syn1/2Bp         |                      | 3.3             |
| ras homolog gene family, member V                                    | Rhov             |                      | 3.1             |
| Rho GTPase activating protein 20                                      | *Arhgap20        |                      | 3.1             |
| Rho GTPase activating protein 4                                       | Arhgap4          |                      | 3.0             |
| spermatogenesis associated 13                                         | Gmip             |                      | 0.3             |
| myosin Ixa                                                            | Rphp2            |                      | 0.3             |
| similar to Nedd4-binding brain specific protein BEAN                  | Arhgap1          |                      | 0.3             |
| FYVE, RhoGEF and PH domain containing 2                              | *Rho             |                      | 0.2             |
| rhodopsin                                                            | Fgd2             |                      | 0.2             |
| Rho GTPase activating protein 1                                       | Dock8            |                      | 0.2             |
| similar to RIKEN cDNA C230052112                                      | Myo9a            |                      | 0.1             |
| similar to Gem-interacting protein                                    | Spata13          |                      | 0.1             |
| lin-7 homolog b                                                      | *Lin7b           |                      | 7.5, 0.2        |
| cytosolic acetyl-CoA hydrolase                                        | Rach             |                      | 6.1, 0.2        |

**21 Rab protein signal transduction**

| RAB11B, member RAS oncogene family                                   | Rab11b           |                      | 14.0            |
| Name | Gene Abbr. | Associated to others | Fold difference |
|------|------------|----------------------|-----------------|
| RAB12, member RAS oncogene family | Rab12 | 12.1 |
| RAB34, member of RAS oncogene family | Rab34 | 5.1 |
| RAB3D, member RAS oncogene family | Rab3d | 4.8 |
| RAB6B, member RAS oncogene family | Rab6b | 4.2 |
| RAB21, member RAS oncogene family | Rab21 | 3.9 |
| RAB8A, member RAS oncogene family | Rab8a | 3.7 |
| low Mr GTP-binding protein | Rab27a | 3.4 |
| RAB8B, member RAS oncogene family | Rab8b | 3.4 |
| RAB13, member RAS oncogene family | Rab13 | 3.2 |
| RAB5B, member RAS oncogene family | Rab5b | 3.0 |
| Rab40b, member RAS oncogene family | Ms4 | 0.3 |
| RAB33b, member of RAS oncogene family | Rab3c | 0.2 |
| Ms4 protein | Chm | 0.1 |
| choroideremia | Rab33b | 0.1 |
| RAB3C, member RAS oncogene family | Rab40b | 0.1 |
| RAB25, member RAS oncogene family | Rab25 | 4.2,0.2 |
| RAB37, member of RAS oncogene family | Rab37 | 3.0,0.2 |

22 Ran protein signal transduction

RAN, member RAS oncogene family | Sipa1L3 | 5.7 |
signal-induced proliferation-associated 1 like 3 | Sipa1L2 | 4.5 |
signal-induced proliferation-associated 1 like 2 | Ran | 2, 3.2 |
GTPase activating RANGAP domain-like 4 | Garnl4 | 0.3 |
similar to RAN protein | Rgd1306195 | 7.0,0.3 |
RAN binding protein 1 | Ranbp1 | 3.2,0.1 |

23 Sar/Arf protein signal transduction

centaurin, gamma 3 | Centg3 | 8.9 |
ADP-ribosylation factor related protein 1 | Arfrp1 | 8.5 |
ADP-ribosylation factor-like 10 | Arl10 | 6.1 |
SAR1a gene homolog 1 | Sar1 | 5.4 |
ADP-ribosylation factor 4-like | Arf4l | 4.2 |
ADP-ribosylation factor interacting protein 2 | Arfip2 | 0.3 |

VIII ER-nuclear signaling pathway

cyclin D1 | Ccnd1 | 15,19, 7.5 |
interferon gamma | Ifng | 17, 6.5 |
p21 (CDKN1A)-activated kinase 1 | Pak1 | 17,20, 3.5 |
heat shock 70kD protein 5 | Hspa5 | 17, 0.1 |
reticulin 1 | Rtn1 | 9.2,0.2 |
protein phosphatase 1, regulatory (inhibitor) subunit 15b | Xbp1 | 4.3,0.3 |
X-box binding protein 1 | Ppp1r15b | 3.2,0.1 |

IX TOR signaling pathway

RhoGAP involved in beta-catenin-N-cadherin and NMDA receptor signaling | Rics | 3.5 |

X Genes associated with intracellular signaling cascade, but can’t be classed definit

InaD-like | Inadl | 4.3 |
PDZ and LIM domain 1 | Pdlim1 | 3.2 |
coronin, actin binding protein 2A | Coro2a | 0.3 |
thioesterase, adipose associated | Thea | 0.03 |
SH3 and cysteine rich domain 3 | Stac3 | 19.9,0.2 |
reversion induced LIM gene | Ril | 7.0,0.2 |
dishevelled 2, dsh homolog | Dvl2 | 4.6,0.2 |
neuralized-like 2 | Neurl2 | 3.9,0.1 |

*the reported genes associated with liver regeneration.