

Integrated microRNA-mRNA analysis of pancreatic ductal adenocarcinoma

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ABSTRACT. The main aim of this study was to explore the underlying molecular mechanisms and potential target molecules of pancreatic adenocarcinoma. The miRNA (GSE32678) and mRNA (GSE32676) expression profiles of patients with pancreatic ductal adenocarcinoma and healthy controls were downloaded from the Gene Expression Omnibus database. Differentially expressed miRNA and differentially expressed genes were identified by analyzing the microarray algorithm

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after data preprocessing. Functional analysis was conducted by the Database for Annotation, Visualization and Integrated Analysis. miRNA-mRNA regulation pairs were obtained in TarMir database. The node degree of *hsa-miR-200c*, *hsa-miR-429*, and *hsa-miR-200b* (miRNA), and *EFNB2*, *MYRIP*, and *PHF17* (mRNA) were extremely high in the miRNA-mRNA network, indicating that these miRNA and mRNA may play a key role in the development of pancreatic cancer. Our study screened out some target miRNAs and mRNAs for pancreatic ductal adenocarcinoma, which may be helpful in its diagnosis and treatment.

Key words: Pancreatic adenocarcinoma; MicroRNA; Differentially expressed gene

INTRODUCTION

Pancreatic adenocarcinoma is a highly lethal disease that is usually diagnosed at an advanced stage of disease progression. This type of cancer has very few or no effective therapies (Long et al., 2012; Siegel et al., 2014). This disease is characterized by an early local regional spread and distant metastasis. The mortality rate of pancreatic adenocarcinoma is almost 100%, because of its propensity for early metastatic spreading, and its resistance to radiation and chemotherapy. Despite the vast amount of accumulated knowledge regarding tumor biology, the efficacy of the available treatment strategies for pancreatic cancer has remained largely unchanged over the past decade. The first-line agent gemcitabine has been observed to show favorable clinical responses, including reduced pain and weight gain (Matano et al., 2000); despite this, the prognosis remains dismal, with a 5-year survival rate of 1-4%, and a median survival period of 4-6 months. In addition, the molecular basis for pancreatic cancer remains to be elucidated. Therefore, there is a need for further research at a molecular level to identify new molecular mechanisms or biomarkers, in an effort to improve the prognosis, diagnosis, and treatment of pancreatic cancer.

MicroRNAs (miRNA) are 18-24-nucleotide long non-coding RNA that bind to the 3'-untranslated region of target transcripts and regulate gene expression by degrading the target mRNA or inhibiting translation (Lee et al., 1993). Previous studies have indicated that miRNA serve as guidance molecules, base pairing with partial or full complementary sequences of target mRNA, leading to translational repression and/or mRNA cleavage. Research conducted to elucidate the mechanism of action of miRNA has revealed that miRNA affect stem cell differentiation, organ development, cell death, phase change in the cell cycle, signal transduction, and several diseases, including cancer (Lionetti et al., 2009; Antonini et al., 2010). Recent studies have focused on miRNA expression profiling of pancreatic adenocarcinoma. Aberrant expression of miRNA, such as miR-21 and miR-155, in the pancreas, often contributes to cancer development and invasion (Giovannetti et al., 2010; Ryu et al., 2010). On the other hand, miRNA such as miR-34 and miR-150 may also suppress the growth and malignant behavior of pancreatic cancer cells (Liu et al., 2011; Srivastava et al., 2011). Several research groups have performed bioinformatic analyses, including gene ontology annotation of molecular function, biological processes and cellular components, and Kyoto Encyclopedia

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of Genes and Genomes (KEGG) pathways and predicted target genes, on mRNA or miRNA displaying altered expression. Despite these, research on the relationship between miRNA and the development of pancreatic adenocarcinoma using high throughput methodologies is extremely rare. This study provides important information to facilitate the elucidation of the physiological and pathological processes of pancreatic adenocarcinoma.

MATERIAL AND METHODS

mRNA and miRNA microarray data

GSE32676 and GSE32678, each containing 32 mRNA or miRNA expression chips from 25 early-stage pancreatic ductal adenocarcinoma (PDAC) samples and 7 non-malignant pancreatic samples, and uploaded by the same contributors, were downloaded from the gene expression omnibus (GEO) database.

Preprocessing of microarray data

mRNA and miRNA microarray data must be preprocessed prior to the identification of differentially expressed genes. Background correction and normalization was performed using the Affy package in R (R Core Team, 2013). Upon the detection of a gene by multiple probes, the mean expression value of those probes was utilized.

Identification of differentially expressed genes and miRNA

The Limma package in the R programming platform was used to identify the differentially expressed genes (DEGs) and miRNA. The Student *t*-test and the Bonferroni's correction method was used with an adjusted P value <0.05 and a $|\log FC|$ value >1.

Functional annotation of DEGs

Functional annotation of the DEGs was performed using the Database for Annotation, Visualization and Integrated Discovery (http://david.abcc.ncifcrf.gov/, DAVID). Gene ontology (GO) terms and KEGG pathways with P values <0.05 and at least 5 genes were selected.

Screening of miRNA-mRNA relationships

The miRNA-mRNA relationships were screened using the TarMir (http://www.tarmir. rgcb.res.in/) database. TarMir integrates a majority of the common miRNA databases, such as TargetScan, miRanda, and Point-in-Time Architecture (PITA), to identify the miRNA-mRNA relationships in a customizable and comprehensive manner. In this method, the miRNA-mRNA mRNA relationships identified in DIANA, miRanda, PITA, and TargetScan were simultaneously retrieved by TarMir, the overlapped genes between DEGs and the target genes of differentially expressed miRNA were filtered, and the miRNA-mRNA regulatory network was constructed using those miRNA-mRNA relationships. The network was visualized using the Cytoscape platform software (Shannon et al., 2003).

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RESULTS

Preprocessing of microarray data and identification of DEGs

Normalized gene and miRNA expression profiles were obtained after background correction and the normalization of microarray data. The box plots of gene expression data before and after preprocessing are shown in Figure 1. Six hundred and twenty DEGs, including 441 up-regulated and 179 down-regulated genes, were identified by the Student *t*-test and Bonferroni's correction. Forty-eight differentially expressed miRNA (27 up-regulated and 21 downregulated miRNA) were also selected.



Figure 1. Expression value of all genes in every sample before and after normalization.

Functional annotation of DEGs

A total of 111 GO terms, such as wound healing, cell adhesion, and biological adhesion, were enriched in the DEGs. In addition, 11 KEGG pathways, containing cell adhesion molecules, small cell lung cancer, and the p53 signaling pathway, which are well-researched aspects of cancers, were found to be significant (Table 1).

miRNA-mRNA relationship

Six thousand and nine hundred and thirty-one miRNA-mRNA regulatory relationships were retrieved from the TarMir database. Among these, 220 relationships were defined by DEGs and differentially expressed miRNA (Table 2). These were used to construct an miRNA-mRNA regulatory network (Figure 2) in PDAC. Corresponding degrees of genes/ miRNAs in the miRNA-mRNA regulatory network are shown in Table 3.

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Category	Pathway name	No. of genes	P value	Genes
KEGG_PATHWAY	O-glycan biosynthesis	7	4.02E-04	GALNT3, GCNT3, GALNT7, GALNT5, GALNT12, C1GALT1, ST6GALNAC1
KEGG_PATHWAY	Cell adhesion molecules	11	0.012884	FIIR, CLDN7, SDC1, PTPRF, ITGA6, CLDN1, CDH1, CDH3, SDC4, SELE, CLDN23
KEGG_PATHWAY	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	8	0.013361	JUP, DSG2, ITGA6, ITGB6, ITGA2, CACNB3, ITGA3, TCF7L2
KEGG_PATHWAY	Tight junction	11	0.014215	F11R, EPB41L3, CLDN7, CTTN, CGN, CLDN1, PRKCI, MYH14, TJP3, CLDN23, LLGL2
KEGG_PATHWAY	Small cell lung cancer	8	0.022157	LAMB3, CCND1, ITGA6, PIAS3, ITGA2, LAMC2, ITGA3, MYC
KEGG_PATHWAY	ECM-receptor interaction	8	0.022157	LAMB3, SDC1, ITGA6, ITGB6, ITGA2, LAMC2, ITGA3, SDC4
KEGG_PATHWAY	p53 signaling pathway	7	0.025923	TP5313, CCND1, SERPINB5, RRM2, SFN, PERP, GADD45B
KEGG_PATHWAY	Pathways in cancer	21	0.026051	WNT3A, BMP4, IL6, EGLN3, ITGA2, EGLN3, ITGA2, CDH1, ITGA3, ZBTB16, MECOM, TCF7L2, JUP, CBLC, LAMB3, CCND1, ITGA6, PIAS3, LAMC2, MYC, GSTP1
KEGG_PATHWAY	Jak-STAT signaling pathway	11	0.03508	CSF3, CBLC, CCND1, IL6, SOCS2, PIAS3, SOCS3, PIM1, LIFR, MYC, GHR
KEGG_PATHWAY	Acute myeloid leukemia	6	0.044307	JUP, CCNDI, PIMI, ZBTB16, MYC, TCF7L2
KEGG_PATHWAY	Aldosterone-regulated sodium reabsorption	5	0.047589	ATP1B1, SGK1, SFN, SCNN1A, IRS1

DISCUSSION

The pathogenesis of pancreatic adenocarcinoma remains poorly understood, which allows for the development of novel preventive and therapeutic interventions. In this study, the miRNA and mRNA expression profiles of patients with early-stage PDAC, as well as those of non-malignant pancreatic samples, were downloaded from gene databases. The miRNA (GSE32678) and mRNA (GSE32676) array deposited in the GEO database was analyzed, resulting in the identification of 620 DEGs from the original dataset, including 441 up-regulated and 179 down-regulated genes.

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Table 2. miRNA-mRNA regulatory relationship comprised of differentially expressed genes and differential	ly
expressed microRNA (miRNA).	

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isa-miR-200a HOXB5 hsa-miR-489 NFIL3 hsa-miR-364 NHS hsa-miR-28-5p NR443 hsa-miR-200a ITGA6 hsa-miR-203 ACSL1 hsa-miR-96 AVLN hsa-miR-28-5p PLEKHA7 hsa-miR-200a MMR1P hsa-miR-203 DCVN1D3 hsa-miR-96 FOXQ1 hsa-miR-28-5p SLC4A11 hsa-miR-200a RHPN hsa-miR-203 DFY1D2 hsa-miR-966 RR11 hsa-miR-488 ADA82 hsa-miR-200a FFAP2A hsa-miR-203 IRS1 hsa-miR-966 NR413 hsa-miR-488 KCN33 hsa-miR-200b ADMTS3 hsa-miR-203 NR143 hsa-miR-966 NR413 hsa-miR-488 KCN35 hsa-miR-200b CDR21 hsa-miR-203 NR143 hsa-miR-966 RH17 hsa-miR-488 SH283 hsa-miR-200b EFNA1 hsa-miR-203 NR43 hsa-miR-166 RHPN2 hsa-miR-488 SH283 hsa-miR-200b EFNA1 hsa-miR-203 NR44 hsa-miR-135a CAMATS9 hsa-miR-488 SH283<	hsa-miR-200a	FNBP1L	hsa-miR-489	EFNA5	hsa-miR-874	DCUNID3	hsa-miR-28-5p	HOXB3
isa-miR-200a ITGA6 hsa-miR-248 NR44.3 hsa-miR-366 ANLN hsa-miR-26-5p PLEKH47 hsa-miR-200a MR4B27B hsa-miR-203 DCUN1D3 hsa-miR-96 FOXQ1 hsa-miR-28-5p SICPA11 hsa-miR-200a RAB27B hsa-miR-203 DCUN1D3 hsa-miR-96 FOXQ1 hsa-miR-28-5p SICPA11 hsa-miR-200a RTFAP2A hsa-miR-203 FKBTP hsa-miR-96 GRILL hsa-miR-488 ADAM9 hsa-miR-200a WTX5A hsa-miR-203 IRS1 hsa-miR-96 NR4A3 hsa-miR-488 KIA1217 hsa-miR-200b ADAMTS3 hsa-miR-203 NR4A3 hsa-miR-96 PKC1 hsa-miR-488 MX45 hsa-miR-200b CDR2L hsa-miR-203 PAP2B hsa-miR-135a ADAMTS9 hsa-miR-488 STR39 hsa-miR-200b LMO hsa-miR-203 PCAS1 hsa-miR-135a CALML1 hsa-miR-356a LAN2 hsa-miR-200b LMC7 hsa-miR-140 PKA2C hsa-miR-135a CHM14 hsa-miR-356a	hsa-miR-200a	HOXB5	hsa-miR-489	NFIL3	hsa-miR-874	NHS	hsa-miR-28-5p	NR4A3
bas-miR-200a MYRIP bas-miR-203 ACSL1 hsa-miR-96 CAMRNI hsa-miR-28-5p SIPRI hsa-miR-200a RHIPN2 hsa-miR-203 DV11912 hsa-miR-96 GRH12 hsa-miR-48 ADAM9 hsa-miR-200a TRAP2A hsa-miR-203 FKBP1B hsa-miR-96 GRH12 hsa-miR-48 ADAM9 hsa-miR-200a WNT5A hsa-miR-203 FKBP1B hsa-miR-96 MYRIP hsa-miR-488 KCNS3 hsa-miR-200b ADAMT33 hsa-miR-203 FIEJ hsa-miR-96 PAK1 hsa-miR-488 KTAS4 hsa-miR-200b CDR21 hsa-miR-203 NFA43 hsa-miR-96 PAK2 hsa-miR-488 STK39 hsa-miR-200b EFNA1 hsa-miR-203 PPA2B hsa-miR-96 RHDV2 hsa-miR-488 STK39 hsa-miR-200b LRRCAA hsa-miR-203 RVEX1 hsa-miR-35a CDR21 hsa-miR-36a CNS2 hsa-miR-200b LRRCAA hsa-miR-203 RVX1 hsa-miR-35a CDR21 hsa-miR-35a EMP12	hsa-miR-200a	ITGA6	hsa-miR-489	NR4A3	hsa-miR-96	ANLN	hsa-miR-28-5p	PLEKHA7
ksa-miR-200a RkB27B hsa-miR-203 DCUNID3 hsa-miR-96 FOXU hsa-miR-28-5p SUC4AII hsa-miR-200a RTHP2 hsa-miR-203 FKBP1B hsa-miR-96 GRHL2 hsa-miR-488 ADAM9 hsa-miR-200a WNT5A hsa-miR-203 FKBP1B hsa-miR-96 MRVI hsa-miR-488 KCNS3 hsa-miR-200b ADAUN hsa-miR-203 ITG21 hsa-miR-96 NR4A3 hsa-miR-488 KIA1217 hsa-miR-200b ADANN hsa-miR-203 NFL3 hsa-miR-96 PROK2 hsa-miR-488 KIA23 hsa-miR-200b EFNA1 hsa-miR-203 PKEX1 hsa-miR-35 ADMTS9 hsa-miR-488 STL39 hsa-miR-200b LMOT hsa-miR-203 PCCS1 hsa-miR-35 ADMTS9 hsa-miR-488 STL39 hsa-miR-200b LMOT hsa-miR-203 TOX3 hsa-miR-35a CDR1L hsa-miR-35a EFNB2 hsa-miR-35a EFNB2 hsa-miR-35a EFNB2 hsa-miR-35a HOX13 hsa-miR-206 HOX23 hsa-miR-35	hsa-miR-200a	MYRIP	hsa-miR-203	ACSL1	hsa-miR-96	CAMK2N1	hsa-miR-28-5p	SIPRI
hsa-miR-200a RHPN2 hsa-miR-203 DPY19L2 hsa-miR-96 GR/L2 hsa-miR-48 ADAM9 hsa-miR-200a WNT5A hsa-miR-203 FKBP1B hsa-miR-96 IRS1 hsa-miR-488 ADR92 hsa-miR-200b MVNT5A hsa-miR-203 IRS1 hsa-miR-96 MYRIP hsa-miR-488 KCNS3 hsa-miR-200b ADAMTS3 hsa-miR-203 NFL3 hsa-miR-96 PAK1 hsa-miR-488 KIA1217 hsa-miR-200b CDR2L hsa-miR-203 NFA3 hsa-miR-96 PROK2 hsa-miR-488 STK39 hsa-miR-200b EFNA1 hsa-miR-203 PEX1 hsa-miR-35a CDML4 hsa-miR-488 STK39 hsa-miR-200b LARCXA hsa-miR-203 SOCS3 hsa-miR-135a CDR1L hsa-miR-356a EFN12 hsa-miR-36a EFN22 hsa-miR-356a EGLN3 hsa-miR-200b MBOAT2 hsa-miR-608 PIP42C hsa-miR-135a EMP1 hsa-miR-141 DCW1D3 hsa-miR-200b PH171 hsa-miR-608 PIP42C <td>hsa-miR-200a</td> <td>RAB27B</td> <td>hsa-miR-203</td> <td>DCUNID3</td> <td>hsa-miR-96</td> <td>FOXQ1</td> <td>hsa-miR-28-5p</td> <td>SLC4A11</td>	hsa-miR-200a	RAB27B	hsa-miR-203	DCUNID3	hsa-miR-96	FOXQ1	hsa-miR-28-5p	SLC4A11
hsa-miR-200a TFAP2.4 hsa-miR-203 FKBP1B hsa-miR-96 MS11 hsa-miR-488 ADR82 hsa-miR-200b MDAMTS3 hsa-miR-203 ITG12 hsa-miR-96 NR413 hsa-miR-488 KLA1217 hsa-miR-200b ADAMTS3 hsa-miR-203 NFLI3 hsa-miR-96 PRK1 hsa-miR-488 MXR45 hsa-miR-200b CDR2L hsa-miR-203 NFL13 hsa-miR-96 PROK2 hsa-miR-488 PH2P2B hsa-miR-200b EFNA1 hsa-miR-203 PRAP2B hsa-miR-96 RHDNTS9 hsa-miR-488 SFL39 hsa-miR-200b LMO7 hsa-miR-203 SOCS3 hsa-miR-135a CALML4 hsa-miR-526a EGN3 hsa-miR-200b MADT2 hsa-miR-608 SP1 hsa-miR-135a EMP1 hsa-miR-526a EGN3 hsa-miR-200b NAP1L2 hsa-miR-608 NRN1 hsa-miR-135a EMP1 hsa-miR-141 FM46C hsa-miR-200b NPL12 hsa-miR-608 RNN1 hsa-miR-135a EMP1 hsa-miR-141 FNM46C <td>hsa-miR-200a</td> <td>RHPN2</td> <td>hsa-miR-203</td> <td>DPY19L2</td> <td>hsa-miR-96</td> <td>GRHL2</td> <td>hsa-miR-488</td> <td>ADAM9</td>	hsa-miR-200a	RHPN2	hsa-miR-203	DPY19L2	hsa-miR-96	GRHL2	hsa-miR-488	ADAM9
hsa-miR-200a WNT54 hsa-miR-203 IRS1 hsa-miR-96 NR4A3 hsa-miR-488 KCNS3 hsa-miR-200b ADAMTS3 hsa-miR-203 ITGA2 hsa-miR-96 NR4A3 hsa-miR-488 KLA1217 hsa-miR-200b CDR2L hsa-miR-203 NR4A3 hsa-miR-96 PAK1 hsa-miR-488 PH2P2B hsa-miR-200b EFNA1 hsa-miR-203 PR4X1 hsa-miR-96 RIPN2 hsa-miR-488 STK39 hsa-miR-200b EFNB2 hsa-miR-203 POEX1 hsa-miR-135a ADAMTS9 hsa-miR-488 STK39 hsa-miR-200b LMO7 hsa-miR-203 SOCS3 hsa-miR-135a CDR2L hsa-miR-56a EGN3 hsa-miR-200b MBOAT2 hsa-miR-608 RN11 hsa-miR-135a EFNB2 hsa-miR-141 DCUN1D3 hsa-miR-200b NAP1L5 hsa-miR-608 RAB39B hsa-miR-135a CHR hsa-miR-141 FM46C hsa-miR-200b PHF17 hsa-miR-83 KC1 hsa-miR-135a RAB39B hsa-miR-135a RAB39B </td <td>hsa-miR-200a</td> <td>TFAP2A</td> <td>hsa-miR-203</td> <td>FKBP1B</td> <td>hsa-miR-96</td> <td>IRSI</td> <td>hsa-miR-488</td> <td>ADRB2</td>	hsa-miR-200a	TFAP2A	hsa-miR-203	FKBP1B	hsa-miR-96	IRSI	hsa-miR-488	ADRB2
hsa-miR-200b ADAMTS3 hsa-miR-203 ITGA2 hsa-miR-96 NR4A3 hsa-miR-488 KIAA1217 hsa-miR-200b CDR2L hsa-miR-203 NFIL3 hsa-miR-96 PRK1 hsa-miR-488 MXRA5 hsa-miR-200b CDR2L hsa-miR-203 PR423 hsa-miR-96 PRK1 hsa-miR-488 STL33 hsa-miR-200b EFNA1 hsa-miR-203 PREX1 hsa-miR-135a CALML4 hsa-miR-488 STL33 hsa-miR-200b LRC3A hsa-miR-203 SOCS3 hsa-miR-135a CALML4 hsa-miR-526a EFNB2 hsa-miR-200b MRO71 hsa-miR-608 BEF1 hsa-miR-135a EFNB2 hsa-miR-526a HOXB3 hsa-miR-200b NAP1L2 hsa-miR-608 NRN1 hsa-miR-135a EMP1 hsa-miR-141 DCUN1D3 hsa-miR-200b PHF17 hsa-miR-608 NRA12 hsa-miR-135a PHF17 hsa-miR-141 FNMPL hsa-miR-200b PHA2B hsa-miR-183 ENC1 hsa-miR-135a RAB39B hsa-miR-141 FNM	hsa-miR-200a	WNT5A	hsa-miR-203	IRSI	hsa-miR-96	MYRIP	hsa-miR-488	KCNS3
hsa-miR-200b ANLN hsa-miR-203 NFIL3 hsa-miR-96 PAK1 hsa-miR-488 MXRA5 hsa-miR-200b EFNA1 hsa-miR-203 NR4A3 hsa-miR-96 RHPN2 hsa-miR-488 PPAP2B hsa-miR-200b EFNA1 hsa-miR-203 PPAP2B hsa-miR-96 RHPN2 hsa-miR-488 STK39 hsa-miR-200b EKND2 hsa-miR-203 SOCS3 hsa-miR-155a CALML4 hsa-miR-868 STK39 hsa-miR-200b LROC8A hsa-miR-203 TOX3 hsa-miR-15a CDR2L hsa-miR-20a ANK2 hsa-miR-200b MBOAT2 hsa-miR-608 RB1 hsa-miR-15a EMP1 hsa-miR-326a EGLN3 hsa-miR-200b MAPL15 hsa-miR-608 RN1 hsa-miR-15a EMP1 hsa-miR-141 DCUN1D3 hsa-miR-200b PH175 hsa-miR-608 RAB39B hsa-miR-135a RAB39B hsa-miR-135a RAB30B hsa-miR-141 FAM46C hsa-miR-200b PH171 hsa-miR-183 INC1 hsa-miR-35a RAB39B	hsa-miR-200b	ADAMTS3	hsa-miR-203	ITGA2	hsa-miR-96	NR4A3	hsa-miR-488	KIAA1217
hsa-miR-200b CDR2L hsa-miR-203 NR4A3 hsa-miR-96 PROK2 hsa-miR-488 PPAP2B hsa-miR-200b EFNA1 hsa-miR-203 PPAP2B hsa-miR-35a ADAMTS9 hsa-miR-488 SH2B3 hsa-miR-200b LRO7 hsa-miR-203 SOCS3 hsa-miR-135a CALML4 hsa-miR-488 SH2B3 hsa-miR-200b LRC8A hsa-miR-203 SOCS3 hsa-miR-135a CALML4 hsa-miR-526a ANK2 hsa-miR-200b MBOAT2 hsa-miR-608 EBF1 hsa-miR-135a EFNB2 hsa-miR-526a EGN3 hsa-miR-200b NAP1L2 hsa-miR-608 NRN1 hsa-miR-135a EMP1 hsa-miR-141 DCUN1D3 hsa-miR-200b PAP2B hsa-miR-183 ENC1 hsa-miR-135a PHF17 hsa-miR-141 FM46C hsa-miR-200b PH2B2 hsa-miR-183 RS1 hsa-miR-35a TRPM4 hsa-miR-141 FMA6S hsa-miR-200b PVR14 hsa-miR-183 RS1 hsa-miR-34c-5p ACS11 hsa-miR-141 FM265	hsa-miR-200b	ANLN	hsa-miR-203	NFIL3	hsa-miR-96	PAKI	hsa-miR-488	MXRA5
hsa-miR-200b EFNA1 hsa-miR-203 PPAP2B hsa-miR-36 RHPN2 hsa-miR-488 SH2B3 hsa-miR-200b LMO7 hsa-miR-203 PREX1 hsa-miR-135a ADAMTS9 hsa-miR-488 SH2B3 hsa-miR-200b LMO7 hsa-miR-203 TOX3 hsa-miR-135a CDR2L hsa-miR-526a EFNB2 hsa-miR-200b MBOAT2 hsa-miR-608 EBF1 hsa-miR-135a CDR2L hsa-miR-526a EGLN3 hsa-miR-200b NAP1L5 hsa-miR-608 RPI4X2C hsa-miR-135a GHR hsa-miR-141 DCUN1D3 hsa-miR-200b PAP1E5 hsa-miR-608 RAB39B hsa-miR-135a RHB3B hsa-miR-141 FM46C hsa-miR-200b PAP1E3 hsa-miR-183 RS1 hsa-miR-135a RAB39B hsa-miR-141 FM46C hsa-miR-200b PROK2 hsa-miR-183 RS1 hsa-miR-35a RCSL hsa-miR-141 FM46C hsa-miR-200b FYRL4 hsa-miR-183 RS1 hsa-miR-35a RDM14 hsa-miR-141 HSA5 </td <td>hsa-miR-200b</td> <td>CDR2L</td> <td>hsa-miR-203</td> <td>NR4A3</td> <td>hsa-miR-96</td> <td>PROK2</td> <td>hsa-miR-488</td> <td>PPAP2B</td>	hsa-miR-200b	CDR2L	hsa-miR-203	NR4A3	hsa-miR-96	PROK2	hsa-miR-488	PPAP2B
hsa-miR-200b EFNB2 hsa-miR-203 PREX1 hsa-miR-135a ADAMTS9 hsa-miR-488 STK39 hsa-miR-200b LMO7 hsa-miR-203 SOCS3 hsa-miR-135a CALML4 hsa-miR-26a ANK2 hsa-miR-200b LRCSA hsa-miR-608 EBF1 hsa-miR-135a CDR2L hsa-miR-526a EGLN3 hsa-miR-200b NAP1L2 hsa-miR-608 NRN1 hsa-miR-135a EMP1 hsa-miR-135a EMP1 hsa-miR-526a HOXB3 hsa-miR-200b NAP1L2 hsa-miR-608 RAB39B hsa-miR-135a GHR hsa-miR-141 DCUN1D3 hsa-miR-200b PHF17 hsa-miR-618 ENC1 hsa-miR-135a RAB39B hsa-miR-141 HOXB5 hsa-miR-200b PRAV2B hsa-miR-183 KIA0101 hsa-miR-34c-5p ACSL1 hsa-miR-141 HOXB5 hsa-miR-200b TFAP2A hsa-miR-183 TCF7L2 hsa-miR-34c-5p ACSL4 hsa-miR-141 RAB27B hsa-miR-200c TSFSF8 hsa-miR-200c ADAMTS3 hsa-miR-34c-5p <td>hsa-miR-200b</td> <td>EFNAI</td> <td>hsa-miR-203</td> <td>PPAP2B</td> <td>hsa-miR-96</td> <td>RHPN2</td> <td>hsa-miR-488</td> <td>SH2B3</td>	hsa-miR-200b	EFNAI	hsa-miR-203	PPAP2B	hsa-miR-96	RHPN2	hsa-miR-488	SH2B3
$ hsa-miR-200b \ LMO7 hsa-miR-203 SOCS3 hsa-miR-135a CALML4 hsa-miR-526a ANK2 \\ hsa-miR-200b LRCC8A hsa-miR-203 TOX3 hsa-miR-135a CDR2L hsa-miR-526a EFNB2 \\ hsa-miR-200b MAP1L2 hsa-miR-608 NRN1 hsa-miR-135a EPNB2 hsa-miR-526a EGLN3 \\ hsa-miR-200b NAP1L2 hsa-miR-608 NRN1 hsa-miR-135a EMP1 hsa-miR-526a HOXB3 \\ hsa-miR-200b NAP1L5 hsa-miR-608 PIP4K2C hsa-miR-135a EMP1 hsa-miR-141 DCUNID3 \\ hsa-miR-200b PHF17 hsa-miR-608 PIP4K2C hsa-miR-135a CSC HCR \\ hsa-miR-200b PHF17 hsa-miR-608 PIP4K2C hsa-miR-135a PHF17 hsa-miR-141 FMM46C \\ hsa-miR-200b PAP2B hsa-miR-183 ENC1 hsa-miR-135a RAB39B hsa-miR-141 FNBP1L \\ hsa-miR-200b PROK2 hsa-miR-183 IRS1 hsa-miR-35a TRPM4 hsa-miR-141 HOXB5 \\ hsa-miR-200b TFAP2A hsa-miR-183 IRS1 hsa-miR-34c-5p ACSL4 hsa-miR-141 MYRIP \\ hsa-miR-200b TFAP2A hsa-miR-183 TCF7L2 hsa-miR-34c-5p ACSL4 hsa-miR-141 MYRIP \\ hsa-miR-21 GRAM3 hsa-miR-200c ADAMTS3 hsa-miR-34c-5p ACSL4 hsa-miR-141 RAB27B \\ hsa-miR-21 GRAM3 hsa-miR-200c ADAMTS3 hsa-miR-34c-5p DKK1 hsa-miR-141 FMP27a \\ hsa-miR-21 MYO6 hsa-miR-200c CDR2L hsa-miR-34c-5p FKBP1B hsa-miR-141 FMP24 \\ hsa-miR-21 PLEKHA1 hsa-miR-200c EFNA1 hsa-miR-34c-5p FOXQ1 hsa-miR-141 WTSA \\ hsa-miR-21 PLEKHA1 hsa-miR-200c EFNB2 hsa-miR-34c-5p FABP1B hsa-miR-141 WTSA \\ hsa-miR-21 PLEKHA1 hsa-miR-200c EFNB2 hsa-miR-34c-5p FABP1B hsa-miR-141 WTSA \\ hsa-miR-21 PLEKHA1 hsa-miR-200c EFNB2 hsa-miR-34c-5p FABP1B hsa-miR-141 WTSA \\ hsa-miR-21 PLEKHA1 hsa-miR-200c EFNB2 hsa-miR-34c-5p FABP1B hsa-miR-92b DNAH9 \\ hsa-miR-21 PLEKHA1 hsa-miR-20c EFNB2 hsa-miR-34c-5p MARCKSL1 hsa-miR-92b DNAH9 \\ hsa-miR-21 ADAM100 hsa-miR-34c-5p MARCKSL1 hsa-miR-92b DNAH9 \\ hsa-miR-29 ADAM10 hsa-miR-34c-5p NRN1 hsa-miR-92b DNAH9 \\ hsa-miR-429 ADNT hsa-miR-20c PAP12 hsa-miR-34a ACSL1 hsa-mi$	hsa-miR-200b	EFNB2	hsa-miR-203	PREXI	hsa-miR-135a	ADAMTS9	hsa-miR-488	STK39
	hsa-miR-200b	LMO7	hsa-miR-203	SOCS3	hsa-miR-135a	CALML4	hsa-miR-526a	ANK2
hsa-miR-200b MBOAT2 hsa-miR-608 EBF1 hsa-miR-135a EFNB2 hsa-miR-526a EGLN3 hsa-miR-200b NAP1L2 hsa-miR-608 NRN1 hsa-miR-135a EMP1 hsa-miR-526a HOXB3 hsa-miR-200b NAP1L5 hsa-miR-608 RP4P2C hsa-miR-135a EMP1 hsa-miR-141 DCUN1D3 hsa-miR-200b PHF17 hsa-miR-608 RAB39B hsa-miR-135a GHR hsa-miR-141 FAM46C hsa-miR-200b PROK2 hsa-miR-183 ENC1 hsa-miR-135a RAB39B hsa-miR-141 FNBP1L hsa-miR-200b PROK2 hsa-miR-183 IK1A0101 hsa-miR-34c-5p ACSL1 hsa-miR-141 HYDS5 hsa-miR-200b TFFP2A hsa-miR-183 TCF12 hsa-miR-34c-5p ACSL4 hsa-miR-141 R4D27B hsa-miR-210 GRAMD3 hsa-miR-200c ADAMTS3 hsa-miR-34c-5p DKK1 hsa-miR-141 R4D27B hsa-miR-21 HFR hsa-miR-200c ADAMTS3 hsa-miR-34c-5p DKK1 hsa-miR-141 <td>hsa-miR-200b</td> <td>LRRC8A</td> <td>hsa-miR-203</td> <td>TOX3</td> <td>hsa-miR-135a</td> <td>CDR2L</td> <td>hsa-miR-526a</td> <td>EFNB2</td>	hsa-miR-200b	LRRC8A	hsa-miR-203	TOX3	hsa-miR-135a	CDR2L	hsa-miR-526a	EFNB2
hsa-miR-200b NAP1L2 hsa-miR-608 NRN1 hsa-miR-135a EMP1 hsa-miR-526a HOXB3 hsa-miR-200b MAP1L5 hsa-miR-608 PIP4K2C hsa-miR-135a GHR hsa-miR-141 DCUNID3 hsa-miR-200b PHF17 hsa-miR-608 RAB39B hsa-miR-135a GHR hsa-miR-141 FAM4C hsa-miR-200b PHP12B hsa-miR-608 RAB39B hsa-miR-135a RAB39B hsa-miR-141 FNBP1L hsa-miR-200b PROK2 hsa-miR-183 ENC1 hsa-miR-135a TRPM4 hsa-miR-141 HOXB5 hsa-miR-200b TKFP2A hsa-miR-183 RIS1 hsa-miR-34c-5p ACSL4 hsa-miR-141 MYRP hsa-miR-200b TNFSF8 hsa-miR-200c ADAMTS3 hsa-miR-34c-5p CBF42T3 hsa-miR-141 RHPN2 hsa-miR-21 GRAMD3 hsa-miR-200c ADAMTS3 hsa-miR-34c-5p DKK1 hsa-miR-141 RHPN2 hsa-miR-21 MYO6 hsa-miR-200c CDR2L hsa-miR-34c-5p DKX1 hsa-miR-141	hsa-miR-200b	MBOAT2	hsa-miR-608	EBF1	hsa-miR-135a	EFNB2	hsa-miR-526a	EGLN3
hsa-miR-200b NAP1L5 hsa-miR-608 PIP4K2C hsa-miR-135a GHR hsa-miR-141 DCUN1D3 hsa-miR-200b PHF17 hsa-miR-608 RAB39B hsa-miR-135a PHF17 hsa-miR-141 FAM46C hsa-miR-200b PPAP2B hsa-miR-183 ENC1 hsa-miR-135a RAB39B hsa-miR-141 FNBP1L hsa-miR-200b PROK2 hsa-miR-183 IRS1 hsa-miR-135a TRPM4 hsa-miR-141 HOXB5 hsa-miR-200b TFAP2A hsa-miR-183 KIA0101 hsa-miR-34c-5p ACSL4 hsa-miR-141 MYRP hsa-miR-200b TTNFSF8 hsa-miR-183 TCF7L2 hsa-miR-34c-5p ACSL4 hsa-miR-141 RAB27B hsa-miR-21 GIAMD3 hsa-miR-200c ADAMTS3 hsa-miR-34c-5p CBF42T3 hsa-miR-141 SOX9 hsa-miR-21 MYO6 hsa-miR-200c CPRA1 hsa-miR-34c-5p FKBP1B hsa-miR-141 SOX9 hsa-miR-21 PLEKHA1 hsa-miR-200c EFNA1 hsa-miR-34c-5p FKBP1B hsa-miR-	hsa-miR-200b	NAP1L2	hsa-miR-608	NRNI	hsa-miR-135a	EMP1	hsa-miR-526a	HOXB3
hsa-miR-200b PHF17 hsa-miR-608 RAB39B hsa-miR-135a PHF17 hsa-miR-141 FAM46C hsa-miR-200b PPAP2B hsa-miR-183 ENC1 hsa-miR-135a RAB39B hsa-miR-141 FNBP1L hsa-miR-200b PROK2 hsa-miR-183 IRS1 hsa-miR-135a TRPM4 hsa-miR-141 HOXB5 hsa-miR-200b PVRL4 hsa-miR-183 KIA.40101 hsa-miR-34c-5p ACSL1 hsa-miR-141 MYRP hsa-miR-200b TKPSF8 hsa-miR-183 TCF7L2 hsa-miR-34c-5p AKS2 hsa-miR-141 RAB27B hsa-miR-210 LIFR hsa-miR-100 ADAMTS3 hsa-miR-34c-5p DKK1 hsa-miR-141 RAB27B hsa-miR-21 LIFR hsa-miR-200c CDR2L hsa-miR-34c-5p DKK1 hsa-miR-141 TEA2A hsa-miR-21 PLEKHA1 hsa-miR-200c EFNA1 hsa-miR-34c-5p GALNT7 hsa-miR-141 WNT5A hsa-miR-21 PLEKHA1 hsa-miR-200c EFNA1 hsa-miR-34c-5p GALNT7 hsa-miR-92b<	hsa-miR-200b	NAP1L5	hsa-miR-608	PIP4K2C	hsa-miR-135a	GHR	hsa-miR-141	DCUNID3
hsa-miR-200bPPAP2Bhsa-miR-183ENC1hsa-miR-135aRAB39Bhsa-miR-141FNBP1Lhsa-miR-200bPROK2hsa-miR-183IRS1hsa-miR-135aTRPM4hsa-miR-141HOXB5hsa-miR-200bPVRL4hsa-miR-183IRS1hsa-miR-34c-5pACSL1hsa-miR-141HOXB5hsa-miR-200bTFAP2Ahsa-miR-183PIM1hsa-miR-34c-5pACSL4hsa-miR-141MYRIPhsa-miR-200bTNFSF8hsa-miR-183TCF7L2hsa-miR-34c-5pACSL4hsa-miR-141R4B27Bhsa-miR-21GRAMD3hsa-miR-200cADAMTS3hsa-miR-34c-5pDKK1hsa-miR-141R4B27Bhsa-miR-21MYO6hsa-miR-200cADLhsa-miR-34c-5pDKK1hsa-miR-141RHPN2hsa-miR-21MYO6hsa-miR-200cCDR2Lhsa-miR-34c-5pFKBP1Bhsa-miR-141TEAP2Ahsa-miR-21PHF17hsa-miR-200cEFNB2hsa-miR-34c-5pFOXQ1hsa-miR-141WNT5Ahsa-miR-21PLEKHA1hsa-miR-200cEFNB2hsa-miR-34c-5pGALNT7hsa-miR-92bADAM10hsa-miR-21PLEKHA1hsa-miR-200cLMO7hsa-miR-34c-5pMARCKSL1hsa-miR-92bDNAJB9hsa-miR-21ADAMTS3hsa-miR-200cLMO7hsa-miR-34c-5pMARCKSL1hsa-miR-92bDNAJB9hsa-miR-21PLEKHA1hsa-miR-200cLMO7hsa-miR-34c-5pMARCKSL1hsa-miR-92bDNAJB9hsa-miR-21ADLAhsa-miR-200cMBOAT2hsa-miR-34c-5p<	hsa-miR-200b	PHF17	hsa-miR-608	RAB39B	hsa-miR-135a	PHF17	hsa-miR-141	FAM46C
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hsa-miR-200bPVRL4hsa-miR-183KIAA0101hsa-miR-34c-5pACSL1hsa-miR-141ITGA6hsa-miR-200bTFAP2Ahsa-miR-183PIM1hsa-miR-34c-5pACSL4hsa-miR-141MYRIPhsa-miR-200bTNFSF8hsa-miR-183TCF7L2hsa-miR-34c-5pANK2hsa-miR-141RAB27Bhsa-miR-21GRAMD3hsa-miR-200cADAMTS3hsa-miR-34c-5pCBFA2T3hsa-miR-141SOX9hsa-miR-21LIFRhsa-miR-200cADLNNhsa-miR-34c-5pDKK1hsa-miR-141TFAP2Ahsa-miR-21PMY06hsa-miR-200cCDR2Lhsa-miR-34c-5pFKBP1Bhsa-miR-141WNT5Ahsa-miR-21PHF17hsa-miR-200cEFNA1hsa-miR-34c-5pFOXQ1hsa-miR-141WNT5Ahsa-miR-21PHEKHA1hsa-miR-200cEFNB2hsa-miR-34c-5pGALNT7hsa-miR-92bCNNM4hsa-miR-21PLEKHA1hsa-miR-200cLMO7hsa-miR-34c-5pJAKMIP1hsa-miR-92bCNNM4hsa-miR-21ADAMTS3hsa-miR-200cLRC8Ahsa-miR-34c-5pMARCKSL1hsa-miR-92bCNNM4hsa-miR-429ADLNhsa-miR-200cNAP1L2hsa-miR-34c-5pNHShsa-miR-92bCNNM4hsa-miR-429CDR2Lhsa-miR-200cNAP1L2hsa-miR-34c-5pNHA2hsa-miR-92bGALNT7hsa-miR-429EFNA1hsa-miR-200cNAP1L2hsa-miR-34c-5pNHA2hsa-miR-92bGALNT7hsa-miR-429EFNA1hsa-miR-200cPHF17hsa-miR-34c	hsa-miR-200b	PROK2	hsa-miR-183	IRS1	hsa-miR-135a	TRPM4	hsa-miR-141	HOXB5
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-200b	PVRL4	hsa-miR-183	KIAA0101	hsa-miR-34c-5p	ACSL1	hsa-miR-141	ITGA6
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-200b	TFAP2A	hsa-miR-183	PIMI	hsa-miR-34c-5p	ACSL4	hsa-miR-141	MYRIP
hsa-miR-21GRAMD3hsa-miR-200cADAMTS3hsa-miR-34c-5pCBFA2T3hsa-miR-141RHPN2hsa-miR-21LIFRhsa-miR-200cANLNhsa-miR-34c-5pDKK1hsa-miR-141SOX9hsa-miR-21MYO6hsa-miR-200cCDR2Lhsa-miR-34c-5pFKBP1Bhsa-miR-141TFAP2Ahsa-miR-21PHF17hsa-miR-200cEFNA1hsa-miR-34c-5pFOXQ1hsa-miR-141WNT5Ahsa-miR-21PLEKHA1hsa-miR-200cEFNB2hsa-miR-34c-5pGALNT7hsa-miR-92bADAM10hsa-miR-21SASH1hsa-miR-200cLMO7hsa-miR-34c-5pJAKMIP1hsa-miR-92bDNAJB9hsa-miR-21ADAMTS3hsa-miR-200cLRRC8Ahsa-miR-34c-5pMARCKSL1hsa-miR-92bDNAJB9hsa-miR-429ADAMTS3hsa-miR-200cMBOAT2hsa-miR-34c-5pMYRIPhsa-miR-92bDNAJB9hsa-miR-429ANLNhsa-miR-200cNAP1L2hsa-miR-34c-5pNHShsa-miR-92bGALNT7hsa-miR-429EFNA1hsa-miR-200cNAP1L2hsa-miR-34c-5pNR14A2hsa-miR-92bGHRhsa-miR-429EFNA1hsa-miR-200cPHF17hsa-miR-34c-5pNRN1hsa-miR-92bGHAD3hsa-miR-429EFNA2hsa-miR-200cPHP17hsa-miR-34c-5pNRN1hsa-miR-92bRAMD3hsa-miR-429LMO7hsa-miR-200cPHP17hsa-miR-34c-5pNRN1hsa-miR-92bNR4A3hsa-miR-429LMO7hsa-miR-200cPKR2hsa-miR-34a <t< td=""><td>hsa-miR-200b</td><td>TNFSF8</td><td>hsa-miR-183</td><td>TCF7L2</td><td>hsa-miR-34c-5p</td><td>ANK2</td><td>hsa-miR-141</td><td>RAB27B</td></t<>	hsa-miR-200b	TNFSF8	hsa-miR-183	TCF7L2	hsa-miR-34c-5p	ANK2	hsa-miR-141	RAB27B
hsa-miR-21LIFRhsa-miR-200cANLNhsa-miR-34c-5pDKK1hsa-miR-141SOX9hsa-miR-21MYO6hsa-miR-200cCDR2Lhsa-miR-34c-5pFKBP1Bhsa-miR-141TFAP2Ahsa-miR-21PHF17hsa-miR-200cEFNA1hsa-miR-34c-5pFOXQ1hsa-miR-141WNT5Ahsa-miR-21PHF17hsa-miR-200cEFNA1hsa-miR-34c-5pFOXQ1hsa-miR-141WNT5Ahsa-miR-21PLEKHA1hsa-miR-200cEFNB2hsa-miR-34c-5pGALNT7hsa-miR-92bDNA400hsa-miR-21SASH1hsa-miR-200cLMO7hsa-miR-34c-5pJAKMIP1hsa-miR-92bCNNM4hsa-miR-219ADAMTS3hsa-miR-200cLRRC8Ahsa-miR-34c-5pMARCKSL1hsa-miR-92bDNAJB9hsa-miR-429ANLNhsa-miR-200cNAP1L2hsa-miR-34c-5pNHShsa-miR-92bGALNT7hsa-miR-429CDR2Lhsa-miR-200cNAP1L2hsa-miR-34c-5pNR4A2hsa-miR-92bGHRhsa-miR-429EFNA1hsa-miR-200cPHF17hsa-miR-34c-5pNR1Ahsa-miR-92bGRAMD3hsa-miR-429EFNA2hsa-miR-200cPHF17hsa-miR-34c-5pSOX4hsa-miR-92bNR4A3hsa-miR-429LMO7hsa-miR-200cPROK2hsa-miR-34aACSL1hsa-miR-92bNR4A3hsa-miR-429LRC8Ahsa-miR-200cPKR2hsa-miR-34aACSL1hsa-miR-92bPLEKHA1hsa-miR-429NAP1L2hsa-miR-200cTKR24hsa-miR-34aACSL1 <td>hsa-miR-21</td> <td>GRAMD3</td> <td>hsa-miR-200c</td> <td>ADAMTS3</td> <td>hsa-miR-34c-5p</td> <td>CBFA2T3</td> <td>hsa-miR-141</td> <td>RHPN2</td>	hsa-miR-21	GRAMD3	hsa-miR-200c	ADAMTS3	hsa-miR-34c-5p	CBFA2T3	hsa-miR-141	RHPN2
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-21	LIFR	hsa-miR-200c	ANLN	hsa-miR-34c-5p	DKKI	hsa-miR-141	SOX9
hsa-miR-21PHF17hsa-miR-200c $EFNA1$ hsa-miR-34c-5p $FOXQ1$ hsa-miR-141 $WNT5A$ hsa-miR-21PLEKHA1hsa-miR-200c $EFNB2$ hsa-miR-34c-5p $GALNT7$ hsa-miR-92b $ADAM10$ hsa-miR-21SASH1hsa-miR-200c $LMO7$ hsa-miR-34c-5p $JAKMIP1$ hsa-miR-92b $ADAM10$ hsa-miR-21SASH1hsa-miR-200c $LMO7$ hsa-miR-34c-5p $JAKMIP1$ hsa-miR-92b $CNNM4$ hsa-miR-429 $ADAMTS3$ hsa-miR-200c $LRC8A$ hsa-miR-34c-5p $MARCKSL1$ hsa-miR-92b $DNAJB9$ hsa-miR-429 $ANLN$ hsa-miR-200c $MBOAT2$ hsa-miR-34c-5p $MYRIP$ hsa-miR-92b $GALNT7$ hsa-miR-429 $EFNA1$ hsa-miR-200c $NAP1L2$ hsa-miR-34c-5p $NR4A2$ hsa-miR-92b $GALNT7$ hsa-miR-429 $EFNA1$ hsa-miR-200c $NAP1L5$ hsa-miR-34c-5p $NRA42$ hsa-miR-92b $GRAMD3$ hsa-miR-429 $EFNB2$ hsa-miR-200c $PHF17$ hsa-miR-34c-5p $NRN1$ hsa-miR-92b $RAA3$ hsa-miR-429 $LMO7$ hsa-miR-200c $PPAP2B$ hsa-miR-34a $ACSL1$ hsa-miR-92b $NR4A3$ hsa-miR-429 $LMO7$ hsa-miR-200c $PVRL4$ hsa-miR-34a $ACSL4$ hsa-miR-92b $PAP2B$ hsa-miR-429 $NAP1L2$ hsa-miR-200c $TFAP2A$ hsa-miR-34a $ACSL4$ hsa-miR-92b $SIPR1$ hsa-miR-429 $NAP1L2$ hsa-miR-200c $TFAP2A$ hsa-miR-34a $ACSL4$ hsa-miR-92b $SIPR1$ <	hsa-miR-21	MYO6	hsa-miR-200c	CDR2L	hsa-miR-34c-5p	FKBP1B	hsa-miR-141	TFAP2A
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-21	PHF17	hsa-miR-200c	EFNAI	hsa-miR-34c-5p	FOXO1	hsa-miR-141	WNT5A
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-21	PLEKHAI	hsa-miR-200c	EFNB2	hsa-miR-34c-5p	$GAL\tilde{N}T7$	hsa-miR-92b	ADAM10
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-21	SASH1	hsa-miR-200c	LMO7	hsa-miR-34c-5p	JAKMIP1	hsa-miR-92b	CNNM4
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-429	ADAMTS3	hsa-miR-200c	LRRC8A	hsa-miR-34c-5p	MARCKSL1	hsa-miR-92b	DNAJB9
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-429	ANLN	hsa-miR-200c	MBOAT2	hsa-miR-34c-5p	MYRIP	hsa-miR-92b	EDNRB
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-429	CDR2L	hsa-miR-200c	NAP1L2	hsa-miR-34c-5p	NHS	hsa-miR-92b	GALNT7
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	hsa-miR-429	EFNAI	hsa-miR-200c	NAP1L5	hsa-miR-34c-5p	NR4A2	hsa-miR-92b	GHR
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hsa-miR-429NAP1L2hsa-miR-200cTFAP2Ahsa-miR-34aANK2hsa-miR-92bSIPR1hsa-miR-429NAP1L5hsa-miR-200cTNFSF8hsa-miR-34aCBFA2T3hsa-miR-92bSOX4hsa-miR-429PHF17hsa-miR-671-5pPHF17hsa-miR-34aDKK1hsa-miR-92bSTK39hsa-miR-429PPAP2Bhsa-miR-182ADAM10hsa-miR-34aFKBP1Bhsa-miR-552DCUN1D3hsa-miR-429PROK2hsa-miR-182ANK2hsa-miR-34aFOXQ1hsa-miR-552ENC1hsa-miR-429PVRL4hsa-miR-182CBFA2T3hsa-miR-34aGALNT7hsa-miR-552SGK1	hsa-miR-429	MBOAT2	hsa-miR-200c	PVRL4	hsa-miR-34a	ACSL4	hsa-miR-92b	PPAP2B
hsa-miR-429 NAP1L5 hsa-miR-200c TNFSF8 hsa-miR-34a CBFA2T3 hsa-miR-2b SOX4 hsa-miR-429 PHF17 hsa-miR-671-5p PHF17 hsa-miR-34a DKK1 hsa-miR-92b STK39 hsa-miR-429 PHP17 hsa-miR-182 ADAM10 hsa-miR-34a FKBP1B hsa-miR-552 DCUN1D3 hsa-miR-429 PROK2 hsa-miR-182 ANK2 hsa-miR-34a FOXQ1 hsa-miR-552 ENC1 hsa-miR-429 PVRL4 hsa-miR-182 CBFA2T3 hsa-miR-34a GALNT7 hsa-miR-552 SGK1	hsa-miR-429	NAP1L2	hsa-miR-200c	TFAP2A	hsa-miR-34a	ANK2	hsa-miR-92b	SIPRI
hsa-miR-429 PHF17 hsa-miR-671-5p PHF17 hsa-miR-34a DKK1 hsa-miR-92b STK39 hsa-miR-429 PPAP2B hsa-miR-182 ADAM10 hsa-miR-34a FKBP1B hsa-miR-552 DCUN1D3 hsa-miR-429 PROK2 hsa-miR-182 ANK2 hsa-miR-34a FOXQ1 hsa-miR-552 ENC1 hsa-miR-429 PVRL4 hsa-miR-182 CBFA2T3 hsa-miR-34a GALNT7 hsa-miR-552 SGK1	hsa-miR-429	NAP1L5	hsa-miR-200c	TNFSF8	hsa-miR-34a	CBFA2T3	hsa-miR-92b	SOX4
hsa-miR-429 PPAP2B hsa-miR-182 ADAM10 hsa-miR-34a FKBP1B hsa-miR-552 DCUN1D3 hsa-miR-429 PROK2 hsa-miR-182 ANK2 hsa-miR-34a FOXQ1 hsa-miR-552 ENC1 hsa-miR-429 PVRL4 hsa-miR-182 CBFA2T3 hsa-miR-34a GALNT7 hsa-miR-552 SGK1	hsa-miR-429	PHF17	hsa-miR-671-5p	PHF17	hsa-miR-34a	DKKI	hsa-miR-92b	STK39
hsa-miR-429 PROK2 hsa-miR-182 ANK2 hsa-miR-34a FOXQ1 hsa-miR-552 ENC1 hsa-miR-429 PVRL4 hsa-miR-182 CBFA2T3 hsa-miR-34a GALNT7 hsa-miR-552 SGK1	hsa-miR-429	PPAP2B	hsa-miR-182	ADAM10	hsa-miR-34a	FKBP1B	hsa-miR-552	DCUNID3
hsa-miR-429 PVRL4 hsa-miR-182 CBFA2T3 hsa-miR-34a GALÑT7 hsa-miR-552 SGK1	hsa-miR-429	PROK2	hsa-miR-182	ANK2	hsa-miR-34a	FOXQ1	hsa-miR-552	ENCI
	hsa-miR-429	PVRL4	hsa-miR-182	CBFA2T3	hsa-miR-34a	$GAL\tilde{N}T7$	hsa-miR-552	SGK1

GO analysis revealed many significantly enriched biological processes, including wound response and healing, cell adhesion, biological adhesion, inflammatory response, and response to corticosteroid stimulus. The KEGG pathway-enrichment analysis revealed a sig-

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nificant overexpression of the o-glycan biosynthesis pathway, cell adhesion molecules, arrhythmogenic right ventricular cardiomyopathy, and tight junction, in the early-stage PDAC samples. Pancreatic ductal adenocarcinoma is characterized by early loco-regional spread and distant metastasis. The development of metastasis is determined by the gradual increase in essential changes in cancerous cells, as well as their communications with different stromal elements in the tumor microenvironment. Cell adhesion and biological adhesion play significant roles in cancer metastasis. Moreover, the inflammatory response and the migration of the myeloid (macrophages, dendritic cells, neutrophils, myeloid-derived suppressor cells) and lymphoid (regulatory T, B and NK cells) immune regulatory cells to the tumor site have been reported to support tumor growth, spread of tumor, and tumor metastasis (Keskinov and Shurin, 2014).



Figure 2. miRNA-mRNA regulation network. Red nodes represent genes and bright green nodes represent miRNAs.

The target genes regulated by the differentially expressed miRNA and mRNA were then identified and further analyzed, in order to define their relationship with miRNA and mRNA; subsequently, an miRNA-mRNA regulatory network was constructed.

A thorough analysis of the regulatory network revealed an extremely high node degree of *hsa-miR-200c*, *hsa-miR-429*, *and hsa-miR-200b* (miRNA), and *EFNB2*, *MYRIP*, and *PHF17* (mRNA), which indicated that these miRNA and mRNA may play a key role in the development of pancreatic cancer. The miR-200 family (*miR-200a*, *miR-200b*, *miR-200c*, *miR-141*, and *miR-429*) is a cluster of miRNA that are highly correlated with epithelial-mesenchymal transition, with *miR-200b* being identified as a critical regulator of tumor invasion,

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Node	Degree	Node	Degree
isa-miR-671-5p	1	НОХВ3	2
LIFR	1	SIPRI	2
AYO6	1	STK39	2
ASH1	1	hsa-miR-489	3
CREM	1	hsa-miR-874	3
H3RFI	1	hsa-miR-552	3
CEP55	1	GHR	3
PY19L2	1	RAR39R	3
TGA2	1	ENBPII	3
DDFY1	1	PHPN2	3
TALAI TOCS2	1		2
	1	ADAMISS	3
LBF1	1	EFNAI LHOZ	3
PIP4K2C	l	LMO/	3
KIAA0101	I	LRRC8A	3
PIMI	1	MBOAT2	3
CF7L2	1	PVRL4	3
CTTN	1	TNFSF8	3
ELMO1	1	ACSL1	3
FGR	1	FKBP1B	3
ARHGAP12	1	IRSI	3
CAMK2NI	1	CBFA2T3	3
GRHL2	1	FOXO1	3
3ZRAPI	1	GALNT7	3
DCLKI	1	SOX4	3
DI FKH 47	1	hsa-miR-425	4
	1	hsa miP 608	4
4D 4M0	1	haa miB 526a	4
	1	nsa-mik-520a	4
ADRB2	1	ANLN	4
KCNS3	l	NAPIL2	4
MXRA5	1	NAP1L5	4
SH2B3	1	PROK2	4
EGLN3	1	NRNI	4
SOX9	1	NHS	4
CNNM4	1	hsa-miR-222	5
DNAJB9	1	hsa-miR-183	5
EDNRB	1	CDR2L	5
SGK1	1	DCUN1D3	5
4D 4MTS9	2	TF4P24	5
	2	NPAA3	5
EMD1	2		5
	2	ANK2 haa miB 21	5
RPM4	2	nsa-mik-21	6
AM46C	2	PPAP2B	6
HOXB5	2	PHF17	7
TGA6	2	MYRIP	7
RAB27B	2	hsa-miR-488	8
WNT5A	2	hsa-miR-135b	9
GRAMD3	2	hsa-miR-135a	9
PLEKHAI	2	hsa-miR-28-5p	9
PAKI	2	EFNB2	9
EFNA5	2	hsa-miR-200a	10
VFIL3	$\frac{1}{2}$	hsa-miR-96	10
TOX3		hsa-miR-141	11
NCI	2	haa m; D 202	11
	2	hsa-mik-203	12
IDAM10	2	nsa-miR-182	13
CIAA1217	2	hsa-miR-92b	13
ICSL4	2	hsa-miR-34c-5p	15
DKK1	2	hsa-miR-34a	15
AKMIPI	2	hsa-miR-200b	16
IARCKSL1	2	hsa-miR-429	16
NR4A2	2	hsa-miR-200c	16
-	-		10

The degree of genes is the number of miRNA that directly interact with it, while the degree of miRNA is denoted by the number of genes that directly interact with it.

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metastasis, and chemosensitivity (Feng et al., 2012). The miR-200 family is associated with the acquisition of epithelial-to-mesenchymal transition and gemcitabine sensitivity in pancreatic adenocarcinoma (Li et al., 2009; Ali et al., 2010; Bao et al., 2011). Previous studies have reported the close association of *EFNB2* with the development of gastric cancer, neuroblastomas, esophageal squamous cell carcinoma, and other tumors (Tang et al., 1999, 2000; Kataoka et al., 2002; Tachibana et al., 2007). However, the relationship between specific genes and pancreatic adenocarcinoma has been rarely reported. We believe that these genes could be potential targets for the diagnosis and treatment of pancreatic adenocarcinoma. In summary, this study provides important information to facilitate the elucidation of the physiological and pathological processes governing pancreatic adenocarcinoma. However, the roles played by these genes in pancreatic adenocarcinoma must be further validated *in vitro* and *in vivo*, using the latest molecular biology techniques.

Conflicts of interest

The authors declare no conflict of interest.

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