Exploration of the involvement of LncRNA in HIV-associated encephalitis using bioinformatics

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Background: HIV-associated encephalitis (HIVE) is one of the common complications of HIV infection, and the pathogenesis of HIVE remains unclear, while IncRNA might be involved it. In this study, we made re-annotation on the expression profiling from HIVE study in public database, identified the IncRNA might be involved in HIVE, and explored the possible mechanism. Methods: In the GEO public database, the microarray expression profile (GSE35864) of three regions of brain tissues (white matter, frontal cortex and basal ganglia brain tissues) was chosen, updated annotation was performed to construct the non-coding-RNA (ncRNA) microarray data. Morpheus was used to identify the differential expressed ncRNA, and Genbank of NCBI was used to identify IncRNAs. The StarBase, PITA and miRDB databases were used to predict the target miRNAs of IncRNA. The TargetScan, PicTar and MiRanda databases were used to predict the target genes of miRNAs. The GO and KEGG pathway analysis were used to make function analysis on the targets genes. Results: Seventeen differentially expressed IncRNAs were observed in the white matter of brain tissues, for which 352 target miRNAs and 6659 target genes were predicted. The GO function analysis indicated that the IncRNAs were mainly involved in the nuclear transcription and translation processes. The KEGG pathway analysis showed that the target genes were significantly enriched in 33 signal pathways, of which 11 were clearly related to the nervous system function. Discussion: The brand-new and different microarray results can be obtained through the updated annotation of the chips, and it is feasible to identify IncRNAs from ordinary chips. The results suggest that IncRNA may be involved in the occurrence and development of HIVE, which provides a new direction for further research on the diagnosis and treatment of HIVE.
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Abstract

**Background:** HIV-associated encephalitis (HIVE) is one of the common complications of HIV infection, and the pathogenesis of HIVE remains unclear, while lncRNA might be involved it. In this study, we made re-annotation on the expression profiling from HIVE study in public database, identified the lncRNA might be involved in HIVE, and explored the possible mechanism.

**Methods:** In the GEO public database, the microarray expression profile (GSE35864) of three regions of brain tissues (white matter, frontal cortex and basal ganglia brain tissues) was chosen, updated annotation was performed to construct the non-cording-RNA (ncRNA) microarray data. Morpheus was used to identify the differential expressed ncRNA, and Genbank of NCBI was used to identify lncRNAs. The StarBase, PITA and miRDB databases were used to predict the target miRNAs of lncRNA. The TargetScan, PicTar and MiRanda databases were used to predict the target genes of miRNAs. The GO and KEGG pathway analysis were used to make function analysis on the targets genes.

**Results:** Seventeen differentially expressed lncRNAs were observed in the white matter of brain tissues, for which 352 target miRNAs and 6659 target genes were predicted. The GO function analysis indicated that the lncRNAs were mainly involved in the nuclear transcription and translation processes. The KEGG pathway analysis showed that the target genes were significantly enriched in 33 signal pathways, of which 11 were clearly related to the nervous system function.

**Discussion:** The brand-new and different microarray results can be obtained through the updated annotation of the chips, and it is feasible to identify lncRNAs from ordinary chips. The results suggest that lncRNA may be involved in the occurrence and development of HIVE, which provides
a new direction for further research on the diagnosis and treatment of HIVE.
Introduction

Cognitive impairment is one of the challenges that HIV patients may face (Clifford & Ances 2013). HIV-1 enters the central nervous system through the blood-brain barrier at the initial infection stage, and a virus replicating area isolated from the body is formed in the central nervous system (Stam et al. 2013). Before the introduction of highly active anti-retroviral therapy (HAART), many HIV patients would soon suffer severe cognitive impairment, which is called HIV associated dementia (HAD), patients with HAD usually suffer from HIV-associated encephalitis (HIVE) (Masliah et al. 2000). Although HAART is very effective at present, HIV-induced brain inflammation has been frequently noticed in autopsy, and neurocognitive test results are abnormal in most HIV patients (Clifford & Ances 2013). Currently, HIV cannot be radically eradicated by any HIV therapy, and the anti-retroviral viruses can hardly pass the blood-brain barrier, so the central nervous system may become a virus repository, that might promote the occurrence and development of HIVE (Kumar et al. 2007). At present, the pathogenesis of HIVE is not very clear. Studying the molecular signaling pathways involved in HIVE would be significance for the prevention and treatment of HIVE.

In the human genome, more than 70% of the genes are transcribed into RNAs, but less than 2% of them are protein coding genes, and most of them are noncoding RNAs (Costa 2010). Non-coding RNAs (ncRNAs) regulate the expression of targeted genes through various pathways, and thus participate in various life processes of cells, tissues and organisms. According to the length, ncRNAs can be divided into small ncRNAs (<200 bp) and long ncRNAs (lncRNAs) (>200 bp). In recent years, studies have found that there are interactions between RNAs of different lengths,
especially the relationship between lncRNA, miRNA and mRNA, which form a regulatory
group of lncRNA-miRNA-mRNA. LncRNAs could be the “molecular sponges” of miRNAs,
that is, LncRNAs could bind to target miRNAs leading to the “silencing effect” attenuation of
miRNAs on target genes, thereby regulating the target genes of miRNAs (Salmena et al. 2011).

This study is aiming to identify the lncRNA might be involved in HIVE from expression profile,
and explore the possible mechanisms.

In recent years, expression microarray technology has played an important role in the research
on the disease occurrence and development, and many research results can be reviewed and
downloaded in the public database. Because updated annotation of microarray results has always
been continuing, new results and novel revelation can be accomplished through the re-annotation
and analysis of published studies on microarray results. In this study, we retrieved the HIVE study
related microarray data from the GEO database, re-annotated and analyzed these data, identified
the lncRNAs that might be involved in the pathogenesis of HIVE, and performed the correlation
analysis (the work flow was shown in Fig.1), aiming to verify the feasibility of identifying
lncRNAs from expression profile from public database and to explore the possible mechanisms of
lncRNAs participating in pathogenesis of HIVE.

**Materials and Methods**

**Microarray data**

The Gene Expression Omnibus (GEO, [http://www.ncbi.nlm.nih.gov/geo](http://www.ncbi.nlm.nih.gov/geo)), curated by the
National Center for Biotechnology Information (NCBI), is a public functional genomics database, and the data could be downloaded for free. In the GEO database, the microarray expression profile (GSE35864) in three regions of the brain, basal ganglia, white matter, and frontal cortex, in normal, HIV infected, HIV infected with neurocognitive impairment, and HIV infected with both neurocognitive impairment and encephalitis patients was chosen. Twenty-four human subjects in four groups were examined: Group A (n=6) HIV-1 uninfected with no neuropathological abnormalities at autopsy; Group B (n=6) HIV-1-infected (HIV+) neuropsychologically normal with no neuropathology; Group C (n=7) HIV+ with substantial HIV-associated neurocognitive impairment (HAND) as defined below, with no encephalitis (HIVE) or substantial neuropathological defect; Group D (n=5) HIV+ with HAND and HIVE. RNA from neocortex, white matter, and neostriatum was processed with the Affymetrix Human Genome U133 Plus 2.0 Array platform.

**Identifying differentially expressed lncRNAs**

First, the latest annotation files of HG-U133_Plus_2 Annotations, CSV format, Release 36 (7/12/16) of the Affymetrix Human Genome U133 Plus 2.0 Array were downloaded from the website [http://www.affymetrix.com/support/technical/annotationfilesmain.affx](http://www.affymetrix.com/support/technical/annotationfilesmain.affx), including the probe set ID, gene symbol, gene title, ensemble gene ID, Refseq transcript ID and information related to the probe. The gene expression data of the chips corresponded to the probe ID, and meanwhile, the probes were labeled with Refseq transcript ID through the NetAffx annotation. The probes with the “NR_” logo were identified in Refseq ID (NR representing nonencoding RNA). Morpheus ([https://software.broadinstitute.org/morpheus/](https://software.broadinstitute.org/morpheus/)) was used to analyze online and
identify the differential expressed “NR_” between the groups (Group A vs. Group D, Group B vs. Group D and Group C vs. Group D) of each region tissue (white matter, frontal cortex and basal ganglia brain tissues). This analysis was based on the t-test and adjusted according to the characteristic that the noise of microarray data was correlated with the peak value of expression data. We considered that p-value <0.01 was statistically significant. The number of upregulation and downregulation was 100). The Wayne map was drawn based on the intersection of the above results to select differential “NR_” participating in the occurrence and development of HIVE. The pseudogenes, rRNAs, microRNAs and other short RNAs (including tRNAs, snRNAs and snoRNAs) were filtered out through Genbank from NCBI database. The final remainder was the differential expressed lncRNAs.

Prediction of target miRNAs of LncRNAs and target genes

The sequences of lncRNAs were retrieved through NCBI Nucleotide (https://www.ncbi.nlm.nih.gov/nucleotide), which were then input into StarBase (http://starbase.sysu.edu.cn/), PITA (https://genie.weizmann.ac.il/pubs/mir07/mir07_data.html) and miRDB (http://www.mirdb.org/), to predict the target miRNAs of the lncRNAs. The miRNAs were input into TargetScan (http://www.targetscan.org/vert_71/), PicTar (http://pictar.mdc-berlin.de/) and MiRanda (http://www.microrna.org/microrna/home.do) to predict the corresponding target genes.

Function of lncRNA target genes and pathway cluster analysis

The Database for Annotation, Visualization and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) is an online program that provides a comprehensive set of functional
annotation tools for researchers to understand biological meaning behind many genes. Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed for the identified DEGs using the DAVID database. After GO functional enrichment analysis, we considered the biology process terms with p-value <0.05 was statistically significant. For KEGG analysis, we considered the subpathway with p-value <0.05 was statistically significant.

Results

1. Identifying differentially expressed IncRNAs

We re-annotated the GSE35864 and preliminarily retained 15901 probes only with the “NR_” logo in the Refseq transcript ID. The Morpheus online tool was used to analyze and identify the differentially expressed probes with the “NR_” logo between the groups (Group A vs. Group D, Group B vs. Group D and Group C vs. Group D) of each region tissue (white matter, frontal cortex and basal ganglia brain tissues). As shown in Fig. 2A, there were differentially expressed probes with the “NR_” logo between different groups in the white matter, among which those that may be involved in the occurrence and development of HIVE were identified, and a total of 63 ncRNAs were identified. As shown in Fig.2B, there were differentially expressed probes with the “NR_” logo between different groups in the frontal cortex, and the intersection was selected from each group. There was only 1 probe labeled with “NR_” intersected. As shown in Fig.2C, there were differentially expressed probes with the “NR_” logo between different groups in the basal ganglia, and the intersection was selected from each group. There were 12 common probes labeled with
“NR_” intersected. All the differential expressed ncRNAs with the “NR_” logo were searched in the GenBank, and 17 IncRNAs were identified in the white matter, without any differentially expressed IncRNAs in the frontal cortex and basal ganglia. These 17 IncRNAs were LINC00308, LOC100507387, SCOC-AS1, ALMS1-IT1, LINC00639, LOC101928847, LOC100134368, ZNF670-ZNF695, SHANK2-AS3, MEG9, SNHG7, TMEM44-AS1, LRRC8C-DT, MASP1, MAPT-AS1, TBX5-AS1, LINC01770. As shown in Figure 3, the expression of LINC00308, LOC100507387, SHANK2-AS3, SNHG7, MAPT-AS1 were significantly increasing in Group D, and the others were significantly decreasing.

2. Prediction of target miRNAs of IncRNAs and target genes

The target miRNAs of the IncRNAs were identified from the database, and a total of 352 target miRNAs were predicted in 17 differentially expressed IncRNAs (Table 1). The 6659 corresponding target genes of miRNAs were predicted by TargetScan, PicTar and MiRanda.

3. GO cluster analysis of target genes

The 6659 target genes were uploaded to the DAVID software, and the significant GO classification and KEGG pathway were selected. GO cell component (CC) analysis showed that the target genes were obviously clustered in the nucleus, cytoplasm, Golgi apparatus, lysosome, plasma membrane, etc. (Fig. 4a, Table 2). GO molecular function (MF) analysis revealed that the target genes were remarkably clustered in transcription factor activity, protein serine/threonine kinase activity, transcription regulator activity, ubiquitin-specific protease activity, etc. (Fig. 4b, Table 2). GO biological process (BP) analysis revealed that the target genes were significantly clustered in regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism, signal
transduction, cell communication, transport etc. (Fig. 4c, Table 2).

4. KEGG pathway analysis of target genes

Table 3 showed that 33 pathways were significantly enriched with target genes ($p<0.05$), which were obtained through KEGG analysis, including mucin type O-Glycan biosynthesis, proteoglycans in cancer, pathways in cancer, glutamatergic synapse, long-term depression and other relevant pathways (Fig. 4d). Eleven of these pathways may be related to the nervous system, including the glutamatergic synapse, axon guidance, Rap1 signaling pathway, Ras signaling pathway, synaptic vesicle cycle, ErbB signaling pathway, TGF-beta signaling pathway, cGMP-PKG signaling pathway, cholinergic synapse, Wnt signaling pathway and MAPK signaling pathway.

Discussion

There are two main highlights in the research. ① The differentially expressed IncRNAs were identified through the re-annotation of published microarray results. ② The target miRNAs of the IncRNAs and target genes were predicted using a bioinformatics method, and GO function and KEGG pathway analyses were performed to learn about the possible mechanisms of IncRNA involved in the occurrence and development of HIVE.

In recent years, hundreds of IncRNAs have been discovered, and the changes in the expression of IncRNAs have been associated with the occurrence and development of many diseases. Plenty of evidence has shown that IncRNA is involved in the replication process of the virus (Zhang et al. 2013) and that IncRNA is involved in the infection process of HIV through
changes in the cellular environment (Barichievy et al. 2015). However, the role of lncRNA in the occurrence and development of HIV-related encephalitis remains unclear. The mRNA, miRNA and lncRNA that were related to the diseases were identified by microarray and bioinformatic method, which has been applied in the study of many human diseases, just the same in the study of HIV-related encephalitis. Because the annotation of microarray results has been continuously updated, some new results may be obtained by the re-annotation and re-analysis of published chips in the common database. In the GEO public database, we retrieved more comprehensive microarray results of HIVE related study (multi-group and multi-organization types), and only differential analysis of the expression of mRNA in different brain tissues (the white matter, frontal cortex and basal ganglia brain tissues) of each group was carried out. We re-annotated the microarray results and identified possible ncRNA probe results to construct the ncRNA microarray results. In addition, we then compared and analyzed the results to identity differentially expressed ncRNAs that may be involved in the occurrence and development of HIVE. We identified 63 probes with the “NR_” logo in the white matter, one probe with the “NR_” logo in the frontal cortex, and 12 probes with the “NR_” logo in basal ganglia. All the probes with the “NR_” logo were retrieved, and it was found that only 17 probes with the “NR_” logo in the white matter were identified as lncRNAs. Among these 17 lncRNAs, expression of five were increasing in Group D, and the others were decreasing. As we found differentially expressed lncRNAs only in white matter, we speculated that cerebral white matter lesions may play an important role in the pathogenesis of HIV-associated encephalitis, which was also consistent with previous research results. The central nervous system injury affected by HIV-1 usually manifested microglial
nodules comprised of multinucleated giant cells and inflammatory cells. These lesions are particularly in white matter (Fischer-Smith et al. 2001) Neuronal damage in HIVE is generally attributed to fully activated microglia/macrophages, especially in white matter (Roberts et al. 2004). In addition, multinucleated giant cells and perivascular demyelination leading to white matter pallor are typical features of HIVE. In addition, these lncRNAs could be used as markers of white matter damage of HIVE. Based on the lncRNA-miRNA-mRNA mechanism, we used bioinformatics tools to predict target miRNAs and target genes of these 17 lncRNAs. GO and KEGG analysis were carried out to make the correlation cluster analysis on target genes, in order to explore the potential mechanisms of lncRNAs participating in HIVE. The GO cell component (CC) analysis results revealed that the target genes were significantly clustered in the nucleus, cytoplasm, Golgi apparatus, lysosome, plasma membrane, etc. The GO molecular function (MF) analysis showed that the target genes were significantly clustered in the transcription factor activity, protein serine/threonine kinase activity, transcription regulator activity, ubiquitin-specific protease activity and other molecular functions. The GO biological process (BP) analysis revealed that the target genes were significantly clustered in the regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism, signal transduction, cell communication, transport and other biological processes. Therefore, it was proven that lncRNAs may be involved in the occurrence and development of HIVE by way of their participation in the process of nuclear transcription and translation. The KEGG pathway analysis showed the target genes were significantly clustered in the mucin type O-glycan biosynthesis, proteoglycans in cancer, pathways in cancer, the glutamatergic synapse, long-term depression and other relevant pathways. In
previous research, it was found that a variety of pathways were involved in neurological disorders and even in the occurrence of HIVE. The pathway of glutamatergic synapse was related with the occurrence of encephalitis, and the patients with anti-NMDAR encephalitis had a diminished function of the glutamatergic synapse (Hughes et al. 2010). The expression changes of the glutamatergic synapse in the brain tissues were associated with the occurrence of hepatic encephalopathy (Montana et al. 2014). For the axon guidance pathway, it has been reported of relevant gene expression impairment of the axon guidance pathway and its downstream pathway (including MAPK pathway, calcium signaling pathway, Jak-STAT signaling pathway and VEGF signaling pathway) in the brain tissues of the patients with HIV-associated dementia, which provided new ideas for the diagnosis and treatment of HIV-associated dementia (Zhou et al. 2012). Both Rap1 signaling pathway and Ras signaling pathway were involved in such nervous system functions as glutamatergic synaptic transmission (Imamura et al. 2003), synaptic excitability (Imamura et al. 2004), synaptic reversibility (Masliah et al. 2004) etc. The abnormal expression of signaling pathway can cause encephalitis and other neuronal dysfunctions. The changes in the synaptic vesicle, especially the synaptic vesicle cycle, can cause abnormal neurotransmitter activity (Cortes-Saladelafont et al. 2016). For the ErbB signaling pathway, there were significant changes in the gene expression of ErbB signaling pathway in the brain tissues of the patients with HIV-associated dementia (Shityakov et al. 2015). The TGF-β signaling pathway was also involved in the pathophysiology of the nervous system, which can limit inflammation and reduce neurological damage in the nervous system infection process (Cekanaviciute et al. 2014). The TGF-β signaling pathway was also related with the tolerance of dendritic
cells (Esebanmen & Langridge 2017). Together with the STAT2 signaling pathway, the TGF-β signaling pathway can inhibit the progression of autoimmune encephalopathy (Xu et al. 2014). For the cGMP-PKG signaling pathway, its abnormality had something to do with the diseases of the nervous system, and reduced kinase activity in the cGMP-PKG signaling pathway was found in rats with hepatic encephalopathy. Cognitive disorders could be relieved when the NO/sGC/cGMP/PKG signaling pathway was inhibited in diabetic rats. The iNOS-NO-cGMP signaling pathway also was involved in nervous system inflammation and myelin formation (Raposo et al. 2014). The activation of the Wnt signaling pathway could promote the occurrence of autoimmune encephalitis (Schneider et al. 2016), and the Wnt signaling pathway was involved in the immunity and tolerance of dendritic cells (Swafford & Manicassamy 2015). Moreover, plasma Dickkopf-related protein 1, the antagonist of the Wnt signaling pathway, was associated with HIV-related cognitive deficits (Yu et al. 2017). Therefore, KEGG analysis showed that most of the significant clustering pathways were related with the function of the nervous system. Thus, the differentially expressed IncRNAs, act as “molecular sponges”, could affect the function of their target miRNAs, and thereby regulating target genes. It can be confirmed that IncRNA is indeed involved in the occurrence and development of HIV-related encephalopathy through the IncRNA-miRNA-gene mechanism. In addition, it could also be indirectly confirmed that it is feasible to construct a new chips by re-annotation and identify differentially expressed IncRNA from a expression chip.

Conclusions
The brand-new microarray results from a different perspective can be constructed through the updated annotation of the precious and published microarray data. In this study, the IncRNA results were obtained through the re-annotation of microarray data, which provides the foundation for further research on the role of IncRNA in the occurrence and development of HIV. From the point of view of the IncRNA-miRNA-target genes, cluster analysis was performed by various bioinformatic methods to explore the role of IncRNA. GO analysis showed that IncRNA may be involved in the occurrence and development of HIV via its participation in the nuclear transcription and translation. The KEGG pathway analysis showed that most of the KEGG pathways with statistical significance were associated with the function of the nervous system. Therefore, we can speculate that IncRNA is indeed involved in the occurrence and development of HIV, which is of great significance for future research on IncRNA on HIV. It is also proved that it is feasible to identify IncRNAs from public database.

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**Figure 1.** Schematic overview of the work flow.

**Figure 2.** Differentially expressed ncRNAs probe sets among Group A, Group B, Group C, Group D in white matter, frontal cortex and basal ganglia. a white matter; b frontal cortex; c basal ganglia. Group A: HIV-1 uninfected with no neuropathological abnormalities at autopsy; Group B: HIV-1-infected (HIV+) neuropsychologically normal with no neuropathology; Group C: HIV+ with substantial HIV-associated neurocognitive impairment (HAND) as defined below, with no encephalitis (HIVE) or substantial neuropathological defect; Group D: HIV+ with HAND and HIVE.

**Figure 3.** Heat map of 17 differentially expressed lncRNAs among Group A, Group B, Group C, Group D in white matter. Group A: HIV-1 uninfected with no neuropathological abnormalities at autopsy; Group B: HIV-1-infected (HIV+) neuropsychologically normal with no neuropathology; Group C: HIV+ with substantial HIV-associated neurocognitive impairment (HAND) as defined below, with no encephalitis (HIVE) or substantial neuropathological defect; Group D: HIV+ with HAND and HIVE.

**Figure 4.** Function of lncRNA target genes and pathway cluster analysis. a GO cell component (CC) analysis; b GO molecular function (MF) analysis; c GO biological process (BP) analysis; d KEGG pathway analysis.
Figure 1

Schematic overview of the work flow.
Figure 2

Differentially expressed ncRNAs probe sets among Group A, Group B, Group C, Group D in white matter, frontal cortex and basal ganglia.

a) white matter; b) frontal cortex; c) basal ganglia. Group A: HIV-1 uninfected with no neuropathological abnormalities at autopsy; Group B: HIV 1-infected (HIV+) neuropsychologically normal with no neuropathology; Group C: HIV+ with substantial HIV-associated neurocognitive impairment (HAND) as defined below, with no encephalitis (HIVE) or substantial neuropathological defect; Group D: HIV+ with HAND and HIVE.
Figure 3

Heat map of 17 differentially expressed IncRNAs among Group A, Group B, Group C, Group D in white matter.

Group A: HIV-1 uninfected with no neuropathological abnormalities at autopsy; Group B: HIV-1-infected (HIV+) neuropsychologically normal with no neuropathology; Group C: HIV+ with substantial HIV-associated neurocognitive impairment (HAND) as defined below, with no encephalitis (HIVE) or substantial neuropathological defect; Group D: HIV+ with HAND and HIVE.
Figure 4

Function of IncRNA target genes and pathway cluster analysis. a GO cell component (CC) analysis; b GO molecular function (MF) analysis; c GO biological process (BP) analysis; d KEGG pathway analysis.
**Table 1** (on next page)

Differentially expressed IncRNAs in white matter and their target miRNAs
| No. | Probe | Official Symbol | Target miRNAs predicted |
|-----|-------|----------------|-------------------------|
| **Upregulated lncRNAs** | | | |
| 1 | NR_038400 | LINC00308 | hsa-miR-1185-2-3p; hsa-miR-1185-1-3p; hsa-miR-6833-3p; hsa-miR-4768-5p; hsa-miR-3127-5p; hsa-let-7f-2-3p; hsa-miR-5187-5p; hsa-miR-5002-3p; hsa-miR-4741; hsa-miR-4675; hsa-miR-3653-3p |
| 2 | NR_038402 /// XR_941286 /// XR_941287 /// XR_941288 /// XR_941289 /// XR_941290 /// XR_941291 /// XR_941292 | LOC100507387 | hsa-miR-6876-5p; hsa-miR-4476; hsa-miR-6865-5p; hsa-miR-6815-5p; hsa-miR-6806-5p; hsa-miR-6739-5p; hsa-miR-6733-5p; hsa-miR-3153; hsa-miR-6878-3p; hsa-miR-4779; hsa-miR-8063; hsa-miR-4738-3p; hsa-miR-5584-5p; hsa-miR-4288; hsa-miR-3688-5p; hsa-miR-1206; hsa-miR-6797-5p; hsa-miR-3978; hsa-miR-1249-5p |
| 3 | NR_073536 | SHANK2-AS3 | hsa-miR-4447; hsa-miR-4713-3p; hsa-miR-516b-5p; hsa-miR-1229-3p; hsa-miR-6832-3p; hsa-miR-504-3p; hsa-miR-1275; hsa-miR-324-5p; hsa-miR-6736-3p; hsa-miR-4443; hsa-miR-676-5p; hsa-miR-4483; hsa-miR-296-5p; hsa-miR-1224-3p; hsa-miR-96-5p; hsa-miR-1271-5p |
| 4 | NR_003672 /// NR_024542 /// NR_024543 | SNHG7 | hsa-miR-6887-5p; hsa-miR-6795-5p; hsa-miR-3201; hsa-miR-4793-5p; hsa-miR-6887-5p; hsa-miR-6795-5p; hsa-miR-3201; hsa-miR-4793-5p; hsa-miR-6836-5p; hsa-miR-6132; hsa-miR-5095; hsa-miR-4267; hsa-miR-6778-3p; hsa-miR-504-3p; hsa-miR-4262; hsa-miR-6890-5p; hsa-miR-425-5p; hsa-miR-378a-5p; hsa-miR-7151-3p |
| 5 | NR_024559 | MAPT-AS1 | hsa-miR-6772-5p; hsa-miR-4463; hsa-miR-511-5p; hsa-miR-3175; hsa-miR-532-5p; hsa-miR-4441; hsa-miR-340-5p; hsa-miR-223-5p; hsa-miR-6895-3p |
| **Downregulated lncRNAs** | | | |
| 1 | NR_033939 | SCOC-AS1 | hsa-miR-1205; hsa-miR-4508; hsa-miR-3194-5p; hsa-miR-4441; hsa-miR-6510-5p; hsa-miR-6836-5p; hsa-miR-6132; hsa-miR-4516; hsa-miR-135b-5p; hsa-miR-135a-5p; hsa-miR-3192-5p; hsa-miR-8081; hsa-miR-6876-5p; hsa-miR-4756-5p; hsa-miR-4739; hsa-miR-1321; hsa-miR-3145-5p; hsa-miR-4427; hsa-miR-4748; hsa-miR-4464; hsa-miR-651-3p; hsa-miR-4524b-3p; hsa-miR-513a-5p; hsa-miR-6794-5p; hsa-miR-4716-3p; hsa-miR-3613-3p; hsa-miR-4668-5p; hsa-miR-6867-5p; hsa-miR-6753-5p; hsa-miR-450a-1-3p; hsa-miR-4752; hsa-miR-6794-3p; hsa-miR-3188; hsa-miR-937-5p; hsa-miR-6882-3p; hsa-miR-4328; hsa-miR-4476; hsa-miR-6727-5p; hsa-miR-5003-5p; hsa-miR-4268; hsa-miR-376c-5p; hsa-miR-376b-5p; hsa-miR-1252-5p; hsa-miR-608; hsa-miR-5581-3p; hsa-miR-4651; hsa-miR-4533 |
| 2 | NR_046762 | ALMS1-IT1 | hsa-miR-4499; hsa-miR-888-5p; hsa-miR-616-5p; hsa-miR-373-5p; hsa-miR-371b-5p; hsa-miR-1285-3p; hsa-miR-539-3p; hsa-miR-485-3p; hsa-miR-3685; hsa-miR-2052; hsa-miR-3143; hsa-miR-9-3p; hsa-miR-1303; |
|   |   |   |
|---|---|---|
| 3 | NR_039982 | LINC00639 |
|   | hsa-miR-548c-3p; hsa-miR-6867-3p; hsa-miR-381-3p; hsa-miR-300; hsa-miR-4801; hsa-miR-4731-3p; hsa-miR-6515-3p; hsa-miR-7844-5p; hsa-miR-506-5p; hsa-miR-5680; hsa-miR-4297; hsa-miR-155-3p; hsa-miR-660-3p; hsa-miR-6847-3p; hsa-miR-200a-3p; hsa-miR-141-3p; hsa-miR-6834-5p; hsa-miR-493-5p; hsa-miR-3911; hsa-miR-6073; hsa-miR-758-5p; hsa-miR-4426; hsa-miR-151a-3p; hsa-miR-323a-3p; hsa-miR-939-3p; hsa-miR-4262; hsa-miR-181b-5p; hsa-miR-181a-5p; hsa-miR-3653-5p; hsa-miR-7108-5p; hsa-miR-4742-5p; hsa-miR-6845-5p; hsa-miR-1227-5p; hsa-miR-3653-3p; hsa-miR-5088-3p; hsa-miR-6090; hsa-miR-631; hsa-miR-6762-5p; hsa-miR-4441; hsa-miR-3123; hsa-miR-6764-5p; hsa-miR-4690-5p; hsa-miR-532-3p; hsa-miR-4297; hsa-miR-4456; hsa-miR-550b-2-5p; hsa-miR-4283; hsa-miR-4281; hsa-miR-4742-5p; hsa-miR-4311; hsa-miR-330-3p; hsa-miR-8089; hsa-miR-4700-5p; hsa-miR-4667-5p |
| 4 | NR_120563 | LOC101928847 |
|   | hsa-miR-645; hsa-miR-134-3p; hsa-miR-3651; hsa-miR-5089-3p; hsa-miR-486; hsa-miR-890; hsa-miR-6512-5p; hsa-miR-6780b-5p; hsa-miR-4725-5p; hsa-miR-4271; hsa-miR-1296-3p; hsa-miR-653-5p; hsa-miR-302f; hsa-miR-491-5p; hsa-miR-6855-5p; hsa-miR-3170; hsa-miR-1236-3p; hsa-miR-93-3p; hsa-miR-663b; hsa-miR-4769-5p; hsa-miR-4654; hsa-miR-548aw; hsa-miR-548d-5p; hsa-miR-548b-5p; hsa-miR-548ay-5p; hsa-miR-548ac-5p; hsa-miR-548ad-5p; hsa-miR-548aj-5p; hsa-miR-4311; hsa-miR-3907; hsa-miR-4284; hsa-miR-744-5p; hsa-miR-6796-5p |
| 5 | NR_024453 | LOC100134368 |
|   | hsa-miR-6742-5p; hsa-miR-663a; hsa-miR-8060; hsa-miR-1827; hsa-miR-107; hsa-miR-103a-3p; hsa-miR-4441; hsa-miR-4456; hsa-miR-6134; hsa-miR-3911; hsa-miR-4478; hsa-miR-654-5p; hsa-miR-541-3p; hsa-miR-4764-5p; hsa-miR-548x-5p; hsa-miR-548g-5p; hsa-miR-548f-5p; hsa-miR-548aj-5p; hsa-miR-4311; hsa-miR-3907; hsa-miR-4284; hsa-miR-744-5p; hsa-miR-6796-5p |
| 6 | NR_037894 | ZNF670-ZNF695 |
|   | hsa-miR-5584-5p; hsa-miR-6780a-5p; hsa-miR-4668-5p; hsa-miR-548t-3p; hsa-miR-548ap-3p; hsa-miR-548aa; hsa-miR-134-3p; hsa-miR-4306; hsa-miR-6764-5p; hsa-miR-1915-3p; hsa-miR-605-3p; hsa-miR-627-3p; hsa-miR-6779-5p; hsa-miR-3689c; hsa-miR-3689b-3p; hsa-miR-3689a-3p; hsa-miR-30b-3p; hsa-miR-1273b-5p; hsa-miR-4482-3p; hsa-miR-3128; hsa-miR-4497; hsa-miR-4297; hsa-miR-548z; hsa-miR-548h-3p; hsa-miR-548d-3p; hsa-miR-548bb-3p; hsa-miR-548ac; hsa-miR-3653-3p |
| 7 | NR_047664 | MEG9 |
|   | hsa-miR-4535; hsa-miR-4319; hsa-miR-7107-3p; hsa-miR-6753-3p; hsa-miR-4447; hsa-miR-6722-3p; hsa-miR-6069; hsa-miR-4426; hsa-miR-6721-5p; hsa-miR-7150; hsa-miR-1275; hsa-miR-7111-5p; hsa-miR-6870-5p; hsa-miR-5698; hsa-miR-4723-5p; hsa-miR-7-5p; hsa-miR-6165; hsa-miR-6502-5p; hsa-miR-1301-5p; hsa-miR-125b-5p; hsa-miR-125a-5p; hsa-miR-1226-5p; hsa-miR-4329; hsa-miR-4692; hsa-miR-4306; hsa-miR-4463; hsa-miR-4483; hsa-miR-205-3p; hsa-miR-8085; hsa-miR-6731-5p; hsa-miR-4283; hsa-miR-
| NR_047573 /// NR_047574 /// NR_047575 | TMEM44-AS1 | hsa-miR-4468; hsa-miR-659-3p; hsa-miR-1304-5p; hsa-miR-4291; hsa-miR-661; hsa-miR-6801-5p; hsa-miR-6742-3p; hsa-miR-6813-5p; hsa-miR-6085; hsa-miR-3922-5p; hsa-miR-4650-5p; hsa-miR-4717-5p; hsa-miR-3119; hsa-miR-597-3p; hsa-miR-7975; hsa-miR-296-5p; hsa-miR-2110; hsa-miR-4468; hsa-miR-659-3p; hsa-miR-1304-5p; hsa-miR-4291; hsa-miR-661; hsa-miR-653-3p; hsa-miR-6823-3p; hsa-miR-2114-3p; hsa-miR-6801-5p; hsa-miR-6742-3p; hsa-miR-4261; hsa-miR-6813-5p; hsa-miR-6085; hsa-miR-3922-5p; hsa-miR-4650-5p; hsa-miR-4717-5p; hsa-miR-3119; hsa-miR-597-3p; hsa-miR-7975; hsa-miR-2110; hsa-miR-4468; hsa-miR-659-3p; hsa-miR-1304-5p; hsa-miR-4291; hsa-miR-661; hsa-miR-6823-3p; hsa-miR-2114-3p; hsa-miR-6801-5p; hsa-miR-6742-3p; hsa-miR-4261; hsa-miR-6813-5p; hsa-miR-6085; hsa-miR-3922-5p; hsa-miR-4650-5p; hsa-miR-4717-5p; hsa-miR-3119; hsa-miR-597-3p; hsa-miR-7975 |
| 9 | NR_033981 | LRR8C-DT | hsa-miR-3914; hsa-miR-194-3p; hsa-miR-937-3p; hsa-miR-608; hsa-miR-4651; hsa-miR-4707-5p; hsa-miR-1256; hsa-miR-561-5p; hsa-miR-4456; hsa-miR-1233-3p |
| 10 | NR_033519 | MASP1 | hsa-miR-4283; hsa-miR-6746-3p; hsa-miR-4441; hsa-miR-4763-5p; hsa-miR-1286; hsa-miR-5092; hsa-miR-4267; hsa-miR-4478; hsa-miR-1207-5p; hsa-miR-4531; hsa-miR-6768-3p; hsa-miR-4522; hsa-miR-6752-3p; hsa-miR-518c-5p; hsa-miR-6773-5p; hsa-miR-6724-5p; hsa-miR-6081; hsa-miR-6805-3p; hsa-miR-5691; hsa-miR-6718-5p; hsa-miR-203b-3p; hsa-miR-4316; hsa-miR-1976; hsa-miR-3116; hsa-miR-1254; hsa-miR-376b-3p; hsa-miR-376b-3p |
| 11 | NR_038440 | TBX5-AS1 | hsa-miR-450b-5p; hsa-miR-4455; hsa-miR-765; hsa-miR-4532; hsa-miR-5192; hsa-miR-4428; hsa-miR-4419a; hsa-miR-296-5p; hsa-miR-6859-5p; hsa-miR-3916; hsa-miR-4263; hsa-miR-6802-3p; hsa-miR-3914; hsa-miR-933; hsa-miR-6805-5p; hsa-miR-129-5p; hsa-miR-1184; hsa-miR-6828-3p; hsa-miR-6129; hsa-miR-2115-3p; hsa-miR-4463; hsa-miR-4261; hsa-miR-3116; hsa-miR-1254; hsa-miR-4516; hsa-miR-2110; hsa-miR-1273-3p; hsa-miR-6125; hsa-miR-491-5p |
| 12 | NR_125994 /// NR_125995 /// NR_125996 | LINC01770 | hsa-miR-4723-5p; hsa-miR-7111-5p; hsa-miR-6870-5p; hsa-miR-5698; hsa-miR-1275; hsa-miR-4268; hsa-miR-4261; hsa-miR-4532; hsa-miR-604; hsa-miR-4723-5p; hsa-miR-7111-5p; hsa-miR-6870-5p; hsa-miR-5698; hsa-miR-1275; hsa-miR-4268; hsa-miR-4261; hsa-miR-4532; hsa-miR-604; hsa-miR-1227-5p; hsa-miR-4723-5p; hsa-miR-7111-5p; hsa-miR-6870-5p; hsa-miR-5698; hsa-miR-4447; hsa-miR-1275; hsa-miR-2861; hsa-miR-4268; hsa-miR-4267; hsa-miR-4261; hsa-miR-4532; hsa-miR-4707-5p; hsa-miR-6885-5p; hsa-miR-4717-5p; hsa-miR-3119; hsa-miR-597-3p; hsa-miR-7975 |
miR-328-5p; hsa-miR-6811-3p; hsa-miR-604; hsa-miR-3620-3p
**Table 2** (on next page)

GO analysis of targeted genes of target miRNAs of lncRNAs
### Table 2. GO analysis of targeted genes of target miRNAs of lncRNAs

| Cellular component                  | No. of genes in the dataset | No. of genes in the background dataset | Percentage of genes | Fold enrichment (Hypergeometric test) | P-value (Hypergeometric test) | Bonferroni method | BH method | Q-value (Storey-Tibshirani method) |
|------------------------------------|-----------------------------|----------------------------------------|---------------------|---------------------------------------|-----------------------------|-------------------|-----------|-----------------------------------|
| Nucleus                            | 2639                        | 5847                                   | 39.63058            | 1.303398                              | 1.48E-89                   | 1.16E-86          | 1.16E-86  | 2.80835E-86                      |
| Cytoplasm                          | 2501                        | 5684                                   | 37.55819            | 1.270663                              | 5.38E-69                   | 4.22E-66          | 2.11E-66  | 5.1183E-66                       |
| Golgi apparatus                    | 463                         | 897                                    | 6.952996            | 1.490606                              | 9.01E-27                   | 7.07E-24          | 2.36E-24  | 5.71401E-24                      |
| Lysosome                           | 710                         | 1620                                   | 10.66226            | 1.265659                              | 7.19E-16                   | 5.64E-13          | 1.41E-13  | 3.42035E-13                      |
| Plasma membrane                    | 1407                        | 3479                                   | 21.1293             | 1.167915                              | 1.7E-15                    | 1.33E-12          | 2.67E-13  | 6.47199E-13                      |
| Perinuclear region                 | 76                          | 131                                    | 1.141313            | 1.675468                              | 3.52E-08                   | 2.76E-05          | 4.6E-06   | 1.11666E-05                      |
| Cytoplasmic vesicle                | 87                          | 160                                    | 1.306502            | 1.570333                              | 2.23E-07                   | 0.000175          | 2.5E-05   | 6.05744E-05                      |
| Endosome                           | 146                         | 303                                    | 2.192521            | 1.391539                              | 6.7E-07                    | 0.000526          | 6.57E-05  | 0.000159399                      |
| Endoplasmic reticulum              | 453                         | 1104                                   | 6.802823            | 1.184963                              | 3.05E-06                   | 0.00239           | 0.000266  | 0.00064421                       |
| Actin cytoskeleton                 | 70                          | 132                                    | 1.051209            | 1.531521                              | 1.04E-05                   | 0.008169          | 0.000817  | 0.001981917                      |
| Perinuclear region of cytoplasm    | 64                          | 119                                    | 0.961105            | 1.553224                              | 1.36E-05                   | 0.010642          | 0.000967  | 0.002347236                      |
| Cytosol                            | 474                         | 1178                                   | 7.118186            | 1.162006                              | 2.03E-05                   | 0.015898          | 0.001325  | 0.00321486                      |
| Ubiquitin ligase complex           | 28                          | 43                                     | 0.420484            | 1.880674                              | 4.37E-05                   | 0.034276          | 0.002637  | 0.006396921                      |
| Membrane                           | 156                         | 350                                    | 2.342694            | 1.287188                              | 6.52E-05                   | 0.051154          | 0.003654  | 0.008864862                      |
| Transcriptional repressor complex  | 14                          | 17                                     | 0.210242            | 2.378503                              | 7.49E-05                   | 0.058683          | 0.003912  | 0.009491763                      |
| ER-Golgi intermediate compartment  | 21                          | 30                                     | 0.315363            | 2.021761                              | 8.29E-05                   | 0.064958          | 0.00406   | 0.009850062                      |
| Intracellular membrane-bounded organelle | 65                     | 127                                    | 0.976123            | 1.478128                              | 8.85E-05                   | 0.069388          | 0.004082  | 0.009902896                      |
| Nuclear pore                       | 26                          | 42                                     | 0.390449            | 1.787959                              | 0.000277                   | 0.21717           | 0.012065  | 0.029271889                      |
| Nucleolus                          | 492                         | 1257                                   | 7.388497            | 1.130329                              | 0.000312                   | 0.24482           | 0.012885  | 0.031262049                      |

| Molecular function                 | No. of genes in the dataset | No. of genes in the background dataset | Percentage of genes | Fold enrichment (Hypergeometric test) | P-value (Hypergeometric test) | Bonferroni method | BH method | Q-value (Storey-Tibshirani method) |
|------------------------------------|-----------------------------|----------------------------------------|---------------------|---------------------------------------|-----------------------------|-------------------|-----------|-----------------------------------|
| Transcription factor activity      | 450                         | 842                                    | 6.757771            | 1.543387                              | 2.32E-30                   | 5.21E-28          | 5.21E-28  | 1.16521E-27                      |
| Protein serine/threonine kinase    | 171                         | 301                                    | 2.567953            | 1.640629                              | 1.98E-15                   | 4.43E-13          | 2.22E-13  | 4.96214E-13                      |
| Biological process                                               | No. of genes in the dataset | No. of genes in the background dataset | Percentage of genes | Fold enrichment | P-value (Hypergeometric test) | Bonferroni method | BH method | Q-value (Storey-Tibshirani method) |
|----------------------------------------------------------------|----------------------------|----------------------------------------|---------------------|----------------|-----------------------------|-------------------|----------|----------------------------------|
| Regulation of nucleobase,                                       | 1222                       | 2828                                   | 18.3511             | 1.247854       | 7.26E-25                    | 1.29E-22          | 1.29E-22 | 3.32593E-22                      |

- **Transcription regulator activity**
  - No. of genes: 391
  - No. of genes in the background dataset: 832
  - Percentage of genes: 5.87154
  - Fold enrichment: 3.83E-14
  - P-value: 8.57E-12
  - Bonferroni method: 2.86E-12
  - BH method: 6.39436E-12

- **Ubiquitin-specific protease activity**
  - No. of genes: 195
  - No. of genes in the background dataset: 377
  - Percentage of genes: 2.928368
  - Fold enrichment: 1.493736
  - P-value: 4.7E-12
  - Bonferroni method: 1.05E-09
  - BH method: 5.88953E-10

- **GTPase activity**
  - No. of genes: 118
  - No. of genes in the background dataset: 222
  - Percentage of genes: 1.772038
  - Fold enrichment: 1.535027
  - P-value: 9.96E-09
  - Bonferroni method: 2.23E-06
  - BH method: 4.98462E-07

- **Cytoskeletal protein binding**
  - No. of genes: 111
  - No. of genes in the background dataset: 218
  - Percentage of genes: 1.666917
  - Fold enrichment: 1.470468
  - P-value: 5E-07
  - Bonferroni method: 0.000112
  - BH method: 1.87E-05

- **Receptor signaling complex scaffold activity**
  - No. of genes: 154
  - No. of genes in the background dataset: 322
  - Percentage of genes: 2.31266
  - Fold enrichment: 1.381177
  - P-value: 5.95E-07
  - Bonferroni method: 0.000133
  - BH method: 1.9E-05

- **GTPase activity**
  - No. of genes: 61
  - No. of genes in the background dataset: 112
  - Percentage of genes: 0.916053
  - Fold enrichment: 1.572947
  - P-value: 1.27E-05
  - Bonferroni method: 0.002853
  - BH method: 0.000798111

- **Protein serine/threonine phosphatase activity**
  - No. of genes: 162
  - No. of genes in the background dataset: 366
  - Percentage of genes: 2.432798
  - Fold enrichment: 1.287259
  - P-value: 7.4E-05
  - Bonferroni method: 0.016579
  - BH method: 0.001805

- **Receptor signaling complex scaffold activity**
  - No. of genes: 154
  - No. of genes in the background dataset: 322
  - Percentage of genes: 2.31266
  - Fold enrichment: 1.381177
  - P-value: 5.95E-07
  - Bonferroni method: 0.000133
  - BH method: 1.9E-05

- **Guanyl-nucleotide exchange factor activity**
  - No. of genes: 61
  - No. of genes in the background dataset: 112
  - Percentage of genes: 0.916053
  - Fold enrichment: 1.572947
  - P-value: 1.27E-05
  - Bonferroni method: 0.002853
  - BH method: 0.000798111

- **RNA binding**
  - No. of genes: 162
  - No. of genes in the background dataset: 366
  - Percentage of genes: 2.432798
  - Fold enrichment: 1.287259
  - P-value: 7.4E-05
  - Bonferroni method: 0.016579
  - BH method: 0.001805

- **Protein serine/threonine phosphatase activity**
  - No. of genes: 162
  - No. of genes in the background dataset: 366
  - Percentage of genes: 2.432798
  - Fold enrichment: 1.287259
  - P-value: 7.4E-05
  - Bonferroni method: 0.016579
  - BH method: 0.001805

- **Receptor signaling protein serine/threonine kinase activity**
  - No. of genes: 12
  - No. of genes in the background dataset: 14
  - Percentage of genes: 0.180207
  - Fold enrichment: 2.475567
  - P-value: 0.000125
  - Bonferroni method: 0.027935
  - BH method: 0.00254

- **Receptor binding**
  - No. of genes: 65
  - No. of genes in the background dataset: 129
  - Percentage of genes: 0.976123
  - Fold enrichment: 1.455213
  - P-value: 0.00016
  - Bonferroni method: 0.035854
  - BH method: 0.002925

- **Phosphoric diester hydrolase activity**
  - No. of genes: 20
  - No. of genes in the background dataset: 29
  - Percentage of genes: 0.300345
  - Fold enrichment: 1.991908
  - P-value: 0.00017
  - Bonferroni method: 0.038025
  - BH method: 0.002925

- **Voltage-gated ion channel activity**
  - No. of genes: 65
  - No. of genes in the background dataset: 130
  - Percentage of genes: 0.976123
  - Fold enrichment: 1.44402
  - P-value: 0.000213
  - Bonferroni method: 0.047665
  - BH method: 0.003406

- **Transporter activity**
  - No. of genes: 237
  - No. of genes in the background dataset: 576
  - Percentage of genes: 3.559093
  - Fold enrichment: 1.188246
  - P-value: 0.000563
  - Bonferroni method: 0.126085
  - BH method: 0.008406

- **Cell adhesion molecule activity**
  - No. of genes: 151
  - No. of genes in the background dataset: 356
  - Percentage of genes: 2.267608
  - Fold enrichment: 1.224936
  - P-value: 0.001256
  - Bonferroni method: 0.281361
  - BH method: 0.017585

- **Cytoskeletal anchoring activity**
  - No. of genes: 23
  - No. of genes in the background dataset: 39
  - Percentage of genes: 0.345397
  - Fold enrichment: 1.703376
  - P-value: 0.001598
  - Bonferroni method: 0.357936
  - BH method: 0.021055

- **Ligand-dependent nuclear receptor activity**
  - No. of genes: 21
  - No. of genes in the background dataset: 35
  - Percentage of genes: 0.315363
  - Fold enrichment: 1.733021
  - P-value: 0.001876
  - Bonferroni method: 0.420189
  - BH method: 0.022115

- **Lipid kinase activity**
  - No. of genes: 21
  - No. of genes in the background dataset: 35
  - Percentage of genes: 0.315363
  - Fold enrichment: 1.733021
  - P-value: 0.001876
  - Bonferroni method: 0.420189
  - BH method: 0.022115

- **Biological process**
  - No. of genes in the dataset: 1222
  - No. of genes in the background dataset: 2828
  - Percentage of genes: 18.3511
  - Fold enrichment: 1.247854
  - P-value: 7.26E-25
  - Bonferroni method: 1.29E-22
  - BH method: 1.29E-22
  - Q-value (Storey-Tibshirani method): 3.32593E-22
| Category                                      | Value1 | Value2 | Value3 | Value4 | Value5 | Value6 | Value7 | Value8 | Value9 |
|-----------------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| nucleoside, nucleotide and nucleic acid metabolism | 1561   | 3934   | 23.44196| 1.145882| 7.17E-14| 1.28E-11| 6.38E-12| 1.6434E-11|
| Cell communication                            | 1449   | 3713   | 21.76002| 1.126977| 2.68E-10| 4.77E-08| 1.59E-08| 4.09544E-08|
| Transport                                     | 492    | 1215   | 7.388497| 1.169402| 6.4E-06 | 0.001139| 0.000285| 0.000733478|
| Regulation of gene expression, epigenetic      | 38     | 66     | 0.570656| 1.662869| 0.000112| 0.019988| 0.003998| 0.010295646|
| Regulation of translation                      | 10     | 13     | 0.150173| 2.221911| 0.002286| 0.406912| 0.067819| 0.174664437|
| Regulation of cell growth                      | 13     | 21     | 0.195225| 1.788221| 0.009711| 1       | 0.244311| 0.629212828|
| Vesicle-mediated transport                     | 11     | 17     | 0.16519 | 1.869187| 0.01098 | 1       | 0.244311| 0.629212828|
| Cellular morphogenesis during differentiation   | 3      | 3      | 0.045052| 2.887818| 0.041511| 1       | 0.525479| 1       |
| Intracellular signaling cascade                | 3      | 3      | 0.045052| 2.887818| 0.041511| 1       | 0.525479| 1       |
| Morphogenesis                                 | 3      | 3      | 0.045052| 2.887818| 0.041511| 1       | 0.525479| 1       |
| Cell proliferation                            | 19     | 39     | 0.285328| 1.407265| 0.0485  | 1       | 0.525479| 1       |
Table 3 (on next page)

KEGG pathway analysis of targeted genes of target miRNAs of IncRNAs
| KEGG pathway                        | p-value    | Genes                                                                 |
|-------------------------------------|------------|----------------------------------------------------------------------|
| Mucin type O-Glycan biosynthesis    | 4.72E-23   | C1GALT1 GALNT1 GALNT6 GALNT3 GALNT10 GALNT13 B4GALT5 GALNT6 GALNT8   |
|                                     |            | POC1B-GALNT4 GALNT7 GCNT1 GALNT4 GALNT16                              |
| Proteoglycans in cancer             | 3.48E-09   | CD44 PLCE1 PPP1CC ERBB4 MTOR ROCK1 VMP1 IGF1 SOS1 TGFB2 CBLB TP53     |
|                                     |            | LUM RDX FZD7 CAMK2B DDX5 RAF1 SMAD2 PPP1R12B FGFR1 MET MRAS ANK2 SDC4 |
|                                     |            | ITGAV ELK1 PRKCB GPC3 PIK3R1 PDPK1 TIMP3 STAT3 MAPK1 ROCK2 IGF2       |
|                                     |            | PRKACA ARHGFE12 FZD3 WNT5A PTPN11 FZD6 PDCD4 ITPR1 WNT8B EGFR ANK3   |
|                                     |            | CAV2 CBL CCND1 PIK3CA HPSE FR52 ERBB3 WNT4 FAS ERBB2 GRB2 HBEFGF       |
|                                     |            | PTK2 IQGAP1 FZD1 WNT7A CAMK2A FGF2 PRKACB PIK3CB VEGFA SOS2 FZD4      |
|                                     |            | WNT9B ITGA2 PTCH1 IGF1R CAMK2D ITPR2 THBS1 GAB1 SDC2 WNT7B WNT3       |
|                                     |            | ESR PPP1CB ANK1 WNT2B KRAS HSPG2 BRAF FLNA TWIST1 AKT3 DROSRA ROHA    |
|                                     |            | HIV1A PRKCA IGF CAMK2G WNT16 NRAS TIAM1 FN1 PPP1R12A PIK3R3 RPS6KB1   |
|                                     |            | EIF4B                                                                |
| Pathways in cancer                  | 1.10E-07   | COL4A6 PTGER3 MTOR ROCK1 GNB5 COL4A1 SUFU CCDC6 ARHGFE11 IGF1 SOS1   |
|                                     |            | TGFB2 GL2 GL2 GL2 CBLB TP53 PTEN CDK6 PDGFRB EP300 JUP FZD7 TGFBR2   |
|                                     |            | RAF1 COL4A5 SMAD2 PML EGF GNAI3 HHIP FGFR1 MET LPAR3 CREBBP MAX DVL3 |
|                                     |            | PIAS2 CRK CUL2 TCF7L2 PDGFB FGFR2 ITGAV GNAI2 SHH CTNNA1 STK36 PRKCB  |
|                                     |            | PIK3R1 CHUK PDGFR A ADCY4 PLCB4 PLCB1 STAT3 MAPK1 ROCK2 PGF ADCY2    |
|                                     |            | CTBP1 PRKACA ARHGFE12 XIAP FZD3 WNT5A EGLN3 FZD6 SMAD3 CSF2RA BIRC5 |
|                                     |            | WNT8B FGF7 COL4A4 GNAI1 EGFR FGF12 IKBBK1 TGFB1 CBL AXIN2 F2RL3       |
|                                     |            | ITGA6 CCND1 RUNX1T1 PIK3CA NKK3-1 MSH6 BMP2 FGF9 LAMC3 WNT4 FIGF       |
|                                     |            | GNG3 ERBB2 TTPM3 DAPK2 ARNT CDH1 NFKB1A PTK2 FZD1 PDGFA DCC WNT7A     |
|                                     |            | RALA GNAQ BCL2 SKP2 MLH1 TCEB1 PRKACB FGF2 STAT5B GNG2 PIK3CB CXCL12 |
|                                     |            | APC BDKRB2 SMAD4 VEGFA SOS2 FZD4 GNA12 WNT9B LPAR1 ITGA2 MAPK5 EDNRA |
|                                     |            | PTCH1 TPR IGF1R TRAF3 F2R ADCY5 CSF1R GNAI1 BCL2L1 FGF18 RASGRP2     |
|                                     |            | STK4 CASP8 MAPK10 AR HDAC2 WNT7B WNT3 FGF20 WNT2B ETS1 E2F3 KRAS CTNN |
| Pathway                                                                 | Score   | Genes                                                                                     |
|------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------|
| Long-term depression                                                   | 6.64E-07| CACNA1A RAF1 NRAS GRIA2 GUCY1A2 KRAS GNA12 GNAI1 BRAF PRKCB IGF1R GNAI3 NOS1 ITPR2 PPP2R1B PLCB4 PLCB1 MAPK1 JMID7-PLA2G4B GNAQ GRIA3 GNA11 IGF1 PPP2CA PRKCA GRIA1 PRKG1 GUCY1B3 PLA2G4F PPP2R1A GUCY1A3 ITPR1 GNA12 GNAO1 GRID2 |
| Thyroid hormone signaling pathway                                       | 7.16E-06| DIO2 SIN3A PLC1E1 NCOA2 KRAS MTOR PRKCB PFKFB2 PIK3R1 ATP1A4 NCOA1 GSK3B PDK1 AKT3 PLCB4 PLCB1 MAPK1 NCOA3 MED12L HIF1A PRKCA PRKACB TBC1D4 TP53 PRKACB MED1 STAT1 MED14 PIK3CB EP300 MED17 RAF1 THRB KAT2B NRAS SLC2A1 SLC16A10 MED24 MED13 CREBBP SLC16A2 NOTCH3 CCND1 ATP2A2 PIK3CA NOTCH2 ATP1B2 MED13L PIK3R3 TSC2 ATP1B1 WNT4 HDAC2 ITGA4 |
| Signaling pathways regulating pluripotency of stem cells              | 1.63E-05| FZD1 ACVR2B REST HOXB1 WNT7A IGF1 FGFR2 PIK3C3 HB1A1 APC SMAD4 FZD7 PCGF6 RAF1 FZD4 MEIS1 WNT9B SMAD2 ZIC3 IGF1R FGFR1 ACVR1 KAT6A RIF1 DVL3 JARID2 SMAD9 LIF INHBB TBX3 FGFR2 WNT7B WNT3 IL6ST WNT2B KRAS INHBA BMP2 PCGF3 JAK2 PIK3R1 GSK3B BMPR1A AKT3 STAT3 MAPK1 ZFHX3 ID4 FZD3 PCGF5 ISL1 WNT5A FZD6 SMAD3 PAX6 WNT16 SMARCAD1 SOX2 BMI1 NRAS WNT8B POU5F1B OTX1 SMAD5 LIFR AXIN2 ACVR1C PIK3CA PIK3R3 ACVR2A KLF4 BMP2 WNT4 SKIL INHBC |
| Axon guidance                                                          | 1.65E-05| SEMA4F EPHA5 NGEF CFL2 SEMA3A EPHA7 KRAS PTK2 ROCK1 SLIT3 EFN1B1 PAK6 SEMA3E GSK3B DCC MAPK1 ROCK2 NFATC3 RHOA EPHA4 PAK7 ROBO1 EPHB6 ARHGEF12 SLIT2 ROBO2 EFNA3 CXCL12 NTN1 EPHA3 SEMA4G PPP3R1 PLXNC1 SEMA3C PPP3CA SLIT1 NRAS PAK2 SEMA5B SGRAP3 NFACT2 GNAI1 SEMA6A ABLIM1 EFN3B PAK3 LIMK2 GNAI3 EPHA8 NTRGL1 MET EFNB2 DPYSL2 UNC5B UNC5C NCK1 SEMA5A PLXNA2 UNC5D SGRAP1 NR1PA SEMA4B LRRC4 EPHB2 PPI3CB RASA1 GNAI2 |
| Hippo signaling pathway                                                | 3.59E-05| MOB1B PPI1CC PRKCI DGL1 CDH1 BTRC FZD1 YWHAQ SERPINE1 WNT7A LAT1 TGFB2 TEAD3 PPP2R2D GLI2 YWHAH PPP2R1A APC SMAD4 FZD7 LIMD1 TGFB2 INADL FZD4 LATS2 WNT9B WWTR1 PPP2R2A SMAD2 WWC1 DGL2 YWHA4 FRMD6 BBC3 PARD3 DVL3 CSNK1E NF2 TCF7L2 TEAD1 SNA1 WNT7B T33 PPP1CB WNT2B CTNNAB1 CTNNB1 BMY2 CCND2 RASSF6 FG1I GSK3B BMP1 PAK2R1A CR1A TP73 FZD3 WNT5A MP5 RASSF1 FZD6 SMAD3 CTGF BIRC5 YAP1 WNT16 TP53BP2 SOX2 WNT8B PAR6G SAV1 GDF6 TGFB1 AXIN2 FBXW11 DLG3 PPP2CA CCND1 BMP1 WNT4 |
| Renal cell carcinoma                                                   | 6.78E-05| ARNT ETS1 KRAS B RAF PAK6 PIK3R1 AKT3 MAPK1 PAK7 TCEB1 SOS1 TGFB2 HIF1A HGF RAP1B PIK3CB EP300 RAP1A PTPN1I EGLN3 TGFA RAPGEF1 VEGFA SOS2 RAF1 NRAS PAK2 VHL SLC2A1 PAK3 MET CREBBP PIK3CA CRK CUL2 ARNT PDGFB GAB1 PIK3R3 |
| Arrhythmogenic right ventricular cardiomyopathy (ARVC)                | 0.000143688| ITGA1 CTNN4A1 CTNN3A DSG2 CACNA1C DMD LMNA PKP2 RYR2 ITGB8 DSC2 SLC8A1 CACNG3 JUP CACNA2D1 CACNB3 ITGA2 CACNB2 CACNG7 CACNG8 ITGA6 ATP2A2 ITGB6 TCF7L2 DAG1 CACNB4 GJA1 ITGAV CACNB1 CDH2 SGCD ITGA9 ITGA10 |
| Pathway                                      | Score     | Genes                                                                 |
|----------------------------------------------|-----------|----------------------------------------------------------------------|
| Estrogen signaling pathway                   | 0.0001485 | FKBP5, CREB3L1, CALM3, HBEGF, KRAS, KCNJ3, GABBR1, CALM2, PIK3R1, KCNJ6, ADCY4, CREB3L2, AKT3, PLCB4, PLCB1, MAPK1, GNAQ, ADCY2, KCNJ5, CREB3L3, SOS1, PRKACA, PRKACB, PIK3CB, ATF2, ITPR1, SOS2, RAF1, NRAS, GNA11, EGFR, GNA13, ADCY1, SP1, ITPR2, ADCY5, GABBR2, HSP90AA1, CREB5, PIK3CA, PIK3R3, CALM1, CREB1, GNA12, GNAO1 |
| Focal adhesion                               | 0.0001674 | COL4A6, PPP1CC, COL24A1, PTK2, ROCK1, COL5A1, PK6, PDGFA, VCL, COL3A1, COL4A1, COL11A1, BCL2, IGFl, PARVA, SOS1, ITGB8, PTEN, PDGFRB, PIK3CB, TLN1, RAP1A, FLT1, RAPGEF1, VEGFA, VASP, PARVB, SOS2, COL4A5, RAF1, ITGA2, MAPK8, RELN, EGF, IGFlR, PPP1R12B, PDGFD, MET, THBS1, COL11A2, ITGB6, CRK, PDGFB, MAPK10, ITGAV, COL27A1, ITGA9, PPP1CB, ITGA1, TLN2, ELK1, CCND2, BRF, TNF, FLNA, PRKCB, PIK3R1, GSK3B, PDGFRα, COL1A2, PDPK1, AKT3, VAV3, MAPK1, ROCK2, COL6A3, PGF, RHOA, PAK7, PRKCA, COL6A6, MYLK4, COL1A1, XIAP, HGF, LAMC1, RAP1B, COL4A3, ARHGAP5, PAK2, BCA1, MAPK9, COL4A4, EGFR, PK3, CAV2, FN1, ITGA6, PPP1R12A, CCND1, PIK3CA, PIK3R3, LAMC3, FIGF, ERBB2, ITGA10 |
| Adrenergic signaling in cardiomyocytes        | 0.0002154 | TPM3, CREB3L1, CALM3, SCN7A, PPP1CC, PPP2R5E, ATP1A4, CREB3L2, CACNA1C, PPP2R5D, GNAQ, BCL2, CAMK2A, PPP2R2D, PRKACB, ADRB1, PIK3CB, CACNG3, PPP2R1A, ATF2, CAMK2B, CACNA2D1, PPP2R2A, CACNG7, ATP2B2, GNA13, KCNE1, CAMK2D, ADCY5, ATP2A2, PPP2R3A, CALM1, CACNB4, CACNB1, RPS6KA5, GNAI2, PPP1CB, CALM2, PIK3R1, ADCY4, AKT3, PPP2R1B, PLCB1, PLCB4, MAPK1, ADCY2, CREB3L3, RYR2, PRKCA, PRKACA, PPP1R1A, SLC8A1, ATP2B4, CAMK2G, ATP2B1, CACNB3, CREM, CACNB2, GNAI1, ADCY1, CACNG8, TPM1, PPP2CA, CREB5, PIK3CA, ATP1B2, PIK3R3, ATP1B1, CREB1 |
| Rap1 signaling pathway                        | 0.0003891 | PFN2, CALM3, PLCE1, PRKCI, CDH1, PDGFA, CSF1, RALA, GNAQ, IGFl, FGF2, PDGFRB, RAPGEF2, PIK3CB, TLN1, RAP1A, RAPGEF5, FLT1, INSR, RAPGEF1, VEGFA, VASP, RAF1, NGFR, LPAR1, MAGI3, EGF, GRIN2A, IGFlR, GNAI3, PDGFD, FGRF1, MET, MRAS, F2R, LPAR3, THBS1, ADCY5, CSF1R, PARD3, FGF18, KRIT1, CRK, RASGRF2, PDGFRα, PRKDI, CALM1, CTNND1, FGFR2, GNAI2, MAP2K3, FGF20, TLN2, KRAS, BRAF, CAML2, PRKCB, GRIN2B, FGF1, PIK3R1, RALB, PDGFRα, ADCY4, AKT3, PLCB4, PLCB1, MAPK1, FGF, ADCY2, RHOA, PRKCA, SPECTIN1L-ADORA2A, HGF, RAP1B, EFNA3, FGF14, FGFR6, RAPGEF6, NRAS, BCA1, SIPA1L3, FGF7, PARD6G, GNAI1, EGFR, FGF12, SIPA1L1, FGF23, TIAM1, ADCY1, F2RL3, FARP2, CNR1, MAGI2, PIK3CA, ANGPT2, PIK3R3, FGF9, FIGF, GNAO1 |
| Ras signaling pathway                         | 0.0004250 | CALM3, PLCE1, RASA2, GN5B, PK6, PDGFA, CSF1, JMJD7-PLA2G4B, RALA, IGFl, RASA4, SOS1, KSR1, PLA2G12A, PRKACB, PLA2G2C, FGF2, GN2, PDGFRB, REL, PIK3CB, RAP1A, RAPGEF5, FLT1, INSR, VEGFA, SOS2, RAF1, NGFR, MAPK8, EGF, GRIN2A, IGFlR, RASGRF2, PDGFD, FGRF1, MET, MRAS, RASAL2, CSF1R, RAB5B, BCL2L1, FGF18, PLD2, RASGRP2, SYNGAP1, PDGFB, GAB1, STK4, PLA2G4F, RASA1, MAPK10, CALM1, FGFR2, FGF20, ETS1, ELK1, KRAS, ABL2, GAB2, GNG12, CALM2, PRKCB, GRIN2B, FGF1, PIK3R1, PLD1, RALB, CHUK, PDGFRα, AKT3, MAPK1, FGF, RHOA |
| Pathway                                      | Score   | Genes                                                                 |
|---------------------------------------------|---------|----------------------------------------------------------------------|
| Oxytocin signaling pathway                  | 0.000445043 | CALM3 PPP1CC KCN2 ROCK1 KCN6 CACNA1C JMJD7-PLA2G4B NFATC3 GNAQ CAMK2A PRKAA2 KCNJ5 CAMKK1 PRKACB CAMK1G PIK3CB CACNG3 GUCY1A3 CAMK2B PRKAB2 CACNA2D1 RAF1 CACNG7 GNAI3 CAMK2D PPP1R12B ITPR2 ADCY5 PLA2G4F PPP3CB CALM1 CACNB4 CACNB1 GNAI2 CAMK1 PPP1CB KRAS ELK1 KCNJ3 CALM2 PRKCB PIK3R1 ADCY4 PLCB1 PLCB4 ROCK2 MAPK1 ADCY2 RHOA RYR2 PRKCA PRKACA MYLK4 NFATC1 CAMKK2 CAMK4 PRKAA1 CAMK2G PPP3R1 ITPR1 PPP3CA CAMK1D NRAS GUCY1A2 PRKAC1 NFATC2 CACNB3 CACNB2 GNA11 EGFR ADCY1 CD38 |
| Synaptic vesicle cycle                      | 0.000719318 | ATP6V1H CACNA1A SLC17A6 STX1B UNC13A CACNLX VAMP2 UNC13C ATP6V1A ATP6V0E1 SLC17A7 CLTCL1 ATP6V0B STX2 SLC17A8 ATP6V0A1 SLC18A2 NAPA ATP6V0D2 CACNA1B ATP6V1C1 AP2M1 DNM3 ATP6V1B SYT1 ATP6V0D1 CLTCL4 AP2B1 ATP6V1G2 AP2A1 ATP6V0A2 RIMS1 CPLX2 |
| Glioma                                      | 0.000810759 | RB1 CALM3 RAF1 SOS2 NRAS E2F3 KRAS MTOR BRAF CALM2 EGFR PRKCB PDGFA EGFR PIK3R1 IGF1R CAMK2D PDGFRA AKT3 MAPK1 CAMK2A IGF1 SOS1 CCND1 PRKCA PIK3CA TP53 PTEN PDGFB CDK6 PDGFRB PIK3R3 PIK3CB TGFA CALM1 CAMK2G E2F2 CAMK2B |
| ErbB signaling pathway                      | 0.000950519 | HBEGF ERBB4 ELK1 KRAS PTK2 ABL2 MTOR BRAF PRKCB PK6 PIK3R1 GSK3B BTC AKT3 MAPK1 PK7 CAMK2A SOS1 PRKCA CBLB STAT5B PIK3CB MAP2K4 TGFA CAMK2G CAMK2B SOS2 RAF1 NRAS PK2 MAPK9 EGFR MAPK8 PK3 EGF NRG4 CBL CAMK2D NRG3 NCK1 PIK3CA NRG1 CRK GAB1 RPS6KB1 PIK3R3 MAPK10 ERBB3 ERBB2 |
| Choline metabolism in cancer                | 0.001052847 | CHPT1 DGKA DGKG KRAS MTOR PRKCB PDGFA PCYT1B PIK3R1 SLC44A5 PLD1 PDGFA PLA PDK1 AKT3 MAPK1 JMJD7-PLA2G4B WASL SOS1 HIF1A TSC1 PRKCA LYPLA1 PDGFRB PIK3CB DGK1 DGKH SLC44A1 SOS2 RAF1 NRAS MAPK9 GCPD1 EGFR MAPK8 DGK2 EGFR WAS2 DGKZ SP1 PDGFD SLC23A1 PLD2 PIK3CA DGKD PIK51B1 PDGFB RPS6KB1 PIK3R3 PL2A2G4F TSC2 WASF3 MAPK10 SLC44A3 SLC5A7 PIKG1A |
| TGF-beta signaling pathway                  | 0.001409773 | BMP2R INHBA ROCK1 ACVR2B BMP2R1B MAPK1 AHR AFGF TGFBR2 ID4 EP300 PPP2R1A SMAD3 SMAD4 TGFBR2 CHR DRL1 SMAD2 SMAD5 GDF6 TGFB1R2 SKP1 SPI1 FST ACVR1 SMURF2 THBS1 ACVR1C CIEBBB PPP2CA SMAD9 RPS6KB1 ZFYVE16 ACVR2A INHBB BMP2 INHBC SMURF1 |
| Endocytosis                                 | 0.001595389 | DNAJC6 SH3GL2 ERBB4 PRKCI ASAP2 CLTCL1 AGAP1 CHMP1B HLA-F TGFBR2 PSD4 CBLB AP2M1 DN33 GIT1 ADRB1 ADRB1 AP2A1 SH3GLB1 FLT1 TGFBR2 CYTH3 ASAP1 EHD4 ACAP2 ARAP2 SMAD2 PML EGF IQSEC3 IGFR1 TFR2 EPS MET DAB2 RUFY1 PSD2 F2R SH3KB1 PS3GL3 CSF1R RAR5B PARD3 TSG101 RNF41 PLD2 |
| Pathway                          | P-value |
|---------------------------------|---------|
| cGMP-PKG signaling pathway      | 0.001839639 |
| Prostate cancer                 | 0.002067438 |
| Cholinergic synapse             | 0.002775275 |
| Cocaine addiction              | 0.003037997 |
| Pancreatic cancer               | 0.005050774 |
| Wnt signaling pathway           | 0.008236698 |
| Pathway                          | p-value   | Genes                                       |
|---------------------------------|-----------|---------------------------------------------|
| Amphetamine addiction          | 0.01092   | FZD6 SMAD3 PPP3R1 CAMK2G PPP3CA WNT16 NLK   |
|                                 |           | PRICKLE2 WNT8B MAPK9 NFATC2 SKP1 AXIN2 FBXW11|
|                                 |           | DAAM2 CCND1 SIAH1 WNT4 SOST                |
| Adherens junction               | 0.01143   | PPP1CB CREB3L1 CALM3 PPP1CC CALM2 PRKCB  |
|                                 |           | GRIN2B GRIA4 CREB3L2 CACNA1C PDYN SLC18A2  |
|                                 |           | CAMK2A ARC CREB3L3 PRKCA PRKACA GRIA1 PRKACB|
|                                 |           | ATF2 CAMK4 CAMK2G PPP3R1 CAMK2B PPP3CA GRIA2|
|                                 |           | GRIN2A FOSB CAMK2D ADCY5 GRIA3 CREB5 GRIN3A|
|                                 |           | PPP3CB CALM1 CREB1                         |
| Acute myeloid leukemia          | 0.01743   | RAF1 SOS2 NRAS KRAS MTOR BRAF IKBKB PML    |
|                                 |           | PIK3R1 CHUK AKT3 STAT3 MAPK1 SOS1 RUNX1T1  |
|                                 |           | CCND1 PIK3CA PIM2 PIM1 TCF7L2 STAT5B RPS6KB1|
|                                 |           | PIK3R3 PIK3CB RUNX1 JUP                    |
| MAPK signaling pathway          | 0.02786   | CACNA1A RASA2 MAP4K4 PTPRR RAP1A ATF2 SOS2  |
|                                 |           | RAF1 GNA12 CACNG7 RASGRF2 MRAS MAP3K3       |
|                                 |           | RPS6KA1 CRK RASGAP2 STK4 PLA2G4F CACNB4 MAP2K3|
|                                 |           | FGF20 TAOK3 DUSP6 MAP3K1 BRAF GNG12 NTRK2  |
|                                 |           | CHUK PDGFRA PRKCA PPP3R1 FGF14 PAK2 NRAS    |
|                                 |           | MAP4K3 EGFR ELK4 FGF12 MAP3K4 TGFB1 CACNG8 |
|                                 |           | DUSP4                                       |