Original Article

MiR-182 is up-regulated and targeting Cebpa in hepatocellular carcinoma

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Abstract: MicroRNAs (miRNAs) are endogenous small non-coding RNAs that repress their targets at post transcriptional level. Existing studies have shown that miRNAs are important regulatory genes in hepatocellular carcinoma (HCC), as either tumor suppressors or oncogenes. MiR-122 is normally downregulated in HCC and regarded as a tumor suppressor. Recently miR-122 has been reported to be regulated by CEBPA, which is then involved in a novel pathway to influence proliferation of tumor cells. However it is unknown whether CEBPA is regulated by miRNAs in HCC. In this study, we find that miR-182 is upregulated in HCC model rat, and represses CEBPA in both rat and human. This further improves the current CEBPA/miR-122 pathway that controls the proliferation of tumor cells. These results suggest that miR-182 is a potential oncogene in HCC and could be used as a diagnostic marker and drug target of HCC.

Keywords: miR-182; Cebpa; miR-122; hepatocellular carcinoma (HCC); oncogene

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Introduction

Hepatocellular carcinoma (HCC) accounts for over 90% of liver cancers (1), and it has poor prognosis with only about 5% of patients survive more than five years (2). Thus, HCC is one of the most major health problems, with nearly 600,000 deaths each year across the world (3). Therefore, it is worthwhile to investigate the pathogenesis of HCC, so as to develop effective means of prevention and treatment to this severe cancer (4).

MicroRNAs (miRNAs) are small non-coding RNA molecules that can regulate gene expression by specifically recognizing base-pairing sites to their target mRNAs (5). The miRNA system is conserved from worms to mammals (6,7), which indicates its important functions. MiRNAs are involved in many biological processes including cell cycle, differentiation, development, metabolism, and so on (8-13). Recent studies have emphasized the essential roles of miRNAs in diverse diseases (14-16), especially in cancer (17).

Altered miRNA expression is also observed in HCC (18). For instance, miR-21 is dramatically upregulated in HCC tissues and cell lines to increase HCC cell proliferation through targeting PTEN (19) and PDCD4 (20). Another example is that miR-122 is down-regulated in 70% of HCC (21), and an inverse correlation links miR-122 to cyclin G1 in HCC tissues (22).

Due to its essential functions and typical expression pattern, miR-122 has been recognized as the most important HCC biomarker in HCC (23). Previous reports have demonstrated that the expression of miR-122 is positively

regulated by CEBPA (24). Then miR-122 represses the translation of IGF1R (insulin-like growth factor 1 receptor) and preserves the activity of GSK3B (glycogen synthase kinase-3 beta). Further GSK3B represses cell proliferation and in feedback promotes the expression of CEBPA. This regulatory circuitry is demonstrated to play important roles in hepatocarcinogenesis. To the best of our knowledge, CEBPA is only reported to be a target of miR-124a in leukemia (25).

In this study, we performed deep sequencing for tumor and adjacent normal tissues of HCC model rat (Morris Hepatoma-3924A). We identified 18 down- and 70 up-regulated miRNAs, with absolute normalized frequency fold change of >2 and at least 1,000 read per ten million transcripts, respectively. In our result, miR-122 is the most severely down-regulated miRNA with log2 fold change smaller than –9, which is consistent with previous reports. We also identified that miR-182 is one of the most dramatically up-regulated miRNAs. Existing studies show that miR-182 plays a role in breast cancer (26) and metastasis of melanoma (27) by targeting FOXO1 (26), FOXO3 and microphthalmia-associated transcription factor (27), respectively. However, the function of miR-182 in HCC is largely unknown until now.

Therefore, we employed four algorithms [Targetscan (28), PITA (29), Hitsensor (30) and Tarbase (31)] to find potential targets of miR-182. We performed GO (Gene Ontology) (32) and PATHWAY enrichment analysis for the predicted targets of miR-182 to investigate the potential function of miR-182 in HCC. These analyses identify that miR-182 is a potential upstream regulatory miRNA of CEBPA. CEBPA (CCAAT enhancer binding protein alpha) is reported to be down-regulated in most cancer diseases, for instance, breast cancer (33) and lung cancer (34).

To verify the upregulation of miR-182 in HCC, we performed quantitative RT-PCR (qRT-PCR) of miR-182, CEBPA and miR-122 in 25 tumor samples and 16 adjacent normal samples of HCC model rat, respectively. The results show significantly increased expression of miR-182, reduced expression of CEBPA, and reduced expression of miR-122 in tumor tissues. Correlation analyses reveal significant negative correlation between the expression of (I) miR-182 and CEBPA; (II) miR-182 and miR-122, and positive correlation between the expression of miR-122 and CEBPA. The luciferase assay experiment validated that Cebpa is a direct target of miR-182 in rat. Because the miR-182 complementary site in the 3' untranslated region (UTR) of CEBPA is highly conserved in vertebrates, we further verified that miR-182 also directly targets CEBPA in human. These results verify that miR-182 is an upstream regulator of the established CEPBA/miR-122/GSK3B pathway that regulates the proliferation of tumor cells. These findings suggest that miR-182 could play a role of oncogene in HCC and potentially could be used as a biomarker for the diagnosis and treatment of HCC.

Material and methods

Ethics statement

The housing facilities of animal models is a barrier housing facilities, and it has in keeping with national standard "Laboratory Animal-Requirements of Environment and Housing Facilities" (GB14925-2001). The care of laboratory animal and the animal operation conform to national and Shanghai municipality's regulations for the administration of affairs concerning experimental animals. The protocol was approved by Institutional Animal Care and Use Committee of Zhongshan Hospital of Fudan University (Permit Number: SYXK 2008-0039).

All surgery was performed under ketamine anesthesia, and all efforts were made to minimize suffering.

Collection of experimental samples

A total of 30 male ACI rats with weight 250-300 g (average of 280 g) from the Liver Cancer Institute of Fudan University were performed with liver cancer transplantation (tumor strain: Morris Hepatoma-3924A) successfully. The HCC samples and the adjacent normal (NT) samples were collected two weeks after tumor transplantation. The main steps included: (I) the rats were anesthetized by intraperitoneal injection of ketamine (100 mg/kg); (II) the liver was exposed and the HCC tissues and NT tissues, about 0.5 cm^3, from the liver were taken; (III) all the samples were put into the liquid nitrogen tank immediately; and (IV) the animals were sacrificed by cervical dislocation.

RNA extraction

Tissues were then cut into cubes of about 0.5 cm^3 and kept in liquid nitrogen. RNA was extracted from the frozen tissues using Trizol reagent (Invitrogen) according to the manufacturer's instructions, and qualified with Agarose gel electrophoresis. Unqualified RNA samples were excluded in subsequent experiments. We finally obtained 24 tumor and

16 adjacent normal tissue RNA for further use, of which 14 tumor and 14 adjacent normal tissues were paired.

Deep sequencing

One pair of tumor and adjacent tissues were delivered for deep sequencing using Illumina HiSeq2000 Sequencer. The quality of two RNA samples was further verified using ultraviolet spectrophotometry and 2100 BioAnalyzer (Agilent Technologies, Santa Clara, CA, USA). Deep sequencing was performed by following standard protocols.

Analysis of small RNA sequencing libraries

We analyzed the small RNA libraries as previously reported (35,36). After removing the 3' adapters of reads and discarding reads with low qualities, we obtained about 20.8 million reads with 18 to 45 nucleotides, representing around 983,632 million unique sequences. All the sequences were aligned with mature miRNAs, pre-miRNAs, mRNAs, ncRNA, repeat elements and genome with SOAP2 (37), allowing no mismatches. Mature miRNAs and pre-miRNAs sequences were downloaded from the miRBase (r19, http://mirbase.org). The whole genome and mRNA sequences were downloaded from UCSC Genome Browser (http://genome.ucsc.edu/). The ncRNA sequences were downloaded from the Rfam (http://rfam.sanger.ac.uk/), NONCODE (http://noncode.org), Genomic-tRNA-db (http://gtrnadb.ucsc.edu), and Silva (http://www.arb-silva.de) databases. The repeat element sequences were downloaded from Repbase (http://www.girinst.org/repbase/).

The expression profiles of miRNAs were obtained with reads that had no mismatches to mature rat miRNAs and then were normalized to reads per ten million transcripts (RPTM).

miRNA target prediction

Mature sequences of miRNAs were downloaded from miRBase and the 3' UTR sequence of rat Cebpa and human CEBPA were downloaded from UCSC Genome Browser. The hsa-miR-182 targets predicted by at least two of the four algorithms, Targetscan (28), PITA (29), Hitsensor (30) and Tarbase (31), or experimentally verified from miR2Disease (38), miRecords (39) and TarBASE (31) were combined and used to perform GO enrichment analysis.

GO enrichment analysis of the targets of hsa-miR-182

We conducted GO enrichment analysis for three categories of GO: biological process, cellular component and molecular function separately using the same method. The P-value used for GO enrichment analysis was defined as Eq.[1]:

$$P = \sum_{x \geq c} \frac{\binom{m}{x}\binom{n}{k-x}}{\binom{m+n}{k}} \quad [1]$$

where m was the number of genes in the considering GO term, n was the total number of genes in all the GO terms, k was the number of target genes of miR-182, and c was the number of target genes of miR-182 which belonged to the considering GO term.

Pathway enrichment analysis of the targets of hsa-miR-182

Similarly the data downloaded from PathwayAPI database (40) was utilized to evaluate the pathway enrichment for target genes of miR-182. Three most widely used pathway databases KEGG (http://www.genome.ad.jp/kegg), Ingenuity (http://www.ingenuity.com/), and Wikipath-ways (http://www.wikipathways.org/), were combined in the PathwayAPI database. We evaluated the pathway enrichment for target genes of miR-182 based on the P-value of the hypergeometric test in Eq. [1], where m denoted the number of genes in the considering pathway, n was the total number of genes in all the pathways, k referred to the number of target genes of miR-182, and c was the number of target genes of miR-182 which belonged to the considering pathway.

miRNA real-time PCR analysis

For candidate miRNAs, the reverse transcriptions were carried out using High Capacity RNA-to-cDNA kit (Takara) with no more than 500 ng RNA per 10 μL PCR system as template. qRT-PCR was then taken using TaqMan probe (Roche). Amplification of miRNAs was carried out using the TaqMan probe and Mater Mix (HaoQin) in Roche Light Cycler 480 Real-time PCR system. Gene expression was presented relative to RNU6B gene.

Real-time PCR for mRNA expression

Real-time PCR to measure the mRNA expression of

CEBPA was carried out using SYBR green detection and standard techniques. cDNA was transcribed from total RNA using random 9 primers. PCR primers were designed by MacVector according to the gene sequence, and had been verified. Gene expression was presented relative to β-actin.

Plasmid construction

To generate the specific miRNA expression vector (pSuper-hsa-miR-182 and pSuper-rno-miR-182), we amplified about 400 base-pair genomic regions containing the miRNA precursor sequences, using primers as listed in Supplementary *Figure S1*. The amplified regions were then purified and introduced into pSuper vector by restriction sites BglII and HindIII, and were verified by DNA sequencing. The putative miR-182 binding site in the 3' UTR of target gene (human CEBPA and rat Cebpa, respectively) were cloned into pGLO (E1330, Promega, Madison, WI, USA) vector downstream of firefly luciferase 3' UTR as a primary luciferase signal with rellina luciferase as the normalization signal. The pGLO vector itself provided renilla luciferase signal as normalization to compensate the differences between transfection and harvested efficiencies.

Luciferase reporter assay

293T cells were grown in DMEM containing 10% FBS, 5% glutamine and 100 μg/mL penicillin streptomycin. For luciferase reporter assay, co-transfection was performed with 5 μg of either pSuper-rno-miR-182 (pSuper-has-miR-182) or empty pSuper vector, 300 ng of either pGLO-rno-Cebpa (pGLO-hsa-CEBPA) or empty pGLO vector, using Lipofectamine 2000 (Invitrogen) according to manufacturer's instruction. Total RNA and protein were collected 48 h after transfection and analyzed using the Dual-Luciferase reporter assay System (Promega, Madison, WI, USA). Each transfection had three replicates and was repeated in three independent experiments.

Results

Abundance of miRNAs obtained from hight-throughput sequencing

To obtain miRNAs that are differentially expressed between tumor and adjacent normal tissues in HCC, we perform high throughput sequencing for one pair of tumor and adjacent normal tissue, respectively, using Illumina HiSeq 2000 sequencer. We obtain 20.8 million reads within 18 to 45 nucleotides, representing 983,632 unique sequences. These reads are aligned to different categories allowing no mismatches, including pre-miRNAs, non-coding RNAs (tRNA, rRNA, snRNA, snoRNA, piwiRNA, etc.), mRNAs, repeat elements, and genome (see Materials and Methods). As shown in *Figure 1A*, miRNAs account for about 40% of the obtained reads in both libraries. However, the percentage of unique sequences that are matched to miRNAs only contributes to about 2% of total unique sequences, suggesting miRNAs are highly expressed in all small RNAs (*Figure 1B*).

The deep sequencing reads are mapped to 723 rat miRNAs from miRBase (41) allowing no mismatches and then normalized to RPTM to estimate the expression levels of miRNAs. A total of 452 miRNAs have at least one read in our sequencing profiles (*Table S1*). The most abundant miRNAs include miR-21-5p, miR-22-3p, miR-192-5p, miR-10b-5p, miR-10a-5p, and let-7f-5p as shown in *Figure 1C*.

To identify dis-regulated miRNAs between HCC and normal tissues, the log2 ratios of miRNAs with at least 1,000 RPTM in at least one tissue are calculated for 112 miRNAs. Then we find 18 and 70 miRNAs that show reduced and increased expression levels (with log2 ratios <–1 and log2 ratio >1), respectively, in HCC tissues (*Table S2*). From *Figure 1D* and *Table 1* (with references in *Table S3*), 12 miRNAs are severely down-regulated in HCC tissues with more than four fold changes. miR-122 is the most severely down-regulated miRNA, which is consistent with most previous studies (21,24). A total of 51 miRNAs are upregulated by at least four fold (*Table S2*). Among these 51 upregulated miRNAs, miR-182 is reported to promote breast cancer genesis by targeting FOXO1 (26,42), and metastasis of melanoma by targeting FOXO3 and microphthalmia-associated transcription factor (27).

GO and pathway analysis for the targets of miR-182

Among the top 20 most severely up-regulated miRNAs, we focus our attention on miR-182, because it is previously reported to be responsible for tumor genesis in other cancers with increased expression levels (26,27,42). However, the mechanism how miR-182 is involved in HCC is not clear. As miRNAs function through its target genes, we employed four miRNA target prediction algorithms including Targetscan (28), PITA (29), Hitsensor (30) and Tarbase (31) to predict hsa-miR-182 target genes. Only targets predicted by at least two of these four algorithms are kept as reliable

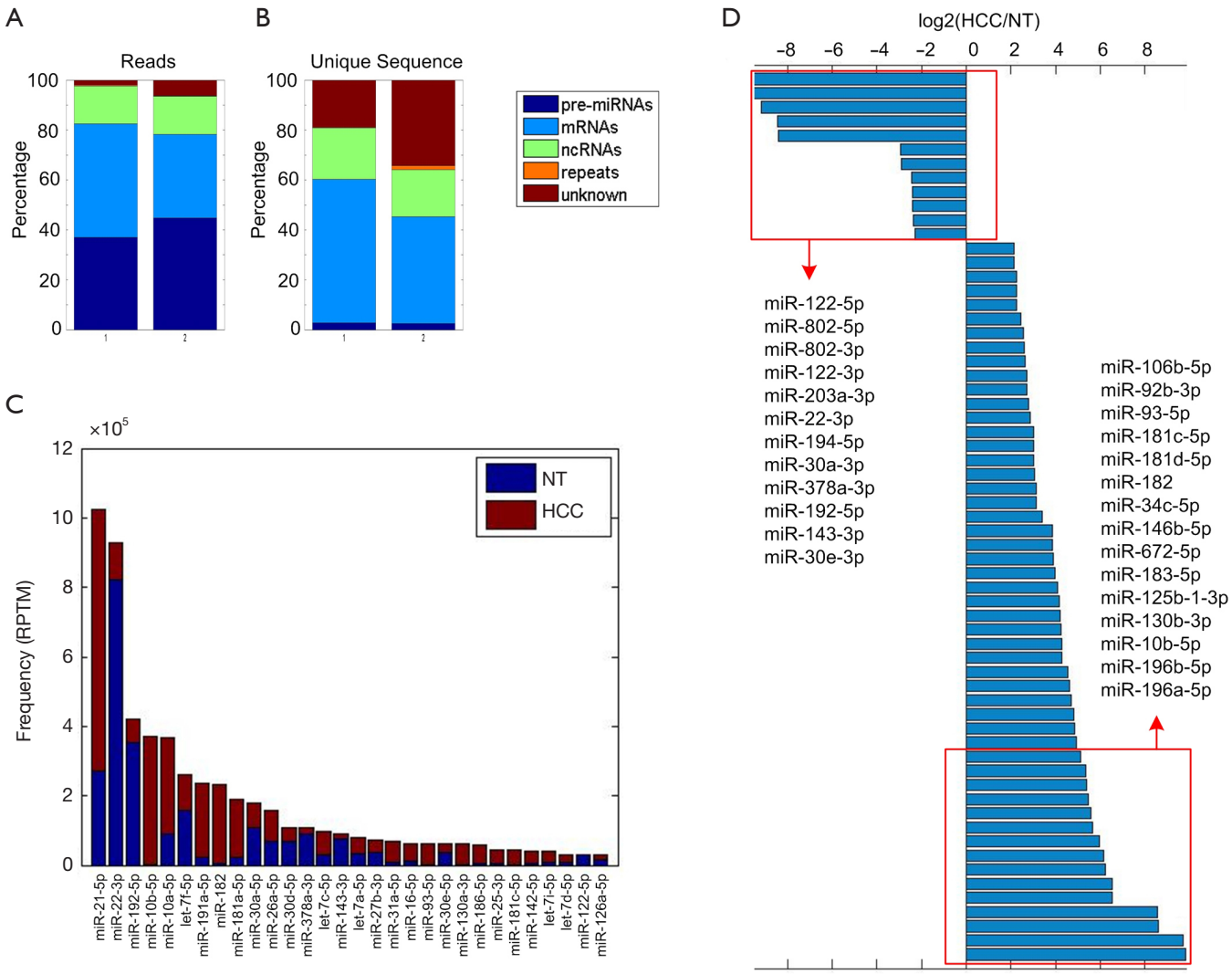

Figure 1 The distributions of reads, top 30 abundant microRNAs (miRNAs) and the log2 ratios of deregulated miRNAs in the sequenced tissues. (A) The distributions of obtained reads in the sequenced tissues. The reads are exclusive mapped to pre-miRNAs from miRBase (r19), refMRNAs from UCSC Genome Browser, classical non-coding RNAs (tRNAs, rRNAs, snRNAs, snoRNAs, etc., see materials and methods), and repeat elements (RepBase, v14) with SOAP2 (37); (B) the distributions of unique sequences in the sequenced tissues; (C) the top 30 miRNAs with the largest numbers of normalized sequencing frequencies; (D) log2 ratios of frequencies of the most dis-regulated miRNAs in tumor tissues over adjacent normal tissues. The log2 ratios of miRNAs with at least 1,000 reads per ten million transcripts (RPTM) are calculated. The 51 miRNAs with the largest and 12 miRNAs with the smallest log2 ratios of tissues without TAI are drawn from bottom.

candidates. We also collect experimentally verified targets of hsa-miR-182 from miR2Disease (38), miRecords (39) and TarBASE (31). The predicted and experimentally verified targets of hsa-miR-182 are combined and used to perform GO and Pathway enrichment analysis. As shown in *Table 2*, hsa-miR-182 is involved in G-protein-couples signaling, IGF-1 signaling and EGFR1 signaling pathway. Besides, *Table 2* show that hsa-miR-182 is also involved in four cancers including colorectal cancer ($P=3.2\times10^{-3}$, hypogeometric test), prostate cancer ($P=4.1\times10^{-3}$, hypogeometric test), chronic myeloid leukemia ($P=7.5\times10^{-3}$, hypogeometric test) and pancreatic cancer ($P=2.9\times10^{-2}$, hypogeometric test). The enriched GO terms of miR-182 targets include nerve growth factor receptor signaling pathway ($P=1.6\times10^{-2}$, hypogeometric test) and protein binding ($P=6.9\times10^{-16}$, hypogeometric test) (*Table S4*).

Table 1 The severely dis-regulated microRNAs (miRNA) and their target genes. The numbers shown in the NT and hepatocellular carcinoma (HCC) columns are the normalized frequencies (RPTM). Log2 ratio column is calculated using log2(HCC/NT). The references of their target genes are listed in *Table S4*

miRNA	NT	HCC	log2 ratio	Reported targets
rno-miR-122-5p	31,306	41	–9.6	IGF-1R, CCNG1, BCW-L
rno-miR-802-5p	2,250	3	–9.6	
rno-miR-802-3p	1,156	2	–9.2	
rno-miR-122-3p	6,001	17	–8.5	
rno-miR-203a-3p	1,699	5	–8.4	
rno-miR-22-3p	820,215	107,270	–2.9	
rno-miR-194-5p	11,587	1,562	–2.9	ACVR2B, RAC1, HBEGF, IGF1R, PTPN12, PTPN13, ITGA9, SOCS2, DNMT3A
rno-miR-30a-3p	3,756	686	–2.5	
rno-miR-378a-3p	90,736	17,145	–2.4	Sufu, Fus-1, CYP2E1, HMOX1
rno-miR-192-5p	353,757	67,283	–2.4	ZEB1, ZEB2, SIP1, TYMS
rno-miR-143-3p	76,299	14,707	–2.4	MACC1, DNMT3A, KRAS, ELK1, Bcl-2
rno-miR-30e-3p	2,240	453	–2.3	
rno-miR-106b-5p	189	6,524	5.1	E2F1, p21
rno-miR-92b-3p	30	1,220	5.3	
rno-miR-93-5p	1,454	60,967	5.4	integrin-beta, FUS1, p21
rno-miR-181c-5p	972	42,558	5.5	SIRT1, BTBD3, TRIM2, TIMP3
rno-miR-181d-5p	71	3,395	5.6	MGMT, TIMP3, Kras, Bcl-2
rno-miR-182	4,521	227,362	5.7	FOXO3, FOXO1, MITF
rno-miR-34c-5p	333	20,948	6.0	CCNE2, CDK4, E2F3, MET, c-MYC
rno-miR-146b-5p	24	1,733	6.2	BRCA1, EGFR
rno-miR-672-5p	32	2,422	6.2	
rno-miR-183-5p	119	10,960	6.5	PDCD4, VIL2
rno-miR-125b-1-3p	16	1,502	6.6	Bmf, BMPR1B
rno-miR-130b-3p	10	3,760	8.6	TP53INP1, RUNX3
rno-miR-10b-5p	961	370,417	8.6	HOXD10, Tiam1
rno-miR-196b-5p	2	1,686	9.7	c-myc, ERG, Fas
rno-miR-196a-5p	3	2,751	9.8	HOXB8, HoxA7, HoxC8, HoxD8, BMP4

In our prediction, CEBPA is one of targets involved in EGFR signaling pathway and Adipogenesis (*Table 2*). Besides, previous study reported a regulatory pathway in HCC with CEBPA as upstream regulator targeting hsa-miR-122 (24). Therefore we next investigate whether hsa-miR-182 influences this pathway by targeting CEBPA.

Validation of miR-182, Cebpa, miR-122 expression in rat samples by qRT-PCR

Expression levels of miR-182 and Cebpa are both estimated in 24 adjacent tumor tissues and 16 HCC tissues respectively. From *Figure 2A*, miR-182 is significantly up-regulated in HCC tissues ($P=4.0\times10^{-9}$, *t*-test), which is consistent with its sequencing result (*Figure 2B*). And miR-122 is down-regulated in HCC tissues ($P=1.3\times10^{-10}$, *t*-test, *Figure 2C*), consistent with sequencing result in *Figure 2D*. Cebpa is significantly down-regulated in HCC tissues ($P=4.6\times10^{-9}$, *t*-test, *Figure 2E*).

Moreover, we plot the relative expression level of miR-182 and Cebpa of 24 adjacent tumor tissues and 16 HCC tissues (of which 14 are paired HCC and NT tissue samples) in *Figure 2F*. Their expression levels show significant negative correlation (CC =–0.79,

Table 2 The significantly enriched pathways of miR-182 targets. Hypergeometric test is used to calculate the P-values. The significant pathways, with multiple test corrected P<0.05, are listed from the smallest to largest corrected P-values. The DB column means the databases of the pathways, where K, W and I mean the KEGG, Wiki and Ingenuity pathway database, respectively

Pathway name	DB	#TGP	#GPathway	P-value
Long-term potentiation	K	24	68	2.2E-03
G-protein coupled signaling	IW	24	73	3.2E-03
Calcium regulation in the cardiac cell	W	39	143	3.2E-03
Colorectal cancer	K	26	83	3.2E-03
Synaptic long term potentiation	I	21	63	3.9E-03
IGF-1 signaling	I	18	51	3.9E-03
sapk-jnk signaling	I	30	105	4.1E-03
TGF-beta signaling	I	25	83	4.1E-03
EGFR1 signaling pathway	W	44	176	4.1E-03
Prostate cancer	K	26	89	4.1E-03
B cell receptor signaling	KW	40	158	4.1E-03
Actin cytoskeleton signaling	I	50	210	4.1E-03
Integrin signaling	I	27	98	7.2E-03
Chronic myeloid leukemia	K	22	75	7.5E-03
cAMP-mediated signaling	I	22	77	1.0E-02
Melanogenesis	K	26	96	1.0E-02
ERK/MAPK signaling	IKW	36	147	1.1E-02
Huntingtons disease	K	11	30	1.1E-02
Long-term depression	K	21	74	1.2E-02
Calcium signaling	I	15	48	1.5E-02
Regulation of actin cytoskeleton	WK	47	212	2.0E-02
Synaptic long term depression	I	28	112	2.0E-02
G13 signaling pathway	W	12	37	2.1E-02
Endochondral ossification	W	18	64	2.1E-02
VEGF signaling	I	19	69	2.2E-02
PPAR-alpha/RXR-alpha signaling	I	27	109	2.2E-02
Insulin signaling pathway	KW	32	135	2.2E-02
p53 signaling	IK	15	51	2.2E-02
Adipogenesis	W	31	130	2.2E-02
Focal adhesion	K	43	196	2.6E-02
Circadian	W	14	48	2.8E-02
Kit receptor signaling pathway	W	18	67	2.9E-02
Pancreatic cancer	K	19	72	2.9E-02

#, means number. The #TGP column lists the number of miR-182 targets that appear in the pathway of the row. Star means that CEBPA is one of the miR-182 targets in the pathway. The pathways that appear in more than one database are combined with two or three characters in the DB column and the P-values of these cases are the smallest values of the databases in the DB column. #GPathway lists the total number of genes in the pathway. The P-value column lists the multiple test corrected P-values calculated with the Benjamini and Hochberg method (43).

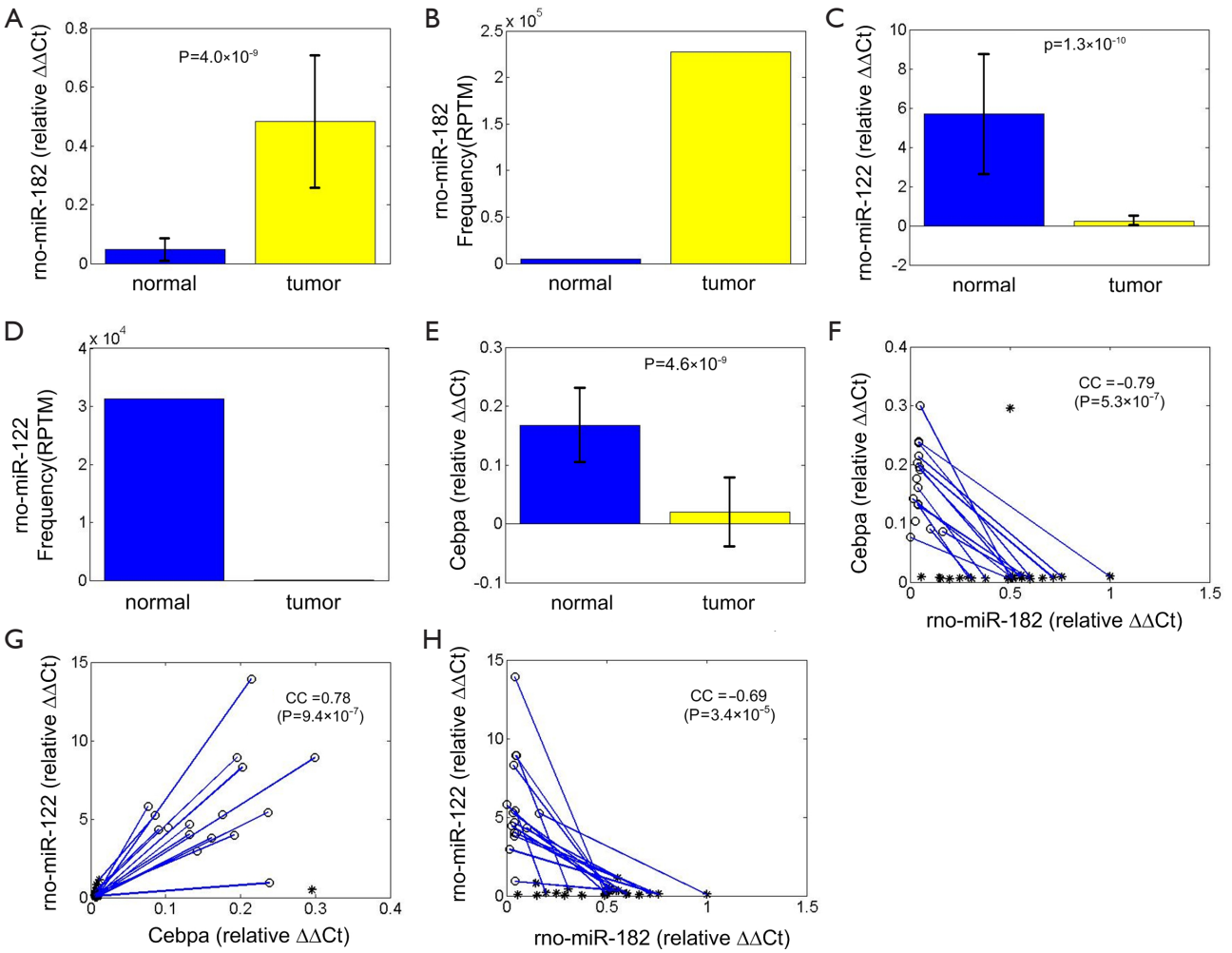

Figure 2 The expression levels of miR-182, Cebpa and miR-122, and their correlations. (A) The normalized frequencies [reads per ten million transcripts (RPTM), Reads Per Ten Million transcripts] of miR-182 in the sequenced tissues; (B) the expression levels of miR-182 using qRT-PCR. The values shown are standardized to RNU6B; (C) the normalized frequencies (RPTM) of miR-182 in the sequenced tissues; (D) the expression levels of miR-182 using qRT-PCR. The values shown are standardized to RNU6B; (E) the expression levels of Cebpa using qRT-PCR. The values shown are standardized to β-actin; (F) the scatter plot of the expression levels of miR-182 and miR-122; (G) the scatter plot of the expression levels of miR-182 and Cebpa; (H) the scatter plot of the expression levels of Cebpa and miR-122. In part (B), (D), and (E), the normal group has 16 samples and tumor groups has 25 samples; P-values are calculated using Student's t-test; the error bars are standard deviations. In part (F), (G) and (H), the values of a pair of tumor tissue and adjacent normal tissue are linked by a blue line; circles and stars stand for NT and hepatocellular carcinoma (HCC) samples.

$P=5.3\times10^{-7}$, *t*-test), which is also consistent with the assumption that Cebpa is a potential target of miR-182. The expression levels of Cebpa:miR-122 pair and miR-182:miR-122 pair show significant positive (CC =0.78, $P=9.4\times10^{-7}$, *t*-test, *Figure 2G*) and negative correlation (CC =–0.69, $P=3.4\times10^{-5}$, *t*-test, *Figure 2H*), respectively. The correlation analysis reveals that miR-182 should be a potential upstream regulator of CEBPA/miR-122/GSK3B regulatory circuitry. Next we use luciferase assay to verify direct repression of Cebpa by miR-182.

Cebpa is one direct target of miR-182 in rat

The prediction results reveal that Cebpa is a potential target of miR-182 with an 8 mer seed complementary site (*Figure 3A*). To investigate the direct relationship between

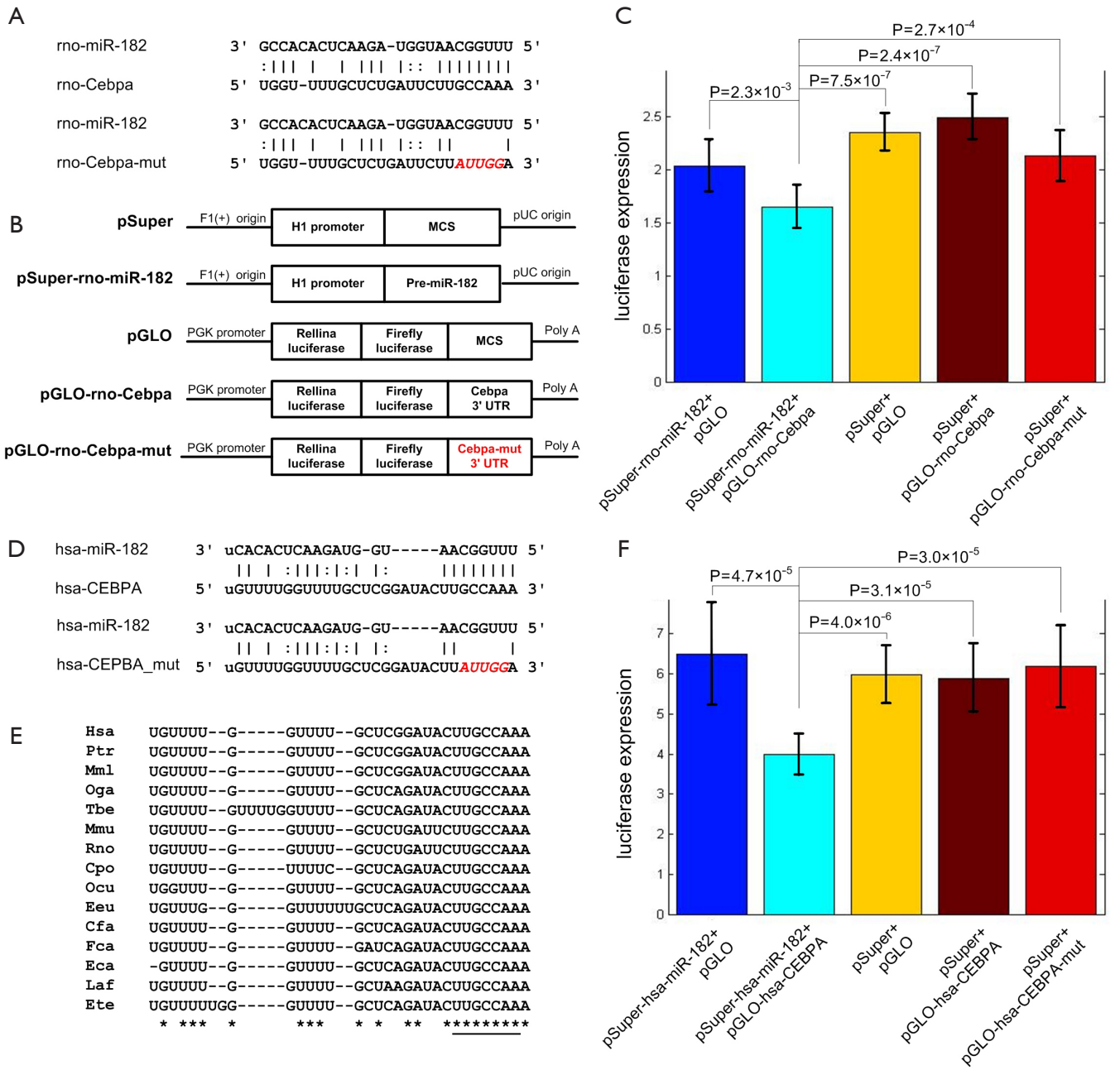

Figure 3 Cebpa is a direct target of miR-182. (A) Rat wild type (upper) and mutated (lower) miR-182 complementary site of Cebpa; (B) human wild type (upper) and mutated (lower) miR-182 complementary site of CEBPA; (C) the conservation of the miR-182 complementary site of Cebpa (results from http://www.targetscan.org). The name of the species are Hsa (Homo sapiens), Ptr (Pan troglodytes), Mml (Macaca mulatta), Oga (Galago senegalensis), Tbe (Tupaia belangeri), Mmu (Mus muculus), Rno (Rattus norvegicus), Cpo (Cavia porcellus), Ocu (Oryctolagus cuniculus), Eeu (Erinaceus europaeus), Cfa (Canis familiaris), Fca (Felis catus), Eca (Equus caballus), Laf (Loxodonta africana), and Ete (Echinops telfairi). The underlined region is the complementary region of miR-182 seed; (D) the plasmids' constructions in rat. The human plasmids are constructed in a similar way; (E) the luciferase expression levels of pSuper-rno-miR-182 + pGLO, pSuper-rno-miR-182 + pGLO-rno-Cebpa, pSuper + pGLO, pSuper + pGLO-rno-Cebpa, pSuper-rno-miR-182 + pGLO-rno-Cebpa-mut, from left to right respectively; (F) the luciferase expression levels of pSuper-hsa-miR-182 + pGLO, pSuper-hsa-miR-182 + pGLO-hsa-CEBPA, pSuper + pGLO, pSuper + pGLO-hsa-CEBPA, pSuper-hsa-miR-182 + pGLO-hsa-CEBPA-mut, from left to right respectively. Statistical analysis is done using Student's *t*-test. In part (E) and (F), the error bars are standard deviations; the number of samples n is nine for all groups.

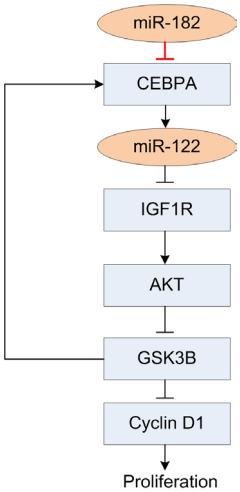

Figure 4 miR-182 plays an important role in CEBPA/miR-122/IGF1R pathway. The arrow from miR-182 to CEBPA is a verified regulatory relation in this study, and other arrows are regulatory relations reported previously (25). Sharp and dull arrows mean activation and repression, respectively.

miR-182 and Cebpa, we employ the dual-luciferase reporter system. The 3' UTR region of Cebpa containing the wild-type and mutated miR-182 complementary site are conducted into luciferase reporter plasmid (pGLO), respectively. HEK 293T cells co-transfected with pSuper-rno-miR-182 plasmid and pGLO-rno-Cebpa plasmid show a significantly decreased luciferase expression level compared to control groups ($P=2.3\times10^{-3}$, 7.5×10^{-7}, and 2.4×10^{-7}, *t*-test, for pSuper-rno-miR-182 + pGLO, pSuper + pGLO, pSuper + pGLO-rno-Cebpa, respectively, *Figure 3B*). And the luciferse expression levels of cells transfected with pGLO-rno-Cebpa-mut are significantly higher than the experiment group ($P=2.7\times10^{-4}$, *t*-test, *Figure 3C*), indicating that miR-182 can directly repress Cebpa by targeting the complementary site in *Figure 3A*.

CEBPA is also a direct target of miR-182 in human

Most rat miRNAs are highly conserved between rat and human (44), implying their essential functions. The miR-182 complementary site in the 3' UTR of human CEBPA (in *Figure 3D*) is highly conserved in vertebrates, including rat and human, as shown in *Figure 3E*. Similarly, we use dual-luciferase reporter assay to verify whether human miR-182 also directly represses the expression of CEBPA. HEK 293T cells co-transfected with pSuper-hsa-miR-182 plasmid and pGLO-hsa-CEBPA show a dramatically reduced luciferase expression level compared to other control groups ($P=4.7\times10^{-5}$, 4.0×10^{-6}, and 3.1×10^{-5}, *t*-test, for pSuper-hsa-miR-182 + pGLO, pSuper + pGLO, pSuper + pGLO-hsa-CEBPA, respectively, *Figure 3F*). Similarly, the luciferase expression levels of cells transfected with pGLO-hsa-CEBPA-mut are also not affected by miR-182 expression ($P=3.0\times10^{-5}$, *t*-test, *Figure 3F*), similar to the results of rno-miR-182 and Cebpa. In summary, these results demonstrate that miR-182's direct repression on CEBPA is conserved in human.

Discussion

In this study we use deep sequencing method to obtain the miRNA expression profiles of HCC and adjacent normal tissues. Our results identify many dis-regulated miRNAs, including many reported HCC-related miRNAs, such as miR-21 and miR-122. For example, in our sequencing data miR-196a-5p and miR-196b-5p are the most up-regulated miRNAs. miR-196 is reported to be involve in some human cancers with higher expression levels (45,46). The well investigated HCC biomarker miR-122, which is down-regulated in more than 70% HCC patients (47), also shows a dramatic reduced expression level in our rat HCC tissues.

To predict the potential functions of miR-182, we perform Gene Ontology and Pathway enrichment analysis for its targets. The results show that miR-182 is involved in multiple cancer pathways (*Table 2*). Previous report has demonstrated that miR-182 can control the expression of FOXO1 (26) in breast cancer to influence tumorigenesis and FOXO3 (27) to promote metastasis of melanoma. However, the importance of miR-182 has not been noticed in HCC.

In this study, we verify that miR-182 directly targets Cebpa through a conserved complementary site in both rat and human. A previous report finds that the CEBPA/miR-122/IGF1R pathway is related with proliferation of HCC cells (24). In this pathway, miR-122 is positively regulated by CEBPA. Then miR-122 downregulates the translation of IGF1R and preserves the activity of GSK3B. Further GSK3B represses cell proliferation and in feedback promotes the expression of CEBPA. This regulatory pathway is demonstrated to play important roles in hepatocarcinogenesis (24). In this study, we find that miR-182 is also an important player of this pathway by directly repressing CEBPA (*Figure 4*). Our results show that the expression levels of miR-182 and Cebpa, miR-182 and

miR-122, Cepba and miR-122 are significantly correlated (CC =–0.79, –0.69, and 0.78, P=5.3×10^{-7}, 3.4×10^{-5}, and 9.4×10^{-7}, respectively, *t*-test, *Figure 2F,H,G* respectively).

In addition, CEBPA, HNF1A (hepatocyte nuclear factor 1-alpha), HNF3B, HNF4A also activates miR-122 during liver development (48). miR-122 subsequently represses CUTL1 (cut-like homeobox 1) (48). These four transcription factors and miR-122 thus cooperate to maintain the balance of differentiation and proliferation in hepatocytes (48). Our results suggest that miR-182 is potentially involved in liver development as well.

In summary, we find that miR-182 is significantly up-regulated in rat HCC tissues. Our results also verify that miR-182 regulates the established CEBPA/miR-122/IGF1R pathway in our rat HCC models by directly repressing Cebpa. We also verify that miR-182 represses CEBPA in human through a conserved complementary site. These indicate that miR-182 is an upstream regulator of Cebpa in both rat and human. Because miR-122 has been recognized as a key regulator in HCC, our results suggest that miR-182 is a potential biomarker for diagnosis and therapeutic target of HCC. In addition, our results suggest that miR-182 might be involved in several other cancers (see *Table 2*).

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Supplementary

Primer name	Sequence
Primer used to amplify precusors of microRNA (miRNA)	
mmu-mir182F	GAAGATCTGCAGGGCTTGAGGAGGTTTTAC
mmu-mir182B	CCAAGCTTCCTTTTCACCGAGAAGAGGTCG
hsa-mir182F	GAAGATCTAGGAAGGACCTTGTCGCAGTTG
has-mir182B	CCAAGCTTTGCAGGGAAACACAGAGTGTCAC
Primer used to amplify mRNAs of rat Cebpa	
Cebpa-for-OCT	AAGAACAGCAACGAGTACCGG
Cebpa-back-OCT	GTCACTGGTCAACTCCAACACC
Sequences of mRNA 3' UTR to construct the pmirGLO plasmid	
hsaCebpa-sense	CTAGCTGTTTTGGTTTTGCTCGGATACTTGCCAAAATGAGACTCTCCGTCGGCAGCT
hsaCebpa-anti	TCGAAGCTGCCGACGGAGAGTCTCATTTTGGCAAGTATCCGAGCAAAACCAAAACAG
hsaCebpa-mut-sense	CTAGCTGTTTTGGTTTTGCTCGGATACTTATTGGAATGAGACTCTCCGTCGGCAGCT
hsaCebpa-mut-anti	TCGAAGCTGCCGACGGAGAGTCTCATTCCAATAAGTATCCGAGCAAAACCAAAACAG
rnoCebpa-sense	CTAGCTGTTTTGTTTTGGTTTTGCTCTGATTCTTGCCAAAATGAGACTCTTCACGAT
rnoCebpa-anti	TCGAATCGTGAAGAGTCTCATTTTGGCAAGAATCAGAGCAAAACCAAAACAAAACAG
rnoCebpa-mut-sense	CTAGCTGTTTTGTTTTGGTTTTGCTCTGATTCTTATTGGAATGAGACTCTTCACGAT
rnoCebpa-mut-anti	TCGAATCGTGAAGAGTCTCATTCCAATAAGAATCAGAGCAAAACCAAAACAAAACAG
Notes: the blue characters are restriction sites, the red characters are 2 to 6 of miR-182 complementary site.	

Figure S1 Primers and sequences used in the study.

Table S1 Rat microRNAs (miRNAs) with at least 1 read in our sequencing libraries

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	234,860	270,729	912,244	754,749
rno-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	711,543	820,215	129,654	107,270
rno-miR-10b-5p	CCCUGUAGAACCGAAUUUGUGU	834	961	447,713	370,417
rno-miR-10a-5p	UACCCUGUAGAUCCGAAUUUGUG	78,712	90,733	336,331	278,265
rno-miR-192-5p	CUGACCUAUGAAUUGACAGCC	306,887	353,757	81,323	67,283
rno-miR-182	UUUGGCAAUGGUAGAACUCACACCG	3,922	4,521	274,806	227,362
rno-miR-191a-5p	CAACGGAAUCCCAAAAGCAGCUG	20,759	23,929	257,282	212,863
rno-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	137,990	159,065	124,866	103,308
rno-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	19,704	22,713	201,637	166,825
rno-miR-30a-5p	UGUAAACAUCCUCGACUGGAAG	93,571	107,862	84,247	69,702
rno-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	61,506	70,900	105,054	86,917
rno-let-7c-5p	UGAGGUAGUAGGUUGUAUGGUU	25,562	29,466	82,963	68,640
rno-miR-30d-5p	UGUAAACAUCCCCGACUGGAAG	61,449	70,834	45,409	37,569
rno-miR-378a-3p	ACUGGACUUGGAGUCAGAAGG	78,714	90,736	20,723	17,145
rno-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	29,866	34,427	54,955	45,467
rno-miR-143-3p	UGAGAUGAAGCACUGUAGCUCA	66,190	76,299	17,776	14,707
rno-miR-31a-5p	AGGCAAGAUGCUGGCAUAGCUG	6,418	7,398	74,299	61,472

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-27b-3p	UUCACAGUGGCUAAGUUCUGC	31,257	36,031	46,531	38,498
rno-miR-93-5p	CAAAGUGCUGUUCGUGCAGGUAG	1,261	1,454	73,689	60,967
rno-miR-130a-3p	CAGUGCAAUGUUAAAAGGGCAU	1,932	2,227	70,729	58,518
rno-miR-16-5p	UAGCAGCACGUAAAUAUUGGCG	11,427	13,172	59,787	49,465
rno-miR-186-5p	CAAAGAAUUCUCCUUUUGGGCU	5,610	6,467	63,089	52,197
rno-miR-30e-5p	UGUAAACAUCCUUGACUGGAAG	33,856	39,027	27,372	22,646
rno-miR-25-3p	CAUUGCACUUGUCUCGGUCUGA	3,442	3,968	50,575	41,843
rno-miR-181c-5p	AACAUUCAACCUGUCGGUGAGU	843	972	51,439	42,558
rno-miR-142-5p	CAUAAAGUAGAAAGCACUACU	4,027	4,642	45,673	37,788
rno-let-7i-5p	UGAGGUAGUAGUUUGUGCUGUU	6,657	7,674	41,415	34,265
rno-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	8,683	10,009	26,071	21,570
rno-miR-126a-5p	CAUUAUUACUUUUGGUACGCG	13,668	15,755	18,692	15,465
rno-miR-125a-5p	UCCCUGAGACCCUUUAACCUGUGA	2,449	2,823	29,722	24,591
rno-miR-101b-3p	UACAGUACUGUGAUAGCUGAA	19,485	22,461	8,631	7,141
rno-miR-122-5p	UGGAGUGUGACAAUGGUGUUUG	27,158	31,306	50	41
rno-miR-103-3p	AGCAGCAUUGUACAGGGCUAUGA	4,132	4,763	21,485	17,776
rno-miR-34c-5p	AGGCAGUGUAGUUAGCUGAUUGC	289	333	25,319	20,948
rno-miR-335	UCAAGAGCAAUAACGAAAAAUGU	687	792	22,247	18,406
rno-miR-199a-3p	ACAGUAGUCUGCACAUUGGUUA	4,100	4,726	17,155	14,193
rno-miR-30b-5p	UGUAAACAUCCUACACUCAGCU	6,518	7,513	14,385	11,901
rno-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	776	895	19,840	16,415
rno-miR-125b-5p	UCCCUGAGACCCUAACUUGUGA	2,086	2,405	18,255	15,103
rno-miR-29a-3p	UAGCACCAUCUGAAAUCGGUUA	8,086	9,321	12,132	10,037
rno-miR-151-5p	UCGAGGAGCUCACAGUCUAGU	3,848	4,436	15,525	12,845
rno-miR-151-3p	CUAGACUGAGGCUCCUUGAGG	2,544	2,933	16,773	13,877
rno-miR-301a-3p	CAGUGCAAUAGUAUUGUCAAAGC	513	591	17,572	14,538
rno-miR-872-3p	UGAACUAUUGCAGUAGCCUCCU	433	499	17,374	14,374
rno-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	623	718	16,682	13,802
rno-miR-26b-5p	UUCAAGUAAUUCAGGAUAGGU	10,641	12,266	5,919	4,897
rno-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	2,730	3,147	13,497	11,167
rno-miR-183-5p	UAUGGCACUGGUAGAAUUCACU	103	119	13,247	10,960
rno-miR-126a-3p	UCGUACCGUGAGUAAUAAUGCG	6,009	6,927	7,037	5,822
rno-miR-101a-3p	UACAGUACUGUGAUAACUGAA	5,879	6,777	6,754	5,588
rno-miR-194-5p	UGUAACAGCAACUCCAUGUGGA	10,052	11,587	1,888	1,562
rno-miR-425-5p	AAUGACACGAUCACUCCCGUUGA	425	490	11,363	9,401
rno-miR-27a-3p	UUCACAGUGGCUAAGUUCCGC	1,142	1,316	10,367	8,577
rno-let-7e-5p	UGAGGUAGGAGGUUGUAUAGUU	1,780	2,052	8,154	6,746
rno-miR-351-5p	UCCCUGAGGAGCCCUUUGAGCCUGA	1,029	1,186	8,374	6,928
rno-miR-23a-3p	AUCACAUUGCCAGGGAUUUCC	890	1,026	8,172	6,761
rno-miR-19b-3p	UGUGCAAAUCCAUGCAAAACUGA	1,619	1,866	7,312	6,050
rno-miR-106b-5p	UAAAGUGCUGACAGUGCAGAU	164	189	7,885	6,524

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-28-3p	CACUAGAUUGUGAGCUCCUGGA	4,561	5,258	1,664	1,377
rno-miR-107-3p	AGCAGCAUUGUACAGGGCUAUCA	1,407	1,622	4,610	3,814
rno-miR-29c-3p	UAGCACCAUUUGAAAUCGGUUA	1,174	1,353	4,720	3,905
rno-miR-340-5p	UUAUAAAGCAAUGAGACUGAUU	1,722	1,985	4,009	3,317
rno-miR-92a-3p	UAUUGCACUUGUCCCGGCCUG	979	1,129	4,678	3,870
rno-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUUU	2,670	3,078	2,929	2,423
rno-miR-122-3p	AACGCCAUCAUCACACUAA	5,206	6,001	20	17
rno-miR-320-3p	AAAAGCUGGGUUGAGAGGGCGA	789	910	4,180	3,458
rno-miR-150-5p	UCUCCCAACCCUUGUACCAGUG	1,386	1,598	3,480	2,879
rno-miR-221-3p	AGCUACAUUGUCUGCUGGGUUUC	189	218	4,441	3,674
rno-miR-130b-3p	CAGUGCAAUGAUGAAAGGGCAU	9	10	4,545	3,760
rno-miR-450a-5p	UUUUGCGAUGUGUUCCUAAUGU	576	664	3,867	3,199
rno-let-7d-3p	CUAUACGACCUGCUGCCUUUCU	1,884	2,172	2,555	2,114
rno-miR-106b-3p	CCGCACUGUGGGUACUUGCUGC	106	122	4,205	3,479
rno-miR-872-5p	AAGGUUACUUGUUAGUUCAGG	586	675	3,622	2,997
rno-miR-181d-5p	AACAUUCAUUGUUGUCGGUGGGU	62	71	4,103	3,395
rno-miR-30a-3p	CUUUCAGUCGGAUGUUUGCAGC	3,258	3,756	829	686
rno-miR-423-3p	AGCUCGGUCUGAGGCCCCUCAGU	1,874	2,160	2,024	1,675
rno-miR-100-5p	AACCCGUAGAUCCGAACUUGUG	152	175	3,369	2,787
rno-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	163	188	3,334	2,758
rno-miR-322-5p	CAGCAGCAAUUCAUGUUUUGGA	648	747	2,708	2,240
rno-miR-140-3p	UACCACAGGGUAGAACCACGG	1,540	1,775	1,798	1,488
rno-miR-196a-5p	UAGGUAGUUUCAUGUUGUUGGG	3	3	3,325	2,751
rno-miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	1,201	1,384	2,124	1,757
rno-miR-23b-3p	AUCACAUUGCCAGGGAUUACC	991	1,142	2,250	1,862
rno-miR-222-3p	AGCUACAUCUGGCUACUGGGU	148	171	3,055	2,528
rno-miR-138-5p	AGCUGGUGUUGUGAAUCAGGCCG	73	84	3,093	2,559
rno-miR-672-5p	UGAGGUUGGUGUACUGUGUGUGA	28	32	2,927	2,422
rno-miR-142-3p	UGUAGUGUUUCCUACUUUAUGGA	139	160	2,783	2,303
rno-miR-98-5p	UGAGGUAGUAAGUUGUAUUGUU	723	833	2,146	1,776
rno-miR-20a-5p	UAAAGUGCUUAUAGUGCAGGUAG	369	425	2,449	2,026
rno-miR-146a-5p	UGAGAACUGAAUUCCAUGGGUU	1,531	1,765	1,129	934
rno-miR-24-2-5p	GUGCCUACUGAGCUGAAACAGU	244	281	2,346	1,941
rno-miR-24-3p	UGGCUCAGUUCAGCAGGAACAG	443	511	2,095	1,733
rno-miR-193-3p	AACUGGCCUACAAAGUCCCAGU	1,756	2,024	745	616
rno-miR-30e-3p	CUUUCAGUCGGAUGUUUACAGC	1,943	2,240	547	453
rno-miR-200b-3p	UAAUACUGCCUGGUAAUGAUGAC	391	451	2,093	1,732
rno-miR-451-5p	AAACCGUUACCAUUACUGAGUU	1,313	1,514	1,153	954
rno-miR-342-3p	UCUCACACAGAAAUCGCACCCGU	83	96	2,234	1,848
rno-miR-17-5p	CAAAGUGCUUACAGUGCAGGUAG	86	99	2,172	1,797
rno-miR-28-5p	AAGGAGCUCACAGUCUAUUGAG	1,400	1,614	804	665

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-128-3p	UCACAGUGAACCGGUCUCUUU	257	296	1,941	1,606
rno-miR-146b-5p	UGAGAACUGAAUUCCAUAGGCUGU	21	24	2,095	1,733
rno-miR-196b-5p	UAGGUAGUUUCCUGUUGUUGGG	2	2	2,038	1,686
rno-miR-1839-5p	AAGGUAGAUAGAACAGGUCUUG	565	651	1,432	1,185
rno-miR-802-5p	UCAGUAACAAAGAUUCAUCCU	1,952	2,250	4	3
rno-miR-497-5p	CAGCAGCACACUGUGGUUUGUA	1,082	1,247	803	664
rno-miR-125b-1-3p	ACGGGUUAGGCUCUUGGGAGCU	14	16	1,816	1,502
rno-miR-19a-3p	UGUGCAAAUCUAUGCAAAACUGA	144	166	1,633	1,351
rno-miR-92a-1-5p	AGGUUGGGAUUUGUCGCAAUGCU	180	207	1,528	1,264
rno-miR-145-5p	GUCCAGUUUUCCCAGGAAUCCCU	745	859	829	686
rno-miR-92b-3p	UAUUGCACUCGUCCCGGCCUCC	26	30	1,474	1,220
rno-miR-203a-3p	GUGAAAUGUUUAGGACCACUAG	1,474	1,699	6	5
rno-miR-195-5p	UAGCAGCACAGAAAUAUUGGC	819	944	580	480
rno-miR-505-3p	GUCAACACUUGCUGGUUUCC	206	237	1,140	943
rno-miR-429	UAAUACUGUCUGGUAAUGCCGU	214	247	1,103	913
rno-miR-542-3p	UGUGACAGAUUGAUAACUGAAA	132	152	1,183	979
rno-miR-99a-5p	AACCCGUAGAUCCGAUCUUGUG	943	1,087	330	273
rno-miR-181a-1-3p	ACCAUCGACCGUUGAUUGUACC	150	173	1,113	921
rno-miR-1843-5p	UAUGGAGGUCUCUGUCUGACU	624	719	632	523
rno-miR-421-3p	AUCAACAGACAUUAAUUGGG	51	59	1,159	959
rno-miR-29b-3p	UAGCACCAUUUGAAAUCAGUGUU	93	107	1,062	879
rno-miR-3068-3p	GGUGAAUUGCAGUACUCCAACA	73	84	1,076	890
rno-miR-148b-5p	GAAGUUCUGUUAUACACUCAGG	119	137	944	781
rno-miR-30c-2-3p	CUGGGAGAAGGCUGUUUACUCU	862	994	174	144
rno-miR-802-3p	ACGGAGAGUCUUUGUCACUCAGU	1,003	1,156	3	2
rno-miR-484	UCAGGCUCAGUCCCCUCCCGAU	175	202	825	683
rno-miR-30d-3p	CUUUCAGUCAGAUGUUUGCUGC	557	642	433	358
rno-miR-34b-5p	AGGCAGUGUAAUUAGCUGAUUGU	16	18	946	783
rno-miR-339-5p	UCCCUGUCCUCCAGGAGCUCACG	264	304	675	558
rno-miR-3559-5p	UGACAGACUUAGUACUACAUGA	375	432	563	466
rno-miR-455-5p	UAUGUGCCUUUGGACUACAUCG	160	184	748	619
rno-miR-365-3p	UAAUGCCCCUAAAAAUCCUUAU	615	709	263	218
rno-miR-200a-3p	UAACACUGUCUGGUAACGAUGU	153	176	721	597
rno-miR-96-5p	UUUGGCACUAGCACAUUUUUGCU	7	8	853	706
rno-miR-301b-3p	CAGUGCAAUGGUAUUGUCAAAGC	2	2	835	691
rno-miR-199a-5p	CCCAGUGUUCAGACUACCUGUUC	169	195	630	521
rno-miR-223-3p	UGUCAGUUUGUCAAAUACCCC	121	139	666	551
rno-miR-144-5p	GGAUAUCAUCAUAUACUGUAAGU	355	409	426	352
rno-miR-328a-3p	CUGGCCCUCUCUGCCCUUCCGU	164	189	614	508
rno-miR-339-3p	UGAGCGCCUCGACGACAGAGCCA	266	307	493	408
rno-miR-374-5p	AUAUAAUACAACCUGCUAAGUG	162	187	597	494

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-125b-2-3p	ACAAGUCAGGCUCUUGGGACCU	626	722	130	108
rno-miR-148b-3p	UCAGUGCAUCACAGAACUUUGU	338	390	414	343
rno-miR-130b-5p	ACUCUUUCCCUGUUGCACUACU	3	3	744	616
rno-miR-183-3p	UGAAUUACCGAAGGGCCAUAA	2	2	703	582
rno-miR-375-3p	UUUGUUCGUUCGGCUCGCGUGA	333	384	369	305
rno-miR-361-3p	CCCCCAGGUGUGAUUCUGAUUCGU	243	280	436	361
rno-miR-532-5p	CAUGCCUUGAGUGUAGGACUGU	480	553	166	137
rno-miR-144-3p	UACAGUAUAGAUGAUGUACU	281	324	364	301
rno-miR-322-3p	AAACAUGAAGCGCUGCAACA	113	130	517	428
rno-miR-674-3p	CACAGCUCCCAUCUCAGAACAA	152	175	468	387
rno-miR-361-5p	UUAUCAGAAUCUCCAGGGGUAC	163	188	451	373
rno-miR-582-5p	UACAGUUGUUCAACCAGUUACU	6	7	597	494
rno-miR-6328	AGGCCUGCUCUGAGCCCCCGC	4	5	569	471
rno-miR-181c-3p	ACCAUCGACCGUUGAGUGGACC	19	22	530	438
rno-miR-21-3p	CAACAGCAGUCGAUGGGCUGUC	215	248	320	265
rno-miR-204-5p	UUCCCUUUGUCAUCCUAUGCCU	206	237	294	243
rno-miR-18a-5p	UAAGGUGCAUCUAGUGCAGAUAG	17	20	467	386
rno-miR-582-3p	AACCUGUUGAACAACUGAACCC	17	20	461	381
rno-miR-671	UCCGGUUCUCAGGGCUCCACC	237	273	234	194
rno-miR-191a-3p	GCUGCACUUGGAUUUCGUUCCC	40	46	427	353
rno-miR-152-5p	AGGUUCUGUGAUACACUCCGACU	40	46	426	352
rno-miR-29a-5p	ACUGAUUUCUUUUGGUGUUCAG	18	21	435	360
rno-miR-152-3p	UCAGUGCAUGACAGAACUUGG	87	100	357	295
rno-miR-10a-3p	CAAAUUCGUAUCUAGGGGAAUA	59	68	381	315
rno-miR-34b-3p	AAUCACUAACUCCACUGCCAUC	2	2	430	356
rno-miR-652-3p	AAUGGCGCCACUAGGGUUGUG	38	44	358	296
rno-miR-33-5p	GUGCAUUGUAGUUGCAUUGCA	58	67	335	277
rno-miR-1843-3p	UCUGAUCGUUCACCUCCAUACA	166	191	225	186
rno-miR-598-3p	UACGUCAUCGUCGUCAUCGUUA	43	50	337	279
rno-miR-324-5p	CGCAUCCCCUAGGGCAUUGGUGU	13	15	361	299
rno-miR-34a-5p	UGGCAGUGUCUUAGCUGGUUGU	258	297	113	93
rno-miR-27b-5p	AGAGCUUAGCUGAUUGGUGAACAG	112	129	233	193
rno-miR-99b-3p	CAAGCUCGUGUCUGUGGGUCCG	17	20	316	261
rno-miR-132-3p	UAACAGUCUACAGCCAUGGUCG	17	20	306	253
rno-miR-190a-5p	UGAUAUGUUUGAUAUAUUAGGU	76	88	237	196
rno-miR-203b-3p	UUGAACUGUUAAGAACCACUGG	312	360	0	0
rno-miR-331-3p	GCCCCUGGGCCUAUCCUAGAA	13	15	291	241
rno-miR-1949	UAUACCAGGAUGUCAGCAUAGUU	9	10	293	242
rno-miR-29c-5p	UGACCGAUUUCUCCUGGUGUUC	16	18	284	235
rno-miR-542-5p	CUCGGGGAUCAUCAUGUCACGA	30	35	254	210
rno-miR-344a-3p	UGAUCUAGCCAAAGCCUGACCGU	0	0	283	234

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-139-5p	UCUACAGUGCACGUGUCUCCAG	211	243	65	54
rno-miR-22-5p	AGUUCUUCAGUGGCAAGCUUUA	231	266	44	36
rno-miR-378a-5p	CUCCUGACUCCAGGUCCUGUGU	220	254	52	43
rno-miR-6329	AAUGUGACUCAGCUAUCUGAACA	80	92	192	159
rno-miR-26b-3p	CCUGUUCUCCAUUACUUGGCUC	79	91	180	149
rno-miR-30c-1-3p	CUGGGAGAGGGUUGUUUACUCC	128	148	128	106
rno-miR-15b-3p	CGAAUCAUUAUUUGCUGCUCUA	14	16	237	196
rno-miR-101a-5p	UCAGUUAUCACAGUGCUGAUGC	42	48	205	170
rno-miR-345-5p	UGCUGACCCCUAGUCCAGUGC	134	154	111	92
rno-miR-425-3p	AUCGGGAAUAUCGUGUCCGCC	19	22	224	185
rno-miR-214-3p	ACAGCAGGCACAGACAGGCAG	14	16	226	187
rno-miR-93-3p	ACUGCUGAGCUAGCACUUCCCGA	7	8	232	192
rno-miR-210-3p	CUGUGCGUGUGACAGCGGCUGA	14	16	220	182
rno-miR-3559-3p	AUGUAGUACUGAGUCUGUCGUG	66	76	161	133
rno-miR-145-3p	GGAUUCCUGGAAAUACUGUUC	135	156	89	74
rno-miR-330-5p	UCUCUGGGCCUGUGUCUUAGGC	18	21	205	170
rno-miR-324-3p	CCACUGCCCCAGGUGCUGCUGG	4	5	216	179
rno-miR-338-3p	UCCAGCAUCAGUGAUUUUGUUGA	174	201	43	36
rno-miR-99a-3p	CAAGCUCGUUUCUAUGGGUCUG	200	231	15	12
rno-miR-17-1-3p	ACUGCAGUGAAGGCACUUGUGG	9	10	205	170
rno-miR-25-5p	AGGCGGAGACACGGGCAAUUGC	7	8	207	171
rno-miR-31a-3p	UGCUAUGCCAACAUAUUGCCAUC	28	32	178	147
rno-miR-141-3p	UAACACUGUCUGGUAAAGAUGG	63	73	126	104
rno-miR-125a-3p	ACAGGUGAGGUUCUUGGGAGCC	9	10	167	138
rno-miR-147	GUGUGCGGAAAUGCUUCUGCUA	16	18	156	129
rno-miR-384-5p	UGUAAACAAUUCCUAGGCAAUGU	0	0	170	141
rno-miR-674-5p	GCACUGAGAUGGGAGUGGUGUA	13	15	157	130
rno-miR-32-5p	UAUUGCACAUUACUAAGUUGCA	19	22	144	119
rno-let-7a-1-3p	CUAUACAAUCUACUGUCUUUCC	41	47	116	96
rno-let-7c-2-3p	CUAUACAAUCUACUGUCUUUCC	41	47	116	96
rno-miR-7a-5p	UGGAAGACUAGUGAUUUUGUUGU	1	1	150	124
rno-miR-100-3p	CAAGCUUGUGUCUAUAGGU	0	0	148	122
rno-miR-340-3p	UCCGUCUCAGUUACUUUAUAGCC	25	29	123	102
rno-miR-27a-5p	AGGGCUUAGCUGCUUGUGAGCA	17	20	130	108
rno-miR-140-5p	CAGUGGUUUUACCCUAUGGUAG	58	67	88	73
rno-miR-455-3p	GCAGUCCACGGGCAUAUACACU	65	75	74	61
rno-miR-511-3p	AAUGUGUAGCAAAAGACAGGA	98	113	39	32
rno-miR-188-5p	CAUCCCUUGCAUGGUGGAGGG	35	40	97	80
rno-miR-350	UUCACAAAGCCCAUACACUUUCAC	20	23	112	93
rno-miR-500-3p	AAUGCACCUGGGCAAGGGUUCA	31	36	100	83
rno-miR-877	GUAGAGGAGAUGGCGCAGGG	2	2	129	107

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-127-3p	UCGGAUCCGUCUGAGCUUGGCU	39	45	89	74
rno-miR-499-5p	UUAAGACUUGCAGUGAUGUUU	22	25	101	84
rno-miR-130a-5p	GCUCUUUUCACAUUGUGCUACU	3	3	115	95
rno-miR-449a-5p	UGGCAGUGUAUUGUUAGCUGGU	3	3	115	95
rno-miR-466c-5p	UGUGAUGUGUGCAUGUACAUG	24	28	94	78
rno-miR-434-3p	UUUGAACCAUCACUCGACUCCU	34	39	83	69
rno-miR-1306-5p	CCACCUCCCCUGCAAACGUCCA	3	3	113	93
rno-miR-374-3p	CUUAGCACGUUGUAUUAUUAUU	27	31	88	73
rno-miR-18a-3p	ACUGCCCUAAGUGCUCCUUCU	2	2	108	89
rno-miR-33-3p	CAAUGUUUCCACAGUGCAUCA	17	20	91	75
rno-miR-34c-3p	AAUCACUAACCACACAGCCAGG	2	2	106	88
rno-miR-3473	UCUAGGGCUGGAGAGAUGGCUA	6	7	101	84
rno-miR-532-3p	CCUCCCACACCCAAGGCUUGCA	41	47	63	52
rno-miR-3585-5p	UUCACAAGAAGGUGUCUUUCAU	51	59	46	38
rno-let-7e-3p	CUAUACGGCCUCCUAGCUUUCC	17	20	76	63
rno-miR-411-5p	UAGUAGACCGUAUAGCGUACG	19	22	73	60
rno-miR-192-3p	CUGCCAGUUCCAUAGGUCACAG	70	81	19	16
rno-miR-345-3p	CCCUGAACUAGGGGUCUGGAGA	47	54	41	34
rno-miR-16-3p	ACCAAUAUUAUUGUGCUGCUU	1	1	86	71
rno-miR-325-3p	UUUAUUGAGCACCUCCUAUCAA	0	0	83	69
rno-miR-185-5p	UGGAGAGAAAGGCAGUUCCUGA	6	7	75	62
rno-miR-196a-3p	UCGGCAACAAGAAACUGCCUGA	0	0	80	66
rno-miR-211-5p	UUCCCUUUGUCAUCCUUUGCCU	1	1	78	65
rno-miR-362-3p	AACACACCUGUUCAAGGAUUCA	18	21	61	50
rno-miR-503-3p	GGAGUAUUGUUUCCGCUGCCUGG	12	14	67	55
rno-miR-541-5p	AAGGGAUUCUGAUGUUGGUCACACU	9	10	70	58
rno-miR-212-3p	UAACAGUCUCCAGUCACGGCCA	4	5	73	60
rno-miR-219-1-3p	AGAGUUGCGUCUGGACGUCCCG	9	10	68	56
rno-miR-384-3p	AUUCCUAGAAAUUGUUCACAAU	0	0	75	62
rno-miR-221-5p	ACCUGGCAUACAAUGUAGAUUUC	12	14	55	46
rno-miR-331-5p	GGUCUUGUUUGGGUUUGUU	1	1	66	55
rno-miR-210-5p	AGCCACUGCCCACAGCACACUG	18	21	45	37
rno-miR-664-3p	UAUUCAUUUACUCCCCAGCCUA	16	18	47	39
rno-miR-190b-5p	UGAUAUGUUUGAUAUUAGGUU	7	8	54	45
rno-miR-194-3p	CCAGUGGGGCUGCUGUUAUCU	51	59	8	7
rno-miR-301a-5p	GCUCUGACUUUAUUGCACUAC	0	0	59	49
rno-miR-3074	GAUAUCAGCUCAGUAGGCACCG	0	0	57	47
rno-miR-3068-5p	UUGGAGUUCAUGCAAGUUCUAACCA	5	6	50	41
rno-miR-702-3p	UGCCCACCCUUUACCCCACUCCA	2	2	53	44
rno-miR-10b-3p	ACAGAUUCGAUUCUAGGGGAA	0	0	52	43
rno-miR-19a-5p	UCGUUUUGCAUAGUUGCACU	2	2	50	41

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-363-3p	AAUUGCACGGUAUCCAUCUGU	21	24	30	25
rno-miR-200a-5p	CAUCUUACCGGACAGUGCUGG	8	9	42	35
rno-miR-342-5p	AGGGGUGCUAUCUGUGAUUGAG	12	14	38	31
rno-miR-490-3p	CAACCUGGAGGACUCCAUGCUG	46	53	1	1
rno-miR-466b-5p	UAUGUGUGUGUGUAUGUCCAUG	1	1	45	37
rno-miR-330-3p	GCAAAGCACAGGGCCUGCAGAGA	4	5	40	33
rno-miR-128-1-5p	CGGGGCCGUAGCACUGUCUGA	8	9	32	26
rno-miR-222-5p	GGCUCAGUAGCCAGUGUAGAU	0	0	39	32
rno-miR-505-5p	GGGAGCCAGGAAGUAUUGAUGUU	6	7	33	27
rno-miR-3558-5p	CCAUAGAAGUCAUCCCACAGUGCC	7	8	30	25
rno-miR-326-3p	CCUCUGGGCCCUUCCUCCAGU	16	18	20	17
rno-miR-215	AUGACCUAUGAUUUGACAGACA	21	24	14	12
rno-miR-143-5p	GGUGCAGUGCUGCAUCUCUGG	17	20	15	12
rno-miR-219-5p	UGAUUGUCCAAACGCAAUUCU	1	1	30	25
rno-let-7b-3p	CUAUACAACCUACUGCCUUCCC	7	8	23	19
rno-miR-200c-3p	UAAUACUGCCGGGUAAUGAUG	9	10	21	17
rno-miR-298-5p	GGCAGAGGAGGGCUGUUCUUCCC	5	6	25	21
rno-miR-874-3p	CUGCCCUGGCCCGAGGGACCGA	9	10	20	17
rno-miR-325-5p	CCUAGUAGGUGCUCAGUAAGUGU	0	0	28	23
rno-miR-133a-3p	UUUGGUCCCCUUCAACCAGCUG	20	23	6	5
rno-miR-1839-3p	AGACCUACUUAUCUACCAACAG	6	7	20	17
rno-miR-218a-5p	UUGUGCUUGAUCUAACCAUGU	14	16	12	10
rno-let-7i-3p	CUGCGCAAGCUACUGCCUUGCU	5	6	20	17
rno-miR-132-5p	ACCGUGGCUUUCGAUUGUUACU	1	1	24	20
rno-miR-191b	GAACGAAAUCCAAGUGCAGCU	3	3	22	18
rno-miR-212-5p	ACCUUGGCUCUAGACUGCUUACUG	1	1	24	20
rno-miR-223-5p	CGUGUAUUUGACAAGCUGAGUUG	11	13	14	12
rno-miR-338-5p	AACAAUAUCCUGGUGCUGAGUG	19	22	5	4
rno-miR-1306-3p	GACGUUGGCUCUGGUGGUGAUG	0	0	23	19
rno-miR-196b-3p	UCGACAGCACGACACUGCCUUCA	0	0	23	19
rno-miR-6319	UCAUUCUCGCUGCUCUGGAGU	0	0	23	19
rno-miR-136-3p	CAUCAUCGUCUCAAAUGAGUCU	1	1	21	17
rno-miR-344b-2-3p	GGUAUAACCAAAGCCCGACUGU	0	0	22	18
rno-miR-362-5p	AAUCCUUGGAACCUAGGUGUGAAU	8	9	14	12
rno-miR-205	UCCUUCAUUCCACCGGAGUCUGU	4	5	17	14
rno-miR-200b-5p	CAUCUUACUGGGCAGCAUUGGA	8	9	12	10
rno-miR-201-5p	CACUCAGUAAGGCAUUGUUC	16	18	4	3
rno-miR-409a-3p	AAUGUUGCUCGGUGAACCCC	5	6	15	12
rno-miR-449c-5p	AGGCAGUGCAUUGCUAGCUGG	0	0	20	17
rno-miR-190a-3p	ACUAUAUAUCAAGCAUAUUCCU	2	2	17	14
rno-miR-30b-3p	CUGGGAUGUGGAUGUUUACGUC	8	9	11	9

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-501-3p	AAUGCACCCGGGCAAGGAUUUGG	1	1	18	15
rno-miR-7a-1-3p	ACAACAAAUCACAGUCUGCCAU	11	13	8	7
rno-let-7f-1-3p	CUAUACAAUCUAUUGCCUUCC	2	2	16	13
rno-miR-3577	UCUGUCCCUCUUGGCCCUUAG	4	5	14	12
rno-miR-186-3p	GCCCAAAGGUGAAUUUUUUGG	3	3	14	12
rno-miR-672-3p	ACACACAGUCGCCAUCUUCGA	0	0	17	14
rno-miR-1224	GUGAGGACUGGGGAGGUGGAG	0	0	16	13
rno-miR-421-5p	GGCCUCAUUAAAUGUUUGUUG	0	0	16	13
rno-miR-760-3p	CGGCUCUGGGUCUGUGGGGA	0	0	16	13
rno-miR-96-3p	CAAUCAUGUGCAGUGCCAAUAU	0	0	16	13
rno-miR-9a-5p	UCUUUGGUUAUCUAGCUGUAUGA	8	9	8	7
rno-miR-20a-3p	ACUGCAUUACGAGCACUUACA	0	0	15	12
rno-miR-874-5p	CGGCCCCACGCACCAGGGUAA	2	2	13	11
rno-miR-136-5p	ACUCCAUUUGUUUUGAUGAUGGA	4	5	10	8
rno-miR-503-5p	UAGCAGCGGGAACAGUACUGCAG	0	0	14	12
rno-let-7c-1-3p	CUGUACAACCUUCUAGCUUUCC	11	13	2	2
rno-miR-451-3p	AUGGUAAUGGUUCUCUUGCUGCU	5	6	8	7
rno-miR-511-5p	CAUGCCUUUUGCUCUGCACUC	9	10	4	3
rno-miR-2964	AGAUGUCCAGCCACAAUUCUCG	0	0	12	10
rno-miR-3075	UGUCUGGGAGCAGCCAAGGACAAG	1	1	11	9
rno-miR-598-5p	GCGGUGAUGCCGAUGGUGCGAG	0	0	12	10
rno-miR-146a-3p	ACCUGUGAAGUUCAGUUCUUU	5	6	6	5
rno-miR-146b-3p	CCUAGGGACUCAGUUCUGGUG	0	0	11	9
rno-miR-410-3p	AAUAUAACACAGAUGGCCUGU	4	5	7	6
rno-miR-466b-1-3p	AUACAUACACACACACAUACAC	5	6	6	5
rno-let-7a-2-3p	CUGUACAGCCUCCUAGCUUUCC	1	1	9	7
rno-miR-24-1-5p	GUGCCUACUGAGCUGAUAUCAG	2	2	8	7
rno-miR-301b-5p	GCUCUGACUAGGUUGCACUACU	0	0	10	8
rno-miR-344b-1-3p	GAUAUAACCAAAGCCCGACUGU	0	0	10	8
rno-miR-3585-3p	UGAACGGCCCUUGUUGUGA	6	7	4	3
rno-miR-466b-2-3p	AUAUACAUACACACAUACACA	5	6	5	4
rno-miR-141-5p	UCCAUCUUCCAGUGCAGUGUUG	2	2	7	6
rno-miR-196c-5p	UAGGUAGUUUCGUGUUGUUGGG	0	0	9	7
rno-miR-341	UCGGUCGAUCGGUCGGUCGGU	0	0	9	7
rno-miR-431	UGUCUUGCAGGCCGUCAUGCA	2	2	7	6
rno-miR-499-3p	AACAUCACAGCAAGUCUGUGCU	0	0	9	7
rno-miR-664-2-5p	CUGGCUGGGGAAAAUGAUUGG	6	7	3	2
rno-miR-708-3p	CAACUAGACUGUGAGCUUCUAG	7	8	2	2
rno-miR-101b-5p	UCGGUUAUCAUGGUACCGAUGC	6	7	2	2
rno-miR-107-5p	AGCUUCUUUACAGUGUUGCCUUGU	1	1	7	6
rno-miR-181b-1-3p	CUCACUGAACAAUGAAUGCAA	2	2	6	5

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-32-3p	GCAAUUUAGUGUGUGUGAUAUU	3	3	5	4
rno-miR-378b	AGUGGACUUGGAGUCAGAAGG	3	3	5	4
rno-miR-879-5p	AGAGGCUUAUAGCUCUAAGCC	7	8	1	1
rno-miR-153-3p	UUGCAUAGUCACAAAAGUGAUC	4	5	3	2
rno-miR-293-5p	ACUCAAACUGUGUGACACUUU	7	8	0	0
rno-miR-3547	UGAGCACCACCCCUCUCUCAGAU	0	0	7	6
rno-miR-450a-3p	UAUUGGGAACAUUUUGCAUAA	2	2	5	4
rno-miR-702-5p	GUGAGUGGGGUGGUUGGCAUG	0	0	7	6
rno-miR-92b-5p	AGGGACGGGACGCGGUGCAGUGUU	0	0	7	6
rno-miR-150-3p	CUGGUACAGGCCUGGGGGA	4	5	2	2
rno-miR-202-5p	UUCCUAUGCAUAUACUUCU	0	0	6	5
rno-miR-300-3p	UAUGCAAGGGCAAGCUCUCUUC	1	1	5	4
rno-miR-494-3p	UGAAACAUACACGGGAAACCUCU	0	0	6	5
rno-miR-501-5p	AAUCCUUUGUCCCUGGGUGA	0	0	6	5
rno-miR-615	GGGGGUCCCCGGUGCUCGGAUC	0	0	6	5
rno-miR-6315	UCUGGACAGGACAGGCCCUGAGC	3	3	3	2
rno-miR-181a-2-3p	ACCACCAACCGUUGACUGU	3	3	2	2
rno-miR-181d-3p	CCACCGGGGGAUGAAUGUCA	0	0	5	4
rno-miR-184	UGGACGGAGAACUGAUAAGGGU	1	1	4	3
rno-miR-187-3p	UCGUGUCUUGUGUUGCAGCCGG	2	2	3	2
rno-miR-299a-5p	UGGUUUACCGUCCCACAUACAU	0	0	5	4
rno-miR-337-5p	CGGCGUCAUGCAGGAGUUGAU	0	0	5	4
rno-miR-344b-5p	AGUCAGGCUGCUGGUUAUAUUC	0	0	5	4
rno-miR-3542	AAGGCUCUUCUUUCCUUGCAG	1	1	4	3
rno-miR-540-3p	AGGUCAGAGGUCGAUCCUGGGC	2	2	3	2
rno-miR-652-5p	ACAACCCUAGGAGGGGGUGCCAU	0	0	5	4
rno-miR-708-5p	AAGGAGCUUACAAUCUAGCUGGG	3	3	2	2
rno-let-7f-2-3p	CUAUACAGUCUACUGUCUUUC	2	2	2	2
rno-miR-127-5p	CUGAAGCUCAGAGGGCUCUGAUU	3	3	1	1
rno-miR-188-3p	CUCCCACAUGCAGGGUUUGC	0	0	4	3
rno-miR-193-5p	UGGGUCUUUGCGGGCAAGAUGA	4	5	0	0
rno-miR-20b-3p	ACUGCAGUGUGAGCACUUCUGG	2	2	2	2
rno-miR-224-5p	CAAGUCACUAGUGGUUCCGUUU	3	3	1	1
rno-miR-26a-3p	CCUAUUCUUGGUUACUUGCAC	1	1	3	2
rno-miR-34a-3p	AAUCAGCAAGUAUACUGCCCUA	1	1	3	2
rno-miR-351-3p	GGUCAAGAGGCGCCUGGGAAC	0	0	4	3
rno-miR-369-5p	AGAUCGACCGUGUUAUAUUCGC	0	0	4	3
rno-miR-411-3p	UAUGUAACACGGUCCACUAA	1	1	3	2
rno-miR-434-5p	AGCUCGACUCAUGGUUUGAACCA	1	1	3	2
rno-miR-466c-3p	UAUACAUGCACACAUACACAC	0	0	4	3
rno-miR-6318	CUGCCUGGCGCAGGGCCUGUAG	0	0	4	3

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-6325	AAAGUCAGACAGAGACUCUGCAG	0	0	4	3
rno-miR-134-5p	UGUGACUGGUUGACCAGAGGGG	0	0	3	2
rno-miR-135b-5p	UAUGGCUUUUCAUUCCUAUGUGA	0	0	3	2
rno-miR-20b-5p	CAAAGUGCUCAUAGUGCAGGUAG	1	1	2	2
rno-miR-211-3p	GGCAAGGACAGCAAAGGGGG	0	0	3	2
rno-miR-323-3p	CACAUUACACGGUCGACCUCU	0	0	3	2
rno-miR-3558-3p	ACUGUGGAGGGUUUCUAUGU	0	0	3	2
rno-miR-3583-3p	CCUGACUUCUCUCUUCAUGCAG	1	1	2	2
rno-miR-3594-3p	CACACCGCCUCUGCCCGCUAGU	1	1	2	2
rno-miR-379-3p	CUAUGUAACAUGGUCCACUAAC	0	0	3	2
rno-miR-382-3p	AAUCAUUCACGGACAACACUU	0	0	3	2
rno-miR-433-3p	AUCAUGAUGGGCUCCUCGGUGU	2	2	1	1
rno-miR-487b-3p	AAUCGUACAGGGUCAUCCACUU	0	0	3	2
rno-miR-547-5p	UCACUUCAGGAUGUACCACCCA	3	3	0	0
rno-miR-6317	GUGAACCUGAGAGAAAGGCUC	0	0	3	2
rno-miR-103-1-5p	GGCUUCUUUACAGUGCUGCCUUGU	0	0	2	2
rno-miR-126b	UACCAAAAGUAAUAAUGUGCUG	0	0	2	2
rno-miR-129-5p	CUUUUUGCGGUCUGGGCUUGC	1	1	1	1
rno-miR-138-2-3p	GCUAUUUCACGACACCAGGGU	0	0	2	2
rno-miR-139-3p	UGGAGACGCGGCCCUGUUGGAG	1	1	1	1
rno-miR-201-3p	UGAACAGCGCCUUUCUGUGUAG	2	2	0	0
rno-miR-203a-5p	AGUGGUUCUUAACAGUUCAAC	2	2	0	0
rno-miR-216a-3p	CACAGUGGUCUCUGGGAUUAUG	0	0	2	2
rno-miR-216a-5p	UAAUCUCAGCUGGCAACUGUGA	0	0	2	2
rno-miR-299a-3p	UAUGUGGGACGGUAAACCGCU	0	0	2	2
rno-miR-29b-2-5p	CUGGUUUCACAUGGUGGCUUAG	0	0	2	2
rno-miR-3065-5p	UCAACAAAAUCACUGAUGCU	0	0	2	2
rno-miR-3102	CUCUACUCCCUGCCCCAGCCA	0	0	2	2
rno-miR-3541	UCCCUCCCCCUCACUGCA	1	1	1	1
rno-miR-3566	CUGCCUAACAAUGAACUACC	0	0	2	2
rno-miR-369-3p	AAUAAUACAUGGUUGAUCUUU	1	1	1	1
rno-miR-380-3p	UAUGUAGUAUGGUCCACAUCU	1	1	1	1
rno-miR-381-3p	UAUACAAGGGCAAGCUCU	1	1	1	1
rno-miR-500-5p	AAUCCUUGCUAUCUGGGUGCUUAG	2	2	0	0
rno-miR-547-3p	AUUGGUACUUCUUUAAGUGAGA	1	1	1	1
rno-miR-6324	UCAGUAGGCCAGACAGCAAGCAC	1	1	1	1
rno-miR-6332	CGCAGGGACUGCAAGGAGCCGCA	0	0	2	2
rno-miR-653-5p	UUGAAACAUUCUCUACUGAAC	2	2	0	0
rno-miR-98-3p	CUAUACAACUUACUACUUUCC	0	0	2	2
rno-miR-129-2-3p	AAGCCCUUACCCCAAAAAGCAU	0	0	1	1
rno-miR-133a-5p	AGCUGGUAAAAUGGAACCAAAU	1	1	0	0

Table S1 (*continued*)

Table S1 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)
rno-miR-153-5p	GUCAUUUUUGUGAUGUUGCAGCU	0	0	1	1
rno-miR-17-2-3p	ACUGCACUGCAAGCACUUCUUAC	1	1	0	0
rno-miR-195-3p	CCAAUAUUGGCUGUGCUGCUCCA	1	1	0	0
rno-miR-196c-3p	ACAACAACACCAAACCACCUGA	0	0	1	1
rno-miR-204-3p	GCUGGGAAGGCAAAGGGACGUU	1	1	0	0
rno-miR-23b-5p	GGGUUCCUGGCAUGCUGAUUU	0	0	1	1
rno-miR-292-3p	AAGUGCCGCCAGGUUUUGAGUGU	1	1	0	0
rno-miR-3099	UAGGCUAGAAAGAGGUUGGGGA	0	0	1	1
rno-miR-329-5p	AGAGGUUUUCUGGGUCUCUGUUUC	0	0	1	1
rno-miR-3572	UUACACUUGCCCUUUUUUCCCCAG	1	1	0	0
rno-miR-3583-5p	AGCAUGAAGAGUUCAGAUCACGUU	0	0	1	1
rno-miR-3593-5p	UGGCCUCCGCAGGGUUGAAGCU	0	0	1	1
rno-miR-3594-5p	CCCAGGGCAGAGCAGUGUGAA	0	0	1	1
rno-miR-376b-3p	AUCAUAGAGGAACAUCCACUU	0	0	1	1
rno-miR-382-5p	GAAGUUGUUCGUGGUGGAUUCG	0	0	1	1
rno-miR-466d	AUGUGUGUGUAUGUUCUUUUGU	0	0	1	1
rno-miR-485-3p	CAUACACGGCUCUCCUCUCUUC	0	0	1	1
rno-miR-485-5p	AGAGGCUGGCCGUGAUGAAUUC	0	0	1	1
rno-miR-489-5p	UGUCGUAUGCGUGAUGACACGUUC	1	1	0	0
rno-miR-504	AGACCCUGGUCUGCACUCUGUC	0	0	1	1
rno-miR-509-5p	UACUCCAGAAUAUGGCAAUCAUG	1	1	0	0
rno-miR-539-3p	CAUACAAGGGUAAUUUCUUUUC	0	0	1	1
rno-miR-540-5p	CAAGGGUCACCCUCUGACUCUGU	1	1	0	0
rno-miR-6321	UACUGCAGUGAGUUCUAUGAAGC	0	0	1	1
rno-miR-7b	UGGAAGACUUGUGAUUUUGUUGU	0	0	1	1

RPTM, reads per ten million transcripts.

Table S2 Dis-regulated microRNAs (miRNAs) with at least 1000 RPKM

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)	log2(norm_HCC/ norm_NT)
rno-miR-122-5p	UGGAGUGUGACAAUGGUGUUUG	27,158	31,306	50	41	–9.576600
rno-miR-802-5p	UCAGUAACAAAGAUUCAUCCU	1,952	2,250	4	3	–9.550747
rno-miR-802-3p	ACGGAGAGUCUUUGUCACUCAGU	1,003	1,156	3	2	–9.174926
rno-miR-122-3p	AACGCCAUCAUCACACUAA	5,206	6,001	20	17	–8.463524
rno-miR-203a-3p	GUGAAAUGUUUAGGACCACUAG	1,474	1,699	6	5	–8.408542
rno-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	711,543	820,215	129,654	107,270	–2.934755
rno-miR-194-5p	UGUAACAGCAACUCCAUGUGGA	10,052	11,587	1,888	1,562	–2.891041
rno-miR-30a-3p	CUUUCAGUCGGAUGUUUGCAGC	3,258	3,756	829	686	–2.452917
rno-miR-378a-3p	ACUGGACUUGGAGUCAGAAGG	78,714	90,736	20,723	17,145	–2.403887

Table S2 (*continued*)

Table S2 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)	log2(norm_HCC/ norm_NT)
rno-miR-192-5p	CUGACCUAUGAAUUGACAGCC	306,887	353,757	81,323	67,283	–2.3944450
rno-miR-143-3p	UGAGAUGAAGCACUGUAGCUCA	66,190	76,299	17,776	14,707	–2.3751610
rno-miR-30e-3p	CUUUCAGUCGGAUGUUUACAGC	1,943	2,240	547	453	–2.3059160
rno-miR-99a-5p	AACCCGUAGAUCCGAUCUUGUG	943	1,087	330	273	–1.9933790
rno-miR-28-3p	CACUAGAUUGUGAGCUCCUGGA	4,561	5,258	1,664	1,377	–1.9329860
rno-miR-193-3p	AACUGGCCUACAAAGUCCCAGU	1,756	2,024	745	616	–1.7162070
rno-miR-101b-3p	UACAGUACUGUGAUAGCUGAA	19,485	22,461	8,631	7,141	–1.6532240
rno-miR-26b-5p	UUCAAGUAAUUCAGGAUAGGU	10,641	12,266	5,919	4,897	–1.3246950
rno-miR-28-5p	AAGGAGCUCACAGUCUAUUGAG	1,400	1,614	804	665	–1.2792140
rno-miR-146a-5p	UGAGAACUGAAUUCCAUGGGUU	1,531	1,765	1,129	934	–0.9181740
rno-miR-30d-5p	UGUAAACAUCCCCGACUGGAAG	61,449	70,834	45,409	37,569	–0.9148990
rno-miR-497-5p	CAGCAGCACACUGUGGUUUGUA	1,082	1,247	803	664	–0.9092060
rno-miR-30e-5p	UGUAAACAUCCUUGACUGGAAG	33,856	39,027	27,372	22,646	–0.7852160
rno-miR-451-5p	AAACCGUUACCAUUACUGAGUU	1,313	1,514	1,153	954	–0.6663040
rno-miR-30a-5p	UGUAAACAUCCUCGACUGGAAG	93,571	107,862	84,247	69,702	–0.6299150
rno-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	137,990	159,065	124,866	103,308	–0.6226640
rno-miR-423-3p	AGCUCGGUCUGAGGCCCCUCAGU	1,874	2,160	2,024	1,675	–0.3668700
rno-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUUU	2,670	3,078	2,929	2,423	–0.3451990
rno-miR-101a-3p	UACAGUACUGUGAUAACUGAA	5,879	6,777	6,754	5,588	–0.2783150
rno-miR-140-3p	UACCACAGGGUAGAACCACGG	1,540	1,775	1,798	1,488	–0.2544440
rno-miR-126a-3p	UCGUACCGUGAGUAAUAAUGCG	6,009	6,927	7,037	5,822	–0.2507160
rno-let-7d-3p	CUAUACGACCUGCUGCCUUUCU	1,884	2,172	2,555	2,114	–0.0390490
rno-miR-126a-5p	CAUUAUUACUUUUGGUACGCG	13,668	15,755	18,692	15,465	–0.0268030
rno-miR-27b-3p	UUCACAGUGGCUAAGUUCUGC	31,257	36,031	46,531	38,498	0.0955448
rno-miR-29a-3p	UAGCACCAUCUGAAAUCGGUUA	8,086	9,321	12,132	10,037	0.1067715
rno-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	61,506	70,900	105,054	86,917	0.2938528
rno-miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	1,201	1,384	2,124	1,757	0.3442702
rno-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	29,866	34,427	54,955	45,467	0.4012793
rno-miR-30b-5p	UGUAAACAUCCUACACUCAGCU	6,518	7,513	14,385	11,901	0.6636218
rno-miR-23b-3p	AUCACAUUGCCAGGGAUUACC	991	1,142	2,250	1,862	0.7052904
rno-miR-340-5p	UUAUAAAGCAAUGAGACUGAUU	1,722	1,985	4,009	3,317	0.7407400
rno-miR-150-5p	UCUCCCAACCCUUGUACCAGUG	1,386	1,598	3,480	2,879	0.8493004
rno-miR-1839-5p	AAGGUAGAUAGAACAGGUCUUG	565	651	1,432	1,185	0.8641576
rno-miR-98-5p	UGAGGUAGUAAGUUGUAUUGUU	723	833	2,146	1,776	1.0922432
rno-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	8,683	10,009	26,071	21,570	1.1077283
rno-let-7c-5p	UGAGGUAGUAGGUUGUAUGGUU	25,562	29,466	82,963	68,640	1.2199983
rno-miR-107-3p	AGCAGCAUUGUACAGGGCUAUCA	1,407	1,622	4,610	3,814	1.2335310
rno-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	234,860	270,729	912,244	754,749	1.4791475
rno-miR-29c-3p	UAGCACCAUUUGAAAUCGGUUA	1,174	1,353	4,720	3,905	1.5291607

Table S2 (*continued*)

Table S2 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)	log2(norm_HCC/ norm_NT)
rno-miR-151-5p	UCGAGGAGCUCACAGUCUAGU	3,848	4,436	15,525	12,845	1.5338756
rno-miR-322-5p	CAGCAGCAAUUCAUGUUUUGGA	648	747	2,708	2,240	1.5843186
rno-miR-199a-3p	ACAGUAGUCUGCACAUUGGUUA	4,100	4,726	17,155	14,193	1.5864880
rno-miR-10a-5p	UACCCUGUAGAUCCGAAUUUGUG	78,712	90,733	336,331	278,265	1.6167602
rno-miR-19b-3p	UGUGCAAAUCCAUGCAAAACUGA	1,619	1,866	7,312	6,050	1.6969862
rno-let-7e-5p	UGAGGUAGGAGGUUGUAUAGUU	1,780	2,052	8,154	6,746	1.7170016
rno-miR-24-3p	UGGCUCAGUUCAGCAGGAACAG	443	511	2,095	1,733	1.7618765
rno-miR-92a-3p	UAUUGCACUUGUCCCGGCCUG	979	1,129	4,678	3,870	1.7772881
rno-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	2,730	3,147	13,497	11,167	1.8271926
rno-miR-103-3p	AGCAGCAUUGUACAGGGCUAUGA	4,132	4,763	21,485	17,776	1.8999883
rno-miR-16-5p	UAGCAGCACGUAAAUAUUGGCG	11,427	13,172	59,787	49,465	1.9089337
rno-miR-320-3p	AAAAGCUGGGUUGAGAGGGCGA	789	910	4,180	3,458	1.9259994
rno-miR-200b-3p	UAAUACUGCCUGGUAAUGAUGAC	391	451	2,093	1,732	1.9412396
rno-miR-872-5p	AAGGUUACUUGUUAGUUCAGG	586	675	3,622	2,997	2.1505597
rno-let-7i-5p	UGAGGUAGUAGUUUGUGCUGUU	6,657	7,674	41,415	34,265	2.1586850
rno-miR-151-3p	CUAGACUGAGGCUCCUUGAGG	2,544	2,933	16,773	13,877	2.2422467
rno-miR-20a-5p	UAAAGUGCUUAUAGUGCAGGUAG	369	425	2,449	2,026	2.2530994
rno-miR-450a-5p	UUUUGCGAUGUGUUCCUAAUGU	576	664	3,867	3,199	2.2683658
rno-miR-128-3p	UCACAGUGAACCGGUCUCUUU	257	296	1,941	1,606	2.4398028
rno-miR-351-5p	UCCCUGAGGAGCCCUUUGAGCCUGA	1,029	1,186	8,374	6,928	2.5463349
rno-miR-92a-1-5p	AGGUUGGGAUUUGUCGCAAUGCU	180	207	1,528	1,264	2.6102938
rno-miR-125b-5p	UCCCUGAGACCCUAACUUGUGA	2,086	2,405	18,255	15,103	2.6507264
rno-miR-27a-3p	UUCACAGUGGCUAAGUUCCGC	1,142	1,316	10,367	8,577	2.7043136
rno-miR-23a-3p	AUCACAUUGCCAGGGAUUUCC	890	1,026	8,172	6,761	2.7202059
rno-miR-24-2-5p	GUGCCUACUGAGCUGAAACAGU	244	281	2,346	1,941	2.7881581
rno-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	19,704	22,713	201,637	166,825	2.8767453
rno-miR-186-5p	CAAAGAAUUCUCCUUUUGGGCU	5,610	6,467	63,089	52,197	3.0127984
rno-miR-19a-3p	UGUGCAAAUCUAUGCAAAACUGA	144	166	1,633	1,351	3.0247725
rno-miR-142-5p	CAUAAAGUAGAAAGCACUACU	4,027	4,642	45,673	37,788	3.0251097
rno-miR-31a-5p	AGGCAAGAUGCUGGCAUAGCUG	6,418	7,398	74,299	61,472	3.0547222
rno-miR-125a-5p	UCCCUGAGACCCUUUAACCUGUGA	2,449	2,823	29,722	24,591	3.1228294
rno-miR-191a-5p	CAACGGAAUCCCAAAAGCAGCUG	20,759	23,929	257,282	212,863	3.1530932
rno-miR-25-3p	CAUUGCACUUGUCUCGGUCUGA	3,442	3,968	50,575	41,843	3.3985024
rno-miR-142-3p	UGUAGUGUUUCCUACUUUAUGGA	139	160	2,783	2,303	3.8473706
rno-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	163	188	3,334	2,758	3.8748179
rno-miR-222-3p	AGCUACAUCUGGCUACUGGGU	148	171	3,055	2,528	3.8859282
rno-miR-100-5p	AACCCGUAGAUCCGAACUUGUG	152	175	3,369	2,787	3.9932862
rno-miR-221-3p	AGCUACAUUGUCUGCUGGGUUUC	189	218	4,441	3,674	4.0749516
rno-miR-17-5p	CAAAGUGCUUACAGUGCAGGUAG	86	99	2,172	1,797	4.1820181

Table S2 (*continued*)

Table S2 (*continued*)

miRNA	Seq	NT	norm_NT (RPTM)	HCC	norm_HCC (RPTM)	log2(norm_HCC/norm_NT)
rno-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	776	895	19,840	16,415	4.1969833
rno-miR-425-5p	AAUGACACGAUCACUCCCGUUGA	425	490	11,363	9,401	4.2619606
rno-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	623	718	16,682	13,802	4.2647497
rno-miR-342-3p	UCUCACACAGAAAUCGCACCCGU	83	96	2,234	1,848	4.2667865
rno-miR-335	UCAAGAGCAAUAACGAAAAAUGU	687	792	22,247	18,406	4.5385319
rno-miR-301a-3p	CAGUGCAAUAGUAUUGUCAAAGC	513	591	17,572	14,538	4.6205269
rno-miR-130a-3p	CAGUGCAAUGUUAAAAGGGCAU	1,932	2,227	70,729	58,518	4.7157070
rno-miR-106b-3p	CCGCACUGUGGGUACUUGCUGC	106	122	4,205	3,479	4.8337196
rno-miR-872-3p	UGAACUAUUGCAGUAGCCUCCU	433	499	17,374	14,374	4.8482780
rno-miR-138-5p	AGCUGGUGUUGUGAAUCAGGCCG	73	84	3,093	2,559	4.9290470
rno-miR-106b-5p	UAAAGUGCUGACAGUGCAGAU	164	189	7,885	6,524	5.1092986
rno-miR-92b-3p	UAUUGCACUCGUCCCGGCCUCC	26	30	1,474	1,220	5.3457748
rno-miR-93-5p	CAAAGUGCUGUUCGUGCAGGUAG	1,261	1,454	73,689	60,967	5.3899294
rno-miR-181c-5p	AACAUUCAACCUGUCGGUGAGU	843	972	51,439	42,558	5.4523302
rno-miR-181d-5p	AACAUUCAUUGUUGUCGGUGGGU	62	71	4,103	3,395	5.5794487
rno-miR-182	UUUGGCAAUGGUAGAACUCACACCG	3,922	4,521	274,806	227,362	5.6522054
rno-miR-34c-5p	AGGCAGUGUAGUUAGCUGAUUGC	289	333	25,319	20,948	5.9751465
rno-miR-146b-5p	UGAGAACUGAAUUCCAUAGGCUGU	21	24	2,095	1,733	6.1740934
rno-miR-672-5p	UGAGGUUGGUGUACUGUGUGUGA	28	32	2,927	2,422	6.2419831
rno-miR-183-5p	UAUGGCACUGGUAGAAUUCACU	103	119	13,247	10,960	6.5251424
rno-miR-125b-1-3p	ACGGGUUAGGCUCUUGGGAGCU	14	16	1,816	1,502	6.5526691
rno-miR-130b-3p	CAGUGCAAUGAUGAAAGGGCAU	9	10	4,545	3,760	8.5545889
rno-miR-10b-5p	CCCUGUAGAACCGAAUUUGUGU	834	961	447,713	370,417	8.5903982
rno-miR-196b-5p	UAGGUAGUUUCCUGUUGUUGGG	2	2	2,038	1,686	9.7193888
rno-miR-196a-5p	UAGGUAGUUUCAUGUUGUUGGG	3	3	3,325	2,751	9.8407779

HCC, hepatocellular carcinoma; RPTM, reads per ten million transcripts.

Table S3 The most severely regulated microRNAs (miRNAs) in HCC and their reported target genes

miRNA	NT	HCC	log2_ratio	Reported targets	Ref.
rno-miR-122-5p	31,306	41	–9.6	IGF-1R, CCNG1, BCW-L	(24,47,49)
rno-miR-802-5p	2,250	3	–9.6		
rno-miR-802-3p	1,156	2	–9.2		
rno-miR-122-3p	6,001	17	–8.5		
rno-miR-203a-3p	1,699	5	–8.4		
rno-miR-22-3p	820,215	107,270	–2.9		
rno-miR-194-5p	11,587	1,562	–2.9	ACVR2B, RAC1, HBEGF, IGF1R, PTPN12, PTPN13, ITGA9, SOCS2, DNMT3A	(50,51)
rno-miR-30a-3p	3,756	686	–2.5		
rno-miR-378a-3p	90,736	17,145	–2.4	Sufu, Fus-1, CYP2E1, HMOX1	(52-54)
rno-miR-192-5p	353,757	67,283	–2.4	ZEB1, ZEB2, SIP1, TYMS	(55,56)
rno-miR-143-3p	76,299	14,707	–2.4	MACC1, DNMT3A, KRAS, ELK1, Bcl-2	(57-61)
rno-miR-30e-3p	2,240	453	–2.3		
rno-miR-106b-5p	189	6,524	5.1	E2F1, p21	(62,63)
rno-miR-92b-3p	30	1,220	5.3		
rno-miR-93-5p	1,454	60,967	5.4	integrin-beta FUS1, p21	(64-66)
rno-miR-181c-5p	972	42,558	5.5	SIRT1, BTBD3, TRIM2, TIMP3	(67,68)
rno-miR-181d-5p	71	3,395	5.6	MGMT, TIMP3, Kras, Bcl-2	(68-70)
rno-miR-182	4,521	227,362	5.7	FOXO3, FOXO1, MITF	(27,42)
rno-miR-34c-5p	333	20,948	6.0	CCNE2, CDK4, E2F3, MET, c-MYC	(71)
rno-miR-146b-5p	24	1,733	6.2	BRCA1, EGFR	(72,73)
rno-miR-672-5p	32	2,422	6.2		
rno-miR-183-5p	119	10,960	6.5	PDCD4, VIL2	(74,75)
rno-miR-125b-1-3p	16	1,502	6.6	Bmf, BMPR1B	(76,77)
rno-miR-130b-3p	10	3,760	8.6	TP53INP1, RUNX3	(78,79)
rno-miR-10b-5p	961	370,417	8.6	HOXD10, Tiam1	(80,81)
rno-miR-196b-5p	2	1,686	9.7	c-myc, ERG, Fas	(82-84)
rno-miR-196a-5p	3	2,751	9.8	HOXB8, HoxA7, HoxC8, HoxD8, BMP4	(46,85,86)

Table S4 The enriched GO terms of hsa-miR-182 targets. The meaning of the columns is in the NOTE sheet

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
Biological process							
hsa-miR-182	GO:0048011	Nerve growth factor receptor signaling pathway	ADAM17, ADCY2, ADCY5, ADCY6, APH1A, APH1B, ARHGDIA, ARHGEF2, ARHGEF3, ARHGEF7, BCL11B, BCL2L11, CALM3, CASP2, CASP3, CASP9, CDK1, CREB1, DUSP3, DUSP4, FGD4, FOXO1, FOXO3, FRS2, GDNF, GRB2, HDAC2, IRS1, ITPR1, KIDINS220, MAPK1, MEF2C, NRAS, PCSK6, PDPK1, PIK3R1, PLCG1, PRDM4, PRKACB, PRKAR1A, PRKCA, PRKCE, RAC1, RALB, RAPGEF1, RELA, RICTOR, RPS6KA2, RPS6KA3, RTN4, SHC3, SORT1, SOS1, THEM4, TIAM1, TSPAN1, VAV3	57	210	3.6E-06	1.6E-02
hsa-miR-182	GO:0007268	Synaptic transmission	adcy2, adcy5, adcy6, aldh5a1, atxn3, cacna1e, cacnb2, cacnb4, calm3, cartpt, cbln1, chrna4, creb1, dtna, exoc4, fgf13, gabra1, gabra4, gabrb3, gabrg1, gad2, gjd3, glra3, gnai3, gng12, gng7, gngt1, gria1, gria3, grik3, grin2a, grm1, grm4, grm5, grm6, htr1f, htr2c, kcna1, kcna6, kcnh5, kcnip1, kcnj10, kcnj14, kcnj2, kcnj5, kcnk10, kcnk2, kcnma1, kcnmb1, kcnmb3, kcnn3, kcnq3, kcnq5, lrp6, mapk1, mbl2, mpp2, mpp3, ncald, ncoa2, nptx1, nptx2, pafah1b1, pcdh8, pcdhb11, pcdhb16, pcdhb3, pcdhb4, pde7b, pdpk1, prkacb, prkca, prkcb, rps6ka2, rps6ka3, rps6ka6, sdcbp, slc18a2, slc18a3, slc1a1, slc1a2, slc6a1, syn2, sypl1, syt2, unc13c, vamp1	87	370	8.5E-06	1.9E-02
hsa-miR-182	GO:0007264	Small gtpase mediated signal transduction	ARF4, ARHGAP11A, ARHGAP12, ARHGAP17, ARHGAP20, ARHGAP26, ARHGAP29, ARHGAP36, ARHGAP44, ARHGAP5, ARHGAP6, ARHGDIA, ARHGEF2, ARHGEF3, ARHGEF7, ARL14, ARL4C, ARL5B, BCL11B, CDK1, DNAJC27, DOCK1, FAM13A, FGD4, MAPK1, MRAS, NRAS, OCRL, OPHN1, PDPK1, PRKCSH, RAB10, RAB11A, RAB22A, RAB23, RAB27A, RAB27B, RAB2A, RAB31, RAB3B, RAB3C, RAB40B, RAB43, RAB5B, RAB6A, RAB7A, RAB8B, RAB9B, RABIF, RAC1, RALB, RALGPS1, RALGPS2, RAP2A, RAPGEF1, RAPGEF4, RAPGEF5, RAPGEF6, RASGRP1, RERGL, RHOBTB1, RHOBTB3, RHOF, RHOJ, RHOQ, RND3, RRAS2, SOS1, STARD13, SYDE1, SYDE2, TAGAP, TIAM1, TSPAN1, VAV3, YWHAQ	76	322	2.7E-05	3.9E-02
Molecular function							
hsa-miR-182	GO:0005515*	Protein binding	a1cf, aasdhppt, aatk, abcd2, abl2, ablim1, acaa2, acan, acvr1, acvr2b, adam17, adam22, adam9, adamts4, adcy6, adra2a, adra2c, aff4, ager, agtr1, alg2, alpk3, amot, amotl2, angptl4, ank3, ankib1, ankrd28, ankrd44, antxr2, anxa11, ap3m1, apba2, apbb2, aph1a, aph1b, appbp2, appl1, arf4, arhgap17, arhgap26, arhgdia, arhgef2, arhgef7, arl14, arl4c, arrdc3, artn, asap1, asph, atcay, atf7, atg12, atg14, atg7, atm, atp10d, atp11b, atp11c, atp2b4, atp6v0a2, atp7a, atp8a1, atxn1, atxn3, atxn7, bag1, bcl10, bcl11b, bcl2, bcl2a1, bcl2l1, bcl2l11, bclaf1, bdkrb2, bet1, bicd2, birc5, bmi1, bmpr1b, brd4, brms1l, brpf3, btg1,				

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005515*	Protein binding	bub3, bves, c12orf52, c16orf70, c1d, c21orf33, c21orf7, c5orf30, cab39, cacna1c, cacnb2, cacnb4, cadm1, calb1, calcr, calcrl, calm3, calu, camsap1l1, capn5, cartpt, cask, casp10, casp2, casp3, casp9, cav3, cbfa2t3, cbr4, cbx5, ccdc141, ccdc33, ccdc50, ccdc59, ccl3, ccm2, ccng1, ccny, ccr1, cd164, cd1d, cd226, cd274, cd2ap, cd47, cd59, cdc27, cdc42bpa, cdc42se2, cdc73, cdk1, cdk12, cdk2, cdk6, cdkn2b, ceacam6, cebpa, celf1, chek2, chmp1a, chmp1b, chordc1, cisd2, cited2, clec4g, clic5, cnksr1, cnksr3, cnnm3, cnot4, cnot6l, cnst, cog3, cog5, col13a1, col4a1, colq, cotl1, cpsf7, creb1, creb5, crkl, crtc1, cry2, cse1l, csf2rb, csrnp2, csrp3, ctbp2, ctdsp2, cttn, cttnbp2nl, cul5, cxadr, cybb, cycs, cyfip1, cyld, dact1, dazap2, dcaf7, dcc, dclre1b, dcp2, dcun1d1, ddx11, ddx58, denr, depdc1, deptor, derl1, dhdds, dhh, dicer1, disc1, dixdc1, dlat, dlgap2, dmpk, dnajb6, dnajb9, dnajc21, dnmt3a, dock1, dock4, dock9, dohh, dpep2, dph3, dpysl2, dr1, dscam, dtna, dtnbp1, dtx3l, dusp12, dync1i1, dyrk1a, dzip1, e2f3, edar, edem1, eea1, egln1, egln3, eif2c1, eif2c4, eif2s1, eif3j, eif4b, eif4ebp2, eif5a2, eif6, elavl1, elavl2, ell, elmo1, elovl6, eml1, ep300, epas1, epha3, ephb1, eps8, erbb4, erc2, ercc4, ercc8, erg, erlin2, esr1, esrrg, etf1, evi5, exoc4, exoc8, eya3, ezh2, f2r, f2rl1, faf2, fam123b, fam188a, fbn1, fbxo27, fbxo44, fbxo5, fbxw11, fbxw7, fcho2, fcn3, fech, fgf13, fhit, flnb, flot1, flt1, fmr1, fn1, fnbp1l, fnta, foxn3, foxo1, foxo3, foxp3, frs2, fst, fxn, fyco1, fyttd1, fzd1, fzd5, fzd9, gabpb1, gad2, gan, gart, gcc1, gdnf, gemin5, gemin8, git2, gjd3, gli2, gna13, gnaq, gnl3l, gopc, grb2, grem1, gria1, grin2a, gspt1, gucy2c, hck, hdac2, hdac9, hexim1, hey1, heyl, hif1an, hip1, hipk1, hipk2, hmga2, hook3, hoxa1, hoxa10, hoxa9, hsp90aa1, hspa5, igf1, igf1r, igf2bp1, igf2bp3, ikbkap, il10ra, il13ra1, il33, il4r, il6r, il6st, insig1, insl3, insr, ints5, ints6, ints7, ipo9, irak3, irak4, irf4, irs1, itga6, itgav, itgb1bp1, itm2b, itpr1, jmjd1c, jub, kcnh1, kcnip1, kcnj10, kcnj5, kcnma1, kdm2b, kdm5b, khdrbs3, kiaa0141, kiaa0182, kiaa0408, kiaa1377, kif1b, kif20b, kif3b, kif5c, kitlg, klf13, klhl2, kpna1, kpna3, kpnb1, lars, lasp1, lass2, lca5, lcp2, ldb3, lgi1, lims1, lin28a, lin28b, lman1, lmtk2, lmx1b, lox, lpar1, lphn1, lpp, lrif1, lrp12, lrp2, lrp6, lrpprc, lrrc3, lsm5, lzts1, malt1, map1b, map1lc3b, map3k13, map3k3, map4k2, map4k4, mapk1, mapk10, mapk9, mapre1, mapre3, march5, mark2, masp1, matn3, mavs, mbd4, mbl2, mc2r, mcl1, mdm4, meaf6, mecom, mecp2, med23, mef2bnb, mef2c, mef2d, metap1, mettl9, mgst1, mier1, mitf, mkl2, mll, mllt1, mmab, mmp12, mms22l, mobkl1a, mobkl2b, morf4l1, morf4l2, mpg, mpp2, mpp3, mrpl36, mrpl48, mrvi1, msn, mtdh, mtss1, myb, mycbp2, myh9, myo1e, myo5b, myrip, nanos1, nap1l1, napg, ncapd2, nckap1, ncoa1, ncoa2, ncor1, ncs1, ndrg1, ndufaf4, nedd9, nf1, nhej1, nhlrc1, nin, nipbl, nlgn4x, nme2, npm1, nqo1, nr2c2, nr3c1, nr5a2, nrg1, nrxn1, ntn1, ntng2, nuak1, nudt21, nufip2, nup43, nup50, ocrl, olfm1, optn, orai2, pafah1b1, pag1, paip1, paip2, paip2b, pak3, palld, pard6b, pax8, pbx1, pcgf3, pcgf5, pdcd4, pdk3, pdpk1, pds5b, pdzd2, peak1, pecam1, peg10, pfkfb2, pgr,				

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005515*	Protein binding	phactr2, phb, phf17, phf8, phip, picalm, piga, pigu, pik3r1, pip5k1b, pkhd1, pkn2, plcg1, plekhm2, pmaip1, pmepa1, pnrc2, poldip2, poli, pot1, pou2f1, ppara, ppfia1, ppie, ppm1a, ppm1b, ppm1e, ppm1f, ppp1cb, ppp1cc, ppp1r12a, ppp1r16b, ppp1r2, ppp1r9b, ppp2r1b, ppp2r3a, ppp3ca, ppp6r1, prc1, prdm16, prkaa1, prkaa2, prkacb, prkar1a, prkca, prkcb, prkd1, prkd3, proc, prpf4b, prrc2b, prune, psma2, ptch1, ptgdr, ptgis, ptpn12, ptpre, ptprm, pura, pxmp4, qki, rab11a, rab11fip4, rab22a, rab27a, rab3ip, rab5b, rab6a, rab7a, rab9b, rac1, rad17, rad51, rad51b, ralb, rap2a, rapgef1, rapgef4, rarg, rassf6, rbbp4, rbfox2, rbm15, rbm17, rbm4, rbm5, rbm8a, rcan3, rchy1, rdx, reep1, reep5, rela, reps2, rere, rest, ret, rev1, rgs2, rhbdd1, rhobtb3, rictor, rnf139, rnf144b, rnf182, rnf2, rnf4, rnf41, rnf8, rock1, rps23, rps9, rpusd4, rragd, rras2, rsad2, rtn4, runx1, sbds, sbf2, scai, scube3, sdc2, sec14l3, sec24b, sept14, sept6, sept7, sept9, serinc1, serpinb5, serpinb8, sestd1, setd7, sh3bp2, sh3bp4, sh3d19, sh3pxd2b, shank2, shc3, shox, shroom2, sik2, sik3, sike1, sirpb1, sirt1, ska2, skiv2l2, slain2, slc11a2, slc22a5, slc23a2, slc25a15, slc4a4, slc6a20, slc6a4, slc7a11, slc7a8, sltm, smad3, smad4, smad7, smarca5, smc2, smc6, smcr7, smcr7l, snap23, snca, snrpb2, sntb1, sntb2, snx1, snx17, snx19, snx27, snx33, snx4, snx9, socs4, sos1, sox4, sox5, sox6, sp3, spast, spata13, spns1, spon1, sptb, srpk1, srsf1, ss18, ssh1, stam2, stambp, stard13, stk19, stk38, stradb, strn, stx16, sub1, suv39h2, syncrip, syne2, syngap1, synm, synpo, syt2, tab3, tacc1, taf15, taf4, tbc1d15, tbc1d24, tbl1x, tbl1xr1, tbrg1, tbxa2r, tcf7l1, tcf7l2, tead1, tek, tfap2b, tfap4, tfb1m, tgfb2, tgfbr2, tgfbr3, thbs1, thbs2, thrb, tjp2, tmed10, tmem30b, tnip1, tnks2, tnpo1, tns1, tns3, tob1, tomm20, topors, tox3, tp53inp1, tp53inp2, tpcn2, tpd52, tpr, tra2b, traf3ip1, trak1, trim13, trim32, trim37, trpc5, trpm6, tsga14, tsn, ttc3, u2af2, u2surp, ube2a, ube2b, ube2d4, ube2e1, ube2h, ube2l3, ube3c, uchl5, uhmk1, unc119b, ush2a, usp13, usp32, usp6, vamp1, vamp3, vamp7, vangl1, vapa, vapb, vav3, vldlr, vps13a, wars, wasf2, wasl, wdr5, wipf1, wipi2, wnk1, wsb1, wwtr1, xpo1, yaf2, ywhag, ywhah, ywhaq, zak, zbtb24, zc3h15, zcchc11, zfc3h1, zfp36, zfp36l1, zhx1, zhx2, zhx3, zic3, znf148, znf24, znf295, znf488, znf652, znhit6, znrf1, zxda				
hsa-miR-182	GO:0003779	Actin binding	ablim1, actr2, add3, afap1, aldoa, anln, aqp2, cald1, capza2, ccdc88a, clmn, cnn3, cotl1, diaph1, diaph2, diaph3, dixdc1, flnb, gmfb, hip1, kcnma1, klhl2, klhl4, klhl5, limZch1, map1b, mical3, msn, mtss1, myh6, myh9, myo18b, myo19, myo1d, myo1e, myo3b, myo5b, myo5c, myrip, ncald, neb, ophn1, palld, phactr2, phactr4, ppp1r9a, ppp1r9b, prf1, rdx, serpinb8, shroom2, shroom3, sntb1, sntb2, spire1, sptb, ssh1, ssh2, syne2, synpo, synpo2, tmod1, tmod2, tns1, tpm2, wasf2, wasl, wipf1, ywhah	69	299	3.3E-05	2.5E-02

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0004674	Protein serine/threonine kinase activity	aak1, aatk, acvr1, acvr2b, adck4, alpk3, atm, bmpr1b, cab39, camkk2, cask, cdc42bpa, cdk1, cdk2, chek2, cnksr2, cpne3, dclk1, dclk3, dhdds, dmpk, dstyk, dyrk1a, dyrk2, eef2k, hipk1, hipk2, irak3, irak4, lmtk2, map3k13, map3k2, map4k2, map4k4, mapk1, mark2, mast4, mylk4, myo3b, nek7, nuak1, pak3, pdpk1, phkg2, pkn2, prkaa1, prkaa2, prkacb, prkca, prkcb, prkd1, prpf4b, riok2, rock1, rps6ka2, rps6ka3, rps6ka6, rps6kl1, sgk3, sik2, sik3, snrk, srpk1, stk17a, stk17b, stk19, stk32a, stk35, stk38, taok1, tgfbr2, tlk1, tlk2, trpm6, ttbk1, uhmk1, wnk1, zak	78	356	7.1E-05	3.5E-02
hsa-miR-182	GO:0003729	Mrna binding	A1CF, CELF1, DHFR, DHFRL1, DPEP2, ELAVL1, FMR1, FYTTD1, GRSF1, IGF2BP1, LIN28A, NUDT21, RBM4, RBM5, RBM8A, TRA2B, TSN, ZFP36, ZFP36L1	19	56	1.9E-04	4.7E-02
hsa-miR-182	GO:0004842	Ubiquitin-protein ligase activity	bmi1, cnot4, dtx3l, ercc8, fbxw11, fbxw2, fbxw7, fem1c, hectd2, hecw2, kctd13, kiaa0317, klhl13, klhl21, klhl9, lmo7, malt1, march5, mib1, mmab, nhlrc1, pdzrn4, pja2, rchy1, rfwd3, rlim, rnf130, rnf139, rnf144b, rnf182, rnf2, rnf213, rnf4, rnf41, rnf8, topors, trim13, trim32, trim37, trim9, ttc3, ube2a, ube2b, ube2d4, ube2e1, ube2h, ube2k, ube2l3, ube2q2, ube2ql1, ube2r2, ube2t, ube2w, ube3c, ubr1, zer1, znrf1	57	247	1.6E-04	4.7E-02
hsa-miR-182	GO:0008270	Zinc ion binding	ablim1, acap2, adam17, adam19, adam22, adam9, adamts18, adamts4, adamts5, adamts9, adat2, adh5, adh6, adra2a, aebp2, agap4, agap5, agap7, agap8, ankib1, anubl1, aqpep, arhgef2, asap1, atf7, atxn7, bcl11a, bcl11b, birc5, bmi1, bnc2, brpf3, c11orf95, ca5b, cbfa2t3, cecr1, chd6, chmp1a, chordc1, cnot4, cpxm2, creb5, csrp3, cyld, ddx58, dhh, dnajc21, dnpep, dpysl2, dtna, dtx3l, dtx4, dusp12, dzip1, eea1, egln1, egr3, ep300, eri2, esr1, esrrg, fbxw7, foxp2, foxp3, gdnf, git2, gli2, grin2a, gzf1, helz, hif1an, ikzf1, insl3, isl1, jazf1, jhdm1d, jub, kcmf1, kdm1b, kdm2b, kdm5a, kdm5b, klf13, klf15, klf3, kpnb1, lancl1, lasp1, ldb3, lhx1, lhx8, limch1, lims1, lin28a, lin28b, lmo3, lmo7, lmx1b, lonrf2, lpp, march3, march5, mbnl2, mdm4, mecom, mib1, mical3, mid2, mll, mmab, mmp12, mmp16, mmp24, morc3, mpg, msl2, mtr, mycbp2, mynn, myrip, myt1l, nanos1, napepld, nfx1, nhlrc1, nlrp6, nr1d2, nr2c2, nr3c1, nr4a3, nr5a2, nrg1, nsd1, oas1, oas2, paep, pappa, pcgf3, pcgf5, pde5a, pdzrn4, peg10, pgr, phf13, phf15, phf17, phf19, phf20, phf20l1, phf21b, phf6, phf8, pja2, plag1, plagl2, pnkd, ppara, ppp1r10, prdm1, prdm10, prdm16, prdm4, prickle2, prickle4, prkca, prkcb, prr3, ptgr2, pygo2, rabif, rarg, rbak, rbm4, rbm5, rchy1, rere, rest, rfwd3, rlim, rnf130, rnf139, rnf144b, rnf169, rnf182, rnf183, rnf2, rnf208, rnf212, rnf213, rnf222, rnf4, rnf41, rnf44, rnf8, scrt1, sec24a, sec24b, sh3rf3, sirt1, sirt5, slc11a2, slc18a1, slc30a8, smad3, snai2, snca, sord, sp3, sp7,	350	2,054	1.7E-04	4.7E-02

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0008270	Zinc ion binding	sp8, suv39h2, tab3, taf15, tcf19, thrb, tk1, tll1, topors, trim13, trim32, trim37, trim66, trim7, trim9, tshz2, ttc3, ubox5, ubr1, usp13, usp3, vat1l, whsc1, yaf2, zadh2, zbtb10, zbtb24, zbtb37, zbtb39, zbtb40, zbtb41, zbtb44, zbtb6, zbtb7c, zbtb8a, zbtb8b, zc3h12c, zc3h15, zc3h6, zcchc11, zcchc14, zcchc3, zdhhc15, zdhhc20, zdhhc21, zdhhc3, zdhhc6, zeb2, zfand1, zfand5, zfp1, zfp14, zfp28, zfp3, zfp30, zfp36, zfp36l1, zhx1, zhx2, zhx3, zic2, zic3, zic5, zkscan2, zmat3, zmat4, zmym3, zmym4, znf10, znf148, znf184, znf189, znf197, znf200, znf208, znf211, znf234, znf24, znf248, znf254, znf264, znf267, znf280b, znf286a, znf286b, znf287, znf295, znf304, znf331, znf346, znf35, znf367, znf398, znf445, znf449, znf45, znf460, znf470, znf480, znf483, znf488, znf493, znf497, znf501, znf506, znf528, znf529, znf532, znf554, znf555, znf566, znf585a, znf587, znf605, znf607, znf614, znf621, znf652, znf664, znf697, znf704, znf705a, znf705d, znf706, znf71, znf721, znf74, znf765, znf772, znf783, znf793, znf805, znf814, znf821, znf831, znf850, znf93, znrf1, zxda, zxdb, zzef1				
Cellular component							
hsa-miR-182	GO:0005737	Cytoplasm	a1cf, aagab, aass, abce1, ablim1, actr2, acvr2b, adam17, adam9, adar, adcy2, adra2a, adra2c, adss, afap1, ager, ak5, akap11, aldh18a1, aldh1a2, alg2, amot, amt, anks1a, anp32b, anxa11, apbb2, apol6, appbp2, appl1, aqp7, arf4, arhgap17, arhgap44, arhgap5, arhgap6, arhgdia, arhgef37, arid4a, arl4c, arrdc3, asap1, ascc1, asz1, atf7, atf7ip2, atg4a, atg7, atm, atp1b3, atp2b4, atp6v0a2, atrn, atxn1, atxn3, atxn7, baalc, bag1, bag4, bcas1, bcl10, bcl11a, bcl2, bcl2a1, bcl2l1, bclaf1, bfsp1, bicd2, birc5, bmi1, bnc2, brd4, brms1l, brwd1, btg1, c10orf90, c12orf52, c14orf126, c1orf116, c1orf198, c21orf33, c5orf30, c6orf89, c8orf37, c9orf72, cacna1c, calb2, calm3, camkk2, camsap1, camsap1l1, camta1, capza2, cask, casp3, cbx5, ccdc50, ccdc6, ccdc88a, ccl3, ccm2, cct8l2, cd1d, cd2ap, cdc27, cdc42bpa, cdc42ep3, cdc42se2, cdk2, cdk6, cdkn2b, cdkn2c, cdv3, celf1, celf2, celf5, celf6, chmp2b, chmp7, cited2, cllu1, clmn, clock, cnksr2, cnksr3, cog3, cotl1, cpeb2, cpne3, cramp1l, crtc1, cry2, cse1l, ctdsp2, cttn, cux1, cxadr, cyfip1, d4s234e, dact1, dazap2, dbt, dcaf12, dcaf7, dclk3, ddah1, ddhd1, ddhd2, ddx3x, dera, dgkg, dhdds, diaph1, diaph2, dnai2, dnajb6, dnajb9, dnajc3, dnmt3a, dnpep, dock1, dpep2, dph3, dpyd, dpysl2, dpysl5, dstyk, dtna, dtnbp1, dtx3l, dtx4, dusp12, dusp16, dusp22, dynlt3, dyrk2, dzip1, eea1, eef2k, efs, egln1, egln3, eif2c1, eif2s1, eif4e3, eif5, eif6, elavl1, elmo1, eml1, eml4, ensa, ep300, epas1, epb41l4b, ephb1, erbb4, erc2, erg, eri1, erlin2, etf1, exoc4, exoc5, exoc8, eya3, fam126a,	710	4,077	4.6E-12	2.9E-09

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005737	Cytoplasm	fam136a, farp1, fbxl20, fbxo5, fbxw2, fem1c, fgd4, fgd5, fgf13, fgf9, fgfr1op2, fhit, fkbp5, flnb, flt1, fmr1, fnta, foxo1, foxo3, foxp2, foxp3, frmd4a, frmd4b, frs2, fst, fxr1, fzd1, fzd5, fzd9, gan, gart, gcc1, gemin5, gemin8, gimap8, gins4, gli2, gltp, gnai3, gnaq, gnb1l, gne, gnpda1, gopc, gphn, gprasp2, grb2, grm5, grsf1, hars, haus6, hdac2, hdac9, hectd2, hecw2, hexim1, hey1, heyl, hif1an, hif3a, hip1, hipk1, hipk2, hmgcs1, hook3, hoxa9, hps3, hrnr, hsd17b11, htr2c, htr4, ibtk, ido2, igf2bp1, igf2bp3, ikbkap, ikzf1, il16, ip6k1, ipo9, irak3, irf4, irs1, isl1, katnal1, kazn, kcnn3, kdm5a, khk, kiaa0317, kiaa0513, kiaa1217, kif5c, kitlg, klhl2, klhl21, klhl4, klhl5, klhl7, kpna1, kpnb1, lancl1, lars, ldha, lin28a, lin28b, lmo7, lpar1, lpin1, lpp, lrif1, lsm14a, lyplal1, lzts1, malt1, map4k2, map4k4, map9, mapre1, mapre3, marveld1, mast4, mbd4, mbnl2, mcl1, mcmbp, mcts1, meaf6, mef2c, metap1, mettl8, mical3, mid2, mier1, mkln1, mlf1ip, mlf2, mllt1, mlx, mmab, mmp12, mobkl1a, mobp, mospd1, mpg, mpp2, mpp3, mrpl36, mrps25, msn, mtdh, mtm1, mtmr6, mtr, mtrr, mtss1, myh6, myh9, myo18b, myo19, myo1e, myo3b, naa30, naga, nanos1, nav1, ncapd2, ncs1, ndrg1, ndufc2, necab1, nedd9, nell1, nf1, nfe2l1, nhlrc1, nlrp6, nme1-nme2, nme2, nmnat2, nmt1, nmt2, npm1, nqo1, nr3c1, nr4a3, nr5a2, nrip2, ntn1, nuak1, nudcd1, nudt3, nudt4, nufip2, nxt2, oas1, oas2, oas3, optn, orc5, padi2, pafah1b1, pafah1b2, paip1, paip2, paip2b, pak3, papola, pard6b, parm1, pbx1, pcdh15, pcdhb4, pcmt1, pcmtd1, pcyt1b, pdcd4, pdpk1, pdss2, pdzd2, peak1, peg10, pfas, pfkfb2, pgr, phactr4, phb, phf17, phip, phyhipl, pi4k2a, pi4k2b, pid1, pigh, pigu, pik3r5, pin4, pja2, pkia, pkn2, plcg1, plekha8, plekhh2, plekhm2, pmp2, podxl, pou2f2, ppfia1, ppm1e, ppp1cc, ppp1r9a, ppp1r9b, ppp3ca, ppp6r1, prc1, prdm1, prf1, prickle2, prkca, prkcb, prkce, prkd1, prkd3, proc, prune, prune2, ptgfr, ptgr2, ptgs1, ptgs2, pthlh, ptp4a1, ptpn12, ptpn14, ptpn21, ptpre, ptprm, pura, qki, rab27b, rab3c, rab3gap2, rad51, ralgps1, ralgps2, rapgef6, raph1, rasa4, rbbp9, rbfox2, rbm4, rbm8a, rbp7, rchy1, rdh10, rdx, reep1, rela, rell1, reps2, rest, rexo1l1, rfwd3, rgs17, rgs2, rgs20, rgs5, rgs6, rimkla, rlim, rnf130, rnf144b, rnf182, rnf2, rnf213, rnf4, rpap2, rpl15, rps24, rps6ka2, rps6ka3, rps9, rragd, rrm2b, sacs, samd4a, samd9, sarm1, satb2, sbds, scai, scn3a, sdcbp, sepsecs, sept6, sept7, sept9, serpinb2, serpinb5, sesn2, setx, sfrp4, sgcb, sgk3, sh2d1a, sh3bgrl, sh3bgrl3, sh3pxd2b, shank2, shoc2, shroom2, shroom3, shroom4, sik2, sik3, sirt1, skap2, slc11a2, slc23a2, slc25a15, slc36a2, slc6a4, slc7a2, slc7a8, sltm, smad3, smad4, smad7, smc2, smc4, snai2, snca, snrnp48, sntb1, sntb2, snx1, snx17, snx33, snx4, snx9, socs4, socs6, sox11, sox4, sox7,				

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005737	Cytoplasm	sp7, spag1, spag17, spag9, spam1, spast, spata13, spata2, spata5, spats2l, spry1, spry3, sptb, srd5a1, srpk1, srsf1, ssh1, ssh2, ssu72, stam2, stambp, stk19, stk35, stk38, stradb, strn, stx16, stxbp5l, swap70, syncrip, syne2, syngap1, synpo, taf15, taf4, taf4b, tbc1d15, tbc1d24, tcf7l1, tdrd6, tek, tjp2, tlr7, tmem127, tmod2, tmprss2, tnfaip8, tnfsf11, tnip1, tnks2, tnpo1, tns1, tor1a, tpd52, tpr, traf3ip1, trak1, trdn, trim13, trim32, trim7, trim9, tsc22d3, tsn, tspyl1, ttbk1, ttll10, txlnb, txnl1, txnrd1, ubash3b, ube2b, ube2k, ube2l3, ube2q2, ube3c, uchl5, unc13a, unc13c, unc5cl, ush2a, usp32, usp48, usp6, vamp7, vash2, vav3, vps37a, wars, wasl, wdr26, wdr45l, whsc1, wipi1, wipi2, wnk1, wnt5a, wwtr1, xpo1, xrra1, yaf2, yes1, ywhah, ywhaq, zak, zc3h15, zcchc11, zeb2, zfand5, zfp36, zhx2, zhx3, zic2, zic3, znf346, znf367, znf480, znf830				
hsa-miR-182	GO:0005634*	Nucleus	adar, adh5, adk, adra2a, aebp2, aff4, akap7, aldh1a2, alg2, alpk3, anks1a, anln, anp32b, apbb2, appbp2, appl1, arid4a, arl4c, artn, asxl2, atf7, atf7ip2, atm, atxn1, atxn1l, atxn7, baalc, bach2, bag1, bag4, bcl10, bcl11a, bcl11b, bcl2, bcl2l13, bclaf1, bhlhe22, bhlhe41, birc5, bmi1, bms1, bnc2, brd4, brms1l, brwd1, btg1, bub3, c12orf52, c14orf169, c1d, c21orf33, c21orf7, c2cd2, c5orf20, c9orf72, calb1, camta1, capn7, casp2, casp3, casp9, cbx5, ccdc59, ccnd2, ccng1, ccnj, ccnjl, ccny, cdc27, cdc42se2, cdc73, cdk1, cdk12, cdk2, cdk6, cdkn2b, cdkn2c, cebpa, celf1, celf2, celf5, celf6, cenpl, cers6, cggbp1, chd6, chmp1b, chmp2b, chmp7, cited2, clcc1, clock, cnot4, cnot6, cog3, cog5, cox4i1, cpsf7, cramp1l, creb1, creb3l1, creb3l2, creb5, crtc1, cry2, cse1l, csrnp2, csrnp3, csrp3, cstf2t, ctbp2, ctdsp2, ctdspl, cul5, cux1, cxadr, cycs, cyfip1, d4s234e, dact1, dazap2, dcaf7, dclk3, dclre1b, dcp2, dcun1d4, ddx11, ddx3x, ddx56, depdc1, dgcr14, dhcr24, diexf, dip2b, dlx1, dmrtb1, dnajb6, dnmt3a, dpep2, dph3, dqx1, dscr3, dtnbp1, dtx3l, dusp12, dusp16, dusp22, dusp3, dusp4, dynlt3, dyrk1a, dyrk2, dzip1, ebf1, egln1, egln3, egr3, eid2b, eif2s1, eif6, elavl1, ell2, eomes, ep300, epas1, erbb4, ercc4, ercc8, erg, eri1, esr1, esrrg, etf1, evi5, exoc4, exoc8, eya3, ezh2, fam107a, fam123b, fam188a, fam192a, fbxo5, fbxw11, fev, fgf13, fhit, fkbp5, flnb, flt1, fosb, fosl2, foxd4, foxd4l1, foxd4l3, foxf2, foxj3, foxk1, foxk2, foxn2, foxn3, foxo1, foxo3, foxp2, foxp3, fst, fxr1, gabpb1, gart, gdnf, gemin5, gemin8, gimap8, gins4, gli2, gnl3l, gnpda1, gnptab, gpsm1, grb2, grm1, gzf1, h2bfm, haus6, hck, hdac2, hdac9, hectd2, hecw2, helz, hes2, hexim1, hey1, heyl, hif1an, hif3a, hip1, hipk1, hipk2, hist1h2bd, hist1h2bk, hist2h2bf, hmga2, hoxa1, hoxa9, hsbp1, hspa5, htr2c, ibtk, igf2bp1, igf2bp3,	799	4,875	4.3E-08	1.4E-05

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005634*	Nucleus	ikzf1, il16, ino80d, insl3, insr, ints6, ip6k1, ipo9, irak3, irf4, irs1, isl1, itm2b, jhdm1d, jrkl, jub, kazn, kctd1, kctd13, kdm1b, kdm2b, kdm5a, kdm5b, khdrbs3, khsrp, kiaa0317, kiaa0368, kiaa2022, klf13, klf3, klhl4, klhl7, kpna1, l3mbtl3, lancl1, lass2, lcor, lcorl, lhx1, lhx8, lin28a, lin28b, lmo7, lmx1b, lox, lpin1, lpp, lrif1, lrig1, lrpprc, lsm5, luzp1, luzp4, lzts1, maf, malt1, mamld1, map3k2, map9, mapk1, mapre3, mark2, marveld1, mbd4, mbnl2, mcmbp, mdm1, mdm4, mdn1, meaf6, mecom, mecp2, med14, mef2c, mef2d, meis2, mettl8, mfsd8, mgst1, mier1, mipol1, mitf, mkl2, mkx, mlf1ip, mlf2, mll, mllt1, mlx, mmab, mobkl1a, mobp, morc3, morf4l1, morf4l2, mospd1, mrpl19, mrpl36, msh4, msl3, msn, msra, mtap, mtdh, mtrr, mxd3, mycbp2, myct1, myef2, myh6, myh9, mynn, myo18b, myt1l, nap1l1, nav2, ncapd2, ncoa1, ncoa2, ncoa4, ncor1, ndrg1, necab1, nedd9, nek7, neurod4, nf1, nfe2l1, nfe2l3, nfx1, nhej1, nhlrc1, nhs, nipbl, nme2, nmnat2, nox4, npm1, nr1d2, nr2c2, nr3c1, nr4a3, nr5a2, nrg1, nrip2, nsd1, nuak1, nucks1, nudcd1, nudt12, nudt21, nufip2, numb, nxt2, oas1, oas2, obfc2a, onecut2, orc5, paep, pafah1b1, pak3, palld, papola, pard6b, parm1, parp15, pasd1, pax8, pbx1, pbx3, pcgf3, pcgf5, pdcd4, pdhx, pds5b, pdzd2, peg10, pgr, phb, phf13, phf17, phf19, phf6, phf8, phip, phtf2, picalm, pid1, pigh, pik3r1, pik3r5, pin4, pkia, pkn2, pkp1, plag1, plagl2, plcb4, pmaip1, pmepa1, pnkd, pnrc2, poldip2, poli, pomp, pou2af1, pou2f1, pou2f2, ppara, ppie, ppil4, ppm1a, ppm1e, ppp1cc, ppp1r10, ppp1r16b, ppp3ca, ppp6r1, prc1, prdm1, prdm10, prdm16, prf1, prickle4, prkaa1, prkca, prkcb, prkce, prkd1, prkd3, proc, prpf4b, prune, psmb2, ptgis, ptgs1, ptgs2, pthlh, ptp4a1, ptpre, pura, pygo2, qki, rab3ip, rad17, rad51, rad51b, rapgef5, rapgef6, rarg, rbak, rbbp4, rbbp9, rbfox2, rbm12, rbm15, rbm17, rbm4, rbm5, rbm8a, rbms2, rbmxl1, rchy1, rdh10, rdh14, rela, rere, rest, rexo1l1, rfwd3, rgs17, rgs20, rlim, rnf130, rnf2, rnf4, rnf8, rngtt, rpap2, rps24, rps6ka2, rps6ka3, rragd, rrm2b, rrp1b, runx1, s100pbp, sacs, satb2, sbds, scai, scrt1, sdad1, sdcbp, sec14l3, sepsecs, sept6, sept7, sesn2, setd7, setx, sf3b5, sfmbt2, sfrp4, sgk3, sgms1, sh3bgrl, sh3bgrl2, sh3bgrl3, sh3bp4, sh3d19, shoc2, shox, shroom4, sik2, sim2, sirt1, skiv2l2, slc11a2, slc25a15, slc35a2, slc6a4, sltm, smad3, smad4, smad7, smarca5, smc2, smc4, snai2, snap23, snca, snrk, snrnp48, snrpb2, socs4, sox11, sox4, sox5, sox6, sox7, sp3, sp7, sp8, spag17, spast, spata13, spata2, spns1, spopl, srek1, srpk1, srsf6, ss18, ss18l1, ssu72, stam2, stambp, stk17a, stk17b, stk19, stk38, stradb, stx5, sub1, supt7l, suv39h2, swap70, syap1, syf2, syncrip, syne2, synpo2, tacc1, taf15, taf4, taf4b, tbl1x, tbl1xr1, tbrg1, tc2n, tceal7, tcf19, tcf24, tcf7l1, tcf7l2, tcp10l, tead1, tfap2b, tfap4, tfec, tgif2, tgif2-c20orf24, thrb, tlk1, tlk2, tnip1, tnks2, tnpo1, topors, tox, tox3, tp53inp1, tp53inp2, tra2b, trak1, trim32, trim66,	799	4,875	4.3E-08	1.4E-05

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005634*	Nucleus	trim7, trmt61a, tsc22d3, tshz2, tsn, tsnax, tspan1, tspyl1, ttbk1, ttc3, ttll10, twistnb, txnrd1, u2surp, ubash3a, ubash3b, ube2b, ube2e1, ube2l3, ube2t, ube2w, ube3c, ubox5, uchl5, uhmk1, usp32, usp48, vezt, vgll3, vldlr, vps37a, wdr26, wdr5, whsc1, wipi2, wrb, wtap, wwtr1, xpo1, xrra1, yaf2, ypel1, ywhaq, zak, zbtb10, zbtb24, zbtb37, zbtb39, zbtb40, zbtb41, zbtb44, zbtb6, zbtb8a, zbtb8b, zc3h15, zcchc11, zeb2, zfp1, zfp14, zfp28, zfp3, zfp30, zfp36, zfp36l1, zhx1, zhx2, zhx3, zic2, zic3, zic5, zkscan2, zmat4, zmym3, znf10, znf148, znf184, znf189, znf197, znf200, znf208, znf211, znf234, znf24, znf248, znf254, znf264, znf267, znf280b, znf286a, znf286b, znf287, znf295, znf304, znf331, znf346, znf35, znf367, znf398, znf445, znf449, znf460, znf470, znf480, znf483, znf488, znf493, znf497, znf501, znf528, znf529, znf532, znf554, znf555, znf566, znf585a, znf587, znf605, znf607, znf614, znf621, znf652, znf664, znf697, znf705a, znf705d, znf71, znf721, znf74, znf765, znf772, znf783, znf793, znf805, znf821, znf830, znf850, znf93, zxda, zxdb				
hsa-miR-182	GO:0045202	Synapse	ank3, apbb2, cacnb4, cadm1, cadm2, cbln1, cbln4, ctbp2, cyfip1, dtna, insr, lgi1, lrp6, mgll, mmp12, myrip, nanos1, nlgn4x, nrcam, pcdh15, ppp1r9a, ppp1r9b, prf1, prima1, proc, rimbp2, samd4a, sdc2, shisa9, snap23, snca, sntb1, sntb2, vamp3	34	107	2.3E-06	5.0E-04
hsa-miR-182	GO:0000139	Golgi membrane	ABCB5, AP1S3, B3GALT1, B3GALT2, B3GNT2, BET1, C1GALT1, C3ORF58, CAV3, CBFA2T3, CHST1, CHST10, CHST11, CHST3, CLCN5, COG5, COG6, CUX1, D4S234E, DHCR24, EXT2, FAM198B, FAM20B, FZD5, GAD2, GALNT1, GCC1, GCNT1, GIMAP1, GLCE, GLG1, GNPNAT1, GNPTAB, GOLGA7, GOPC, GOSR1, GPSM1, IL17RD, LMAN1, LMAN2L, MAP4K2, MGAT4A, NCAM1, NDST1, NDST3, NMNAT2, NRAS, PARM1, PDGFD, PJA2, PRKCE, PRKCSH, PROS1, RAB2A, RAB6A, RASGRP1, RIC3, RND3, ROCK1, SEC24A, SEC24B, SGMS1, SLC30A7, SLC33A1, SLC35A1, SLC35A2, SLC35A5, SLC35B4, SLC35C1, ST6GAL1, ST6GALNAC2, ST8SIA2, ST8SIA3, STEAP4, STX16, STX5, SVIP, TLR7, TMEM167B, TNKS2, TPST2, VTI1A, WASL, WIPI1, XYLT1, ZDHHC21, ZDHHC3, ZMPSTE24	88	403	1.4E-05	1.8E-03
hsa-miR-182	GO:0005829	Cytosol	aasdhppt, abcd2, abl2, acp5, adh6, adk, adss, ak5, akap7, aldh1a2, aldoa, amot, amotl2, ap1s3, appl1, arcn1, arhgap11a, arhgap12, arhgap17, arhgap20, arhgap26, arhgap29, arhgap36, arhgap44, arhgap5, arhgap6, arhgdia, arhgef2, arhgef3, arhgef7, as3mt, atat1, atp7a, azin1, bag1, bag4, bcat1, bcl10, bcl2, bcl2l1, bcl2l11, birc5, brpf3, bub3, c21orf7, c2cd2, cab39, cacnb4, calb1, cald1, calm3, capza2, casp10, casp2, casp3, casp9, ccdc88a, ccl3, ccnd2, cdc27, cdk1, cdk2, cdk6, cdkn2b, cdkn2c, cecr1, cenpl, cenpp, cenpq, cep135, chmp1b, chmp2b, chmp7, clock, cnot4, cnot6,	379	2,217	1.2E-05	1.8E-03

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005829	Cytosol	cnot6l, cog5, cpne3, crkl, cul5, cycs, cyld, cyp19a1, dcc, dcp2, dcx, ddx58, dennd1b, dhcr24, dhfr, diaph2, diaph3, dicer1, dixdc1, dmpk, dock1, dock4, dock9, dohh, dpyd, dpysl2, dpysl5, dsg3, dtnbp1, dusp3, echdc1, eea1, eef2k, egln1, eif2c1, eif2c4, eif2s1, eif3j, eif4b, eif4e3, eif5, eif5a2, eif6, elavl1, elmo1, erbb4, etf1, exoc5, fam123b, fam13a, fbxo5, fbxw11, fgd4, fhit, flnb, fnta, foxo1, foxo3, fxn, gad2, gart, gbp1, gemin5, gfpt1, gne, gnl1, gnpda1, gnpnat1, gpsm1, grb2, gtpbp1, haao, hars, hck, hmgcs1, hrnr, hsf2bp, hsp90aa1, ido2, igf2bp1, igf2bp3, insr, irak4, irf4, irs1, itgb1bp1, jub, kdm5a, khk, khsrp, kidins220, kif3b, klhl14, klk2, kpna1, kpna3, kpnb1, lars, lcp2, ldha, lims1, lpin1, lsm5, malt1, map1b, map3k2, map3k3, map4k2, mapk1, mapk10, mapk9, mapre1, mib1, mlf1ip, mmab, mobkl1a, mtap, mtmr7, mtr, mtrr, myh6, myh9, nampt, nanos1, ncald, ncoa2, ncs1, ndrg1, neb, nell1, nhlrc1, nlrp6, nme2, nmt1, nmt2, nqo1, nr3c1, nr4a3, nt5dc3, nup43, oas1, oas2, oas3, ocrl, ophn1, paep, pafah1b1, paip1, pak3, papss2, pard6b, pcdhb16, pdcd4, pde10a, pde11a, pde4d, pde5a, pde6g, pde7a, pde7b, pdhx, pdpk1, pfas, pfkfb2, pfkfb3, pgm2l1, pgm3, pgpep1, phkb, phkg2, pigu, pik3r1, pik3r5, pkn2, plcb4, plcg1, pmaip1, pomp, ppm1a, ppm1b, ppm1f, ppp1cc, ppp3ca, ppp3r1, prdm4, prepl, prkaa1, prkaa2, prkacb, prkar1a, prkca, prkcb, prkce, prkd1, proc, psma2, psmb2, psme4, pstpip2, ptpn12, rab3b, rab3c, rab3ip, rab6a, rac1, rap1gap2, rap2a, rapgef1, rapgef4, rasa4, rasgrp1, rbm8a, rcc2, rdh14, rela, rest, rgs2, rhobtb1, rhof, rhoj, rhoq, ric8b, rictor, rnf41, rock1, rpia, rpl15, rps23, rps24, rps6ka2, rps6ka3, rps6ka6, rps9, rrp1b, rsu1, sar1b, sdcbp, sec24a, sec24b, serpinb8, sfrp1, sh3bgrl, sh3d19, shc3, sike1, ska2, skap2, slc25a15, slc25a21, slc6a4, smad3, smad4, smad7, snca, snx1, snx17, snx27, sos1, spag9, spry1, sptb, stam2, stard13, steap2, stradb, syde1, syde2, syngap1, tab3, tagap, taok1, them4, tiam1, tjp2, tk1, tmod1, tnpo1, tnrc6a, tnrc6b, tp53inp1, tp53inp2, tpm2, tsga14, tspan1, txnrd1, ubash3a, ube2a, ube2e1, ubr1, uchl5, uck2, vav3, vps26b, wars, wasl, wipi1, wipi2, wwtr1, xpo1, yes1, ywhag, zfp36, zfp36l1				
hsa-miR-182	GO:0014069	Postsynaptic density	cacna1c, cald1, camk2n1, disc1, dlgap2, dtnbp1, eps8, erbb4, exoc4, gopc, gria1, gria3, grin2a, grm1, grm5, itpr1, lphn1, lzts1, map1b, mib1, mpp2, mpp3, ncoa2, ncs1, nlgn4x, nr3c1, pja2, plcb4, shank2, sltm, strn, syndig1, synpo	33	113	2.4E-05	1.9E-03
hsa-miR-182	GO:0015629	Actin cytoskeleton	abl2, ablim1, actr2, adam17, afap1, aldoa, anln, arhgap6, bfsp1, c10orf90, cald1, capza2, cask, cd2ap, cdc42ep3, clic5, coro1c, cttnbp2nl, ddx58, fgd4, flnb, ints6, klhl2, marcks, mtss1, myh9, myo1e, myrip, neb, nmt1, ophn1, peak1, podxl, prf1, sept6, sept7, shroom4, snca, sptb, stk17b, synpo, synpo2, wasf2, wasl, wipf1, znf74	46	178	2.4E-05	1.9E-03

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005789	Endoplasmic reticulum membrane	aadac, acer3, acsl5, agpat4, aldh3a2, alg13, alg2, alg9, ano5, antxr2, aph1a, asph, atp10d, atp11c, atp2a2, atp6v0e1, bcap29, bcl2, bet1, c8orf83, cers6, chek2, cisd2, cln8, creb3l1, creb3l2, cyp19a1, cyp1a2, cyp1b1, cyp3a43, cyp51a1, cyp8b1, dhcr24, dhcr7, dio1, dmpk, dnajb9, dtnbp1, edem1, edem3, eif5a2, eif5al1, elovl6, erlin2, ero1lb, ext2, fam69b, fmo4, ggcx, gimap1, gjd3, gpsm1, gria1, hspa5, insig1, itpr1, jkamp, kdelr1, klhl14, ktn1, lass2, lman1, lman2l, lpin1, lrat, lrrc8c, march5, mgst1, mgst2, mrvi1, mtdh, nfe2l1, nox4, nus1, pgap1, piga, pigh, pigu, pja2, ppapdc3, prkcsh, pros1, ptdss1, ptgis, ptgs1, ptgs2, rab2a, rasgrp1, rdh10, ric3, rnf139, rsad2, sar1b, sc5dl, sdcbp, sdr16c5, sec14l3, sec24a, sec24b, serinc1, serinc5, serp1, sez6l, shisa2, slc33a1, slc35d1, slc37a4, slc39a1, sort1, srd5a1, ssr1, tbxas1, tlr7, tmed10, tmed7, tmem189, tmprss4, tor1aip2, trim13, ugt2b17, vamp7, vapa, vapb, wrb, xylt1, zmpste24	126	629	2.0E-05	1.9E-03
hsa-miR-182	GO:0030054	Cell junction	cadm2, camk2n1, cbln1, cbln4, chrm5, chrna4, colq, ctbp2, cxadr, cyfip1, disc1, dlgap2, dtna, dtnbp1, erc2, gabra1, gabra4, gabrb3, gabrg1, gad2, glra3, gopc, gphn, gria1, gria3, grid1, grik3, grin2a, lgi1, lrrc4, lzts1, map1b, mpp2, ncoa2, ncs1, nlgn4x, nmt1, nrxn1, ophn1, pcdh8, pecam1, pja2, pmepa1, ppp1r9a, prima1, ptpn12, rimbp2, samd4a, sh3pxd2b, shank2, shc4, shisa9, slc6a17, snap23, snca, sntb1, sntb2, sspn, stxbp5, sv2b, syn2, syndig1, syt2, tjp2, tnip1, trim9, ttbk1, unc13a, unc13c, vamp1, vamp3, znrf1	72	323	4.0E-05	2.9E-03
hsa-miR-182	GO:0030027	Lamellipodium	amot, apbb2, ccdc88a, cttn, cyfip1, fgd4, fgd5, igf2bp1, itgb1bp1, jub, nedd9, nme2, palld, pdpn, phactr4, pkn2, plcg1, podxl, ppp1r9b, prkcsh, proc, ptprm, rab3ip, raph1, rdx, spata13, spry1, ssh1, swap70, wasf2, wasl	31	107	4.9E-05	3.2E-03
hsa-miR-182	GO:0017053	Transcriptional repressor complex	arid4a, c1d, cbx5, ctbp2, depdc1, hdac2, jazf1, mier1, ncor1, prdm16, rbm15, rest, rlim, sp3, tbl1x, tbl1xr1, tfap4	17	45	7.0E-05	3.9E-03
hsa-miR-182	GO:0005887	Integral to plasma membrane	abcb5, acvr1, acvr2b, adam17, adra2a, adra2c, ager, agtr1, ankh, aph1a, aqp7, atp2a2, atp2b4, atrn, bdkrb2, bmpr1b, btla, btn1a1, c1d, cacnb2, calcr, calcrl, ccr1, ccr8, ccrl1, cd164, cd1d, cd226, cd40lg, cd47, cd55, cd96, ceacam6, ceacam8, celsr1, chrm5, clcn5, cldn1, clec2d, cnot6, csf2rb, cxadr, cxcr5, cybb, dclk1, dscam, ednra, ednrb, efnb2, entpd1, epha3, ephb1, f2r, f2rl1, flrt2, flt1, frs2, gabra1, gabra4, gabrb3, gjd3, glra3, gnrhr, gpc6, gpr183, gpr22, gpr6, gpr68, grik3, grin2a, grm1, grm4, grm5, grm6, hbegf, htr1f, htr4, igdcc3, igf1r, il1rap, il4r, insr, itgav, kcnj10, kcnj2, kcnmb3, kiaa1324, kif20b, kl, klrf1, ktn1, lancl1, lifr, lpar1, lpar4, lppr4, lrp12, mc2r, mmd, mmp12, mmp16, mmp24, mpp2, mpp3, ms4a1, nlgn4x, nprl3, nrcam, nrxn1, numb, opn1lw, opn1mw2, pcdh1, pcdh8, pcdhb11, pcdhb3, pcdhb4, pdpn, phb,	186	1,017	7.6E-05	3.9E-03

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005887	Integral to plasma membrane	pi4k2a, podxl, ppp1r9b, prkd1, prrg1, ptger3, ptgfr, ptprg, ptprm, ptprn2, ret, rhd, scara5, scarb2, scn2a, sdc2, sgcb, sgms2, sirpb1, slc11a2, slc12a2, slc16a2, slc18a2, slc18a3, slc1a1, slc1a4, slc23a2, slc29a2, slc2a8, slc31a1, slc33a1, slc35a1, slc39a6, slc4a4, slc5a3, slc5a6, slc6a1, slc6a15, slc6a17, slc6a20, slc6a4, slc6a6, slc7a2, slc7a6, slc7a8, slco2a1, sltm, sspn, syndig1, sypl1, syt13, tbxa2r, tek, tfrc, tgfbr3, tmprss11f, tmprss2, tnfrsf9, tnfsf11, tnfsf15, tnfsf4, trat1, trpa1, trpc5, tspan9, vamp1, xpr1				
hsa-miR-182	GO:0005730	Nucleolus	adar, aff4, akap11, als2cr8, anks1a, artn, atf7ip2, atxn1, atxn7, baalc, bag4, bclaf1, birc5, bmi1, bms1, brd4, brwd1, bub3, c14orf169, c1d, cask, casp3, cbfa2t3, cbx5, ccnd2, cd2ap, cdc27, cdc42se2, cdk12, cdv3, cggbp1, clock, cog3, cog5, creb1, crtc1, ctdsp2, cux1, dcaf17, dcaf7, ddx11, ddx56, dhx33, diaph2, diexf, dnajb6, dnajb9, dnmt3a, dph3, dyrk2, eif6, ell2, ep300, erbb4, eri1, ezh2, fam188a, fbxo5, fbxw7, fkbp5, flt1, fmr1, fosl2, foxd4, foxd4l1, foxd4l3, foxk1, foxk2, foxp2, fxr1, gdnf, gemin8, gimap8, gnl3l, gnpda1, gpsm1, gzf1, h2bfm, haus6, hexim1, hrnr, ibtk, igf2bp1, igf2bp3, ikbkap, ints6, ip6k1, irf4, itpr1, jhdm1d, kazn, kdm2b, kdm5a, kdm5b, khdrbs3, khsrp, kif20b, klf15, klhl4, klhl7, lin28a, lin28b, lzts1, malt1, map9, mbd4, mcmbp, mdn1, meaf6, mef2c, mef2d, mfsd8, mier1, mllt1, mmab, mobp, morc3, morf4l2, mro, ms4a1, msn, mtdh, mtrr, myef2, myh6, myo18b, myo1e, n4bp1, ncapd2, necab1, npm1, nr2c2, nr3c1, oxr1, paep, pafah1b1, papola, pax8, pbx1, pdcd4, pds5b, pgr, phf6, phf8, pid1, pigh, pin4, pkp1, podxl, pomp, ppm1e, ppp1cb, ppp1cc, ppp3ca, ppp6r1, prc1, prkd3, prpf4b, psmb2, pthlh, qki, rad17, rapgef6, rbfox2, rbm15, rbm17, rbm4, rbm5, rbm8a, rcc2, rchy1, rdx, rere, rest, rgs2, rnf2, rps24, rps9, rrm2b, rrp1b, runx1, sap30l, satb2, sbds, sdad1, sept6, sept7, setx, sh3d19, shroom4, sim2, sirt1, skiv2l2, slc25a15, slc29a2, slc6a4, sltm, smad4, smad7, smarca5, smc4, snap23, snrnp48, snrpb2, sox4, sp8, spag17, spata13, spats2l, srek1, srsf6, stam2, stambp, stk35, stk38, stx16, stx5, sub1, taf15, taf4, taf4b, tbl1xr1, thap2, trim66, trim7, tspyl1, ttc3, twistnb, txnrd1, u2surp, usp48, utp23, vps37a, wasl, wdr26, wdr36, whsc1, wipi2, wrb, wtap, wwtr1, xpo1, yaf2, ywhaq, zbtb10, zc3h15, zcchc11, zeb2, zhx2, zhx3, zmat3, znf148, znf346, znf367, znf470, znf480, znf506, znf74, znf830	259	1,481	7.8E-05	3.9E-03

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005622	Intracellular	a1cf, acpp, adar, adcy2, adcy5, aebp2, akap7, apbb2, arf4, arhgap11a, arhgap12, arhgap26, arhgap29, arhgap44, arhgap5, arhgap6, arhgef2, arhgef3, arhgef37, arhgef7, arl5b, asb1, asb7, bcl11a, bcl11b, bco2, birc5, bnc2, c11orf95, c12orf5, camkk2, capn5, capn7, casp2, casp9, ccl3, ccr7, cdc42bpa, chmp2b, cnksr2, cotl1, creb5, cse1l, cstf2t, dclk1, dcx, depdc1, depdc4, deptor, dgkg, dhdds, dicer1, dixdc1, eea1, egr3, eri2, evi5, fam126b, fam13a, farp1, fgd4, fgd5, foxp3, gart, gdnf, gmfb, gnb1l, grm4, grm6, gspt1, gucy2c, hectd2, il16, il1rap, insl3, jazf1, jmjd1c, kcmf1, kdelr1, kdm5a, kiaa0317, kiaa1244, kif20b, klf13, lep, map1lc3b, mecom, mid2, mpg, mtr, myrip, napg, ncald, ncoa2, nf1, nfasc, nr4a3, nudcd2, nudt4, nup50, nus1, ophn1, paep, pag1, parp8, phf20, pkn2, plag1, plcb4, plxna1, poli, ppfibp2, prdm1, prdm10, prdm16, prkaa1, prkcsh, prkd1, prkd3, rab3gap2, rab40b, rab5b, ralgapb, ralgps1, ralgps2, rap1gap2, rapgef1, rapgef4, rapgef5, rapgef6, rasa4, rasgrp1, rbak, rbm5, rest, rgpd1, rhof, rhoj, rnd3, rnf2, rpia, rras2, sar1b, sarm1, sec14l3, sec14l5, sept9, sfrp1, shank2, shc3, shc4, slc7a8, smad3, smc6, snx1, snx17, snx9, socs4, sos1, sp3, sp8, spata13, stk19, stx16, syngap1, taf15, tbc1d12, tbc1d15, tbc1d22a, tbck, tiam1, ticam2, tmem68, tnip1, tnpo1, tns1, tns3, trim37, tspan1, ttpal, tufm, ube3c, ubl3, uchl5, unc13a, unc13c, usp6nl, vav3, vps13a, wasf2, wsb1, xpo1, yaf2, zbtb37, zbtb44, zbtb7c, zeb2, zfc3h1, zfp1, zfp14, zfp30, zhx2, zhx3, zic2, zic5, zmat4, znf10, znf148, znf184, znf200, znf208, znf211, znf248, znf254, znf267, znf286a, znf304, znf331, znf346, znf35, znf398, znf45, znf460, znf480, znf493, znf497, znf501, znf506, znf528, znf555, znf566, znf585a, znf587, znf607, znf614, znf621, znf652, znf664, znf704, znf705a, znf706, znf721, znf772, znf783, znf793, znf805, znf814, znf821, znf831	249	1,436	1.9E-04	8.6E-03
hsa-miR-182	GO:0005624	Membrane fraction	adam17, adcy2, adcy5, adcy6, akap7, alg2, ank3, aqp2, atp2a2, atp6v0e1, c1d, cald1, casp2, cd59, celsr1, chrna4, chst10, clec2d, cul5, cyp19a1, dhcr24, dscam, eea1, erc2, flot1, foxo3, frs2, gdnf, ggcx, gli2, gnai3, gnaq, gopc, gria1, gria3, grm5, hip1, kdelr1, kif20b, kl, ktn1, l1cam, lrp1b, lrp2, lrp6, map3k13, mctp2, mmd, mmp12, mpp2, mtmr7, mycbp2, nprl3, nras, plxna1, ppm1a, prkca, prkce, pstpip2, ptprn2, rab2a, rab5b, rapgef4, rasgrp1, reck, scarb2, scn1a, scn2a, scn3a, slc12a2, slc16a2, slc18a1, slc18a2, slc18a3, slc1a1, slc1a2, slc23a2, slc24a4, slc33a1, slc39a1, slc5a6, slc6a1, slc7a2, slco2a1, sltm, sntb2, snx1, sord, synm, tgfbr3, tpst2, tspan9, ugt2b17, wnt5a, zmpste24	95	477	2.5E-04	1.1E-02

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0043025	Neuronal cell body	ager, arhgef2, arhgef7, atp2b4, atp7a, bmpr1b, c1d, calb1, calcr, cald1, camk2n1, ccng1, chrna4, cnksr2, cntnap2, cyp19a1, dixdc1, dpysl2, dpysl5, efhc1, exoc4, fzd9, gria1, il6st, kcnip1, lrp6, mbl2, mpp2, mpp3, myo5b, ncam1, ncoa2, nell1, nrsn1, pafah1b1, plxna1, proc, pura, rab2a, rtn4, scn1a, sdc2, shank2, shroom2, slc18a2, sltm, sort1, srd5a1, strn, tgfb2, tmprss4, vti1a	52	229	2.8E-04	1.1E-02
hsa-miR-182	GO:0005667	Transcription factor complex	ascc1, cdk2, clock, creb1, creg1, csrp3, cyfip1, e2f3, ep300, epas1, eya3, foxd4, foxd4l1, foxd4l3, foxf2, foxj3, foxk1, foxk2, foxn2, foxn3, foxo1, foxo3, foxp2, foxp3, foxq1, gart, gdnf, hdac2, hdac9, hoxa10, hoxa9, jub, lpin1, med23, ncor1, nr4a3, pbx1, pbx3, pou2f1, rarg, rela, satb2, smad3, smad4, smad7, sub1, tbl1x, tcf7l1, tcf7l2, tfdp2, wwtr1	51	224	3.0E-04	1.1E-02
hsa-miR-182	GO:0001726	Ruffle	amot, arhgef7, cd2ap, cdk6, cttn, cyfip1, fgd4, fgd5, frmd4b, itgb1bp1, mtm1, mtss1, myh9, nme2, palld, pdpn, plcg1, podxl, rdx, snx9, syngap1, wasf2	22	74	3.9E-04	1.4E-02
hsa-miR-182	GO:0005783	Endoplasmic reticulum	a1cf, acsl5, ahcyl1, alg2, aph1a, asph, atg14, atp10d, atp11b, atp11c, atp2b4, atp7a, atp8a1, bace2, bcap29, bcl2, calcrl, calu, ccdc88a, cds2, chek2, cisd2, clcc1, clec2d, cln8, creb3l2, creg2, ctsc, cyp19a1, derl1, dhcr24, dhcr7, dnajb9, elovl6, entpd5, epm2aip1, erlin2, ero1lb, ext2, fbxw7, fndc3b, gimap8, hspa13, hspa5, insig1, itpr1, kiaa0368, klhl14, ktn1, lass2, lrp2, lrp6, lrpap1, march5, mcfd2, mesdc2, mgst1, mgst2, mtdh, ncoa2, nhlrc1, oas1, oas2, pcmt1, pcsk6, pcyt1b, pdzd2, pgap1, phtf2, pigh, pla2g12a, plod2, pomp, prkca, prkce, ptgis, ptp4a1, rdh14, reep1, ric3, rnf139, rpl15, rras2, rsad2, rtn4, sar1b, sec14l3, serp1, sgms1, slc37a4, slc39a6, slc6a4, spast, srpk1, ssr1, stx5, syncrip, tdrd6, tgfbr3, tlr7, tmed10, tmed7, tmem117, tmem50b, tmprss4, tor1a, tor1aip2, tpd52, tpst2, vapa, vapb, yipf4, yipf6	113	593	4.2E-04	1.4E-02
hsa-miR-182	GO:0030496	Midbody	alpk3, anxa11, birc5, cdk1, cyld, ddx11, gnai3, hspa5, klhl9, mapre3, pdzd2, pkn2, ppp1cc, ptch1, rab11fip4, ralb, rnf8, sccpdh, sept6, sept7, spast, ssh1, topors	23	80	5.0E-04	1.6E-02

Table S4 (*continued*)

Table S4 (*continued*)

miRNA	GO id	GO term	Target gene in GO term	#Target gene in GO term	#GO term gene	P-value	FDR P-value
hsa-miR-182	GO:0005654	Nucleoplasm	a1cf, adar, als2cr8, ankrd28, anxa11, artn, atf7, atm, atxn1, atxn3, c14orf169, calm3, casp3, cbfa2t3, cbx5, cdc27, cdk1, cdk2, cenpp, cenpq, chek2, cpsf7, creb1, ctdsp2, ddx11, dhfr, dhx33, dusp12, dusp3, dusp4, dyrk1a, e2f3, elavl1, ell, ep300, erbb4, ercc4, ercc8, esr1, esrrg, fbxo5, fbxw7, fmr1, foxo1, foxo3, fyttd1, gart, gdnf, gemin5, gins4, git2, gzf1, hdac2, hexim1, jmjd1c, khsrp, kif20b, kpna1, kpna3, kpnb1, lrig1, lrpprc, lzts1, map4k2, mapk1, mapk10, mapk9, mbd4, mcl1, med14, med23, mef2c, mlf1ip, mpg, myo1e, ncoa1, ncoa2, ncor1, nkx2-2, npm1, nr1d2, nr2c2, nr3c1, nr4a3, nr5a2, nudt21, nup50, orc5, pak3, papola, pax8, pdpk1, pdzd2, pgr, phb, phf13, pmepa1, poldip2, poli, polr3g, pot1, pou2f1, ppara, ppp1r9b, prdm4, prkaa2, prkacb, prkca, psma2, psmb2, rad17, rad51, rad51b, rarg, rbbp4, rbm4, rbm5, rbm8a, rela, rev1, rnf169, rngtt, rps6ka2, rps6ka3, rps6ka6, rrm2b, sbds, setx, sf3b3, sf3b5, sirt1, slc25a15, smad3, smad4, smarca5, snrpb2, srsf1, srsf6, syncrip, syne2, taf4, taf4b, tbl1x, tbl1xr1, tcf7l1, tcf7l2, tead1, tfdp2, thrb, tjp2, tpr, u2af2, ube2e1, ube2t, wtap, wwtr1, xpo1, zfp36l1, znf367, znf45	160	896	7.4E-04	2.3E-02
hsa-miR-182	GO:0005901	Caveola	atp1b3, cav3, efna5, erbb4, f2r, flot1, hck, igf1r, insr, irs1, kcnma1, lrp6, mapk1, ptch1, ptgis, ptgs2, tgfbr2	17	56	1.3E-03	3.9E-02
hsa-miR-182	GO:0005792	Microsome	aadac, aldh3a2, appl1, aqp7, atp2a2, atp2b4, bcl2, clcc1, cyb5b, cyp1a2, cyp1b1, cyp3a43, cyp51a1, cyp8b1, dhcr7, dio1, dtna, fmo4, glg1, grm1, h6pd, hspa13, igf1r, insr, irs1, itpr1, lman1, lrat, mgst1, mgst2, oas1, oas2, oas3, plcb4, pomp, ppp1r3d, ppp3ca, prkcsh, ptgs1, ptgs2, rdh10, rpia, sc5dl, slc7a11, snap23, snx9, sort1, srd5a1, srpk1, stx16, syncrip, tbxas1, tmed10, tnks2, uck2, ugt2b17, vamp3	57	274	1.5E-03	4.1E-02
hsa-miR-182	GO:0005769	Early endosome	ankrd27, aqp2, atp11b, atp9a, chmp1a, cntnap2, diaph2, eea1, epha3, kiaa0368, lmtk2, lrp6, mapk1, nipa1, numb, ocrl, parm1, ptp4a1, rab22a, rab31, sgk3, slc11a2, snx1, snx16, snx17, snx27, sort1, stambp, steap2, trak1, usp32, wasf2	32	134	1.6E-03	4.4E-02

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