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Lung Cancer-Specific Circular RNAs as Biomarkers

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14. ABSTRACT

The major goal of this application is to determine whether lung cancer cells differentially express circular RNAs such that these circular RNAs may serve as novel biomarkers for lung cancer diagnosis and prognosis. There are two Tasks in this application. First, we will perform microarray profiling to determine whether lung cancer cells display different patterns of circular RNAs from those of normal cells. Second, we will determine whether differential expression of circular RNAs can also be detected in cell culture models. Third, we will determine whether circular RNAs can be detected in circulation system. The success of this study may lead to novel clinical applications such as identification of biomarkers or therapeutic targets for lung cancer.

15. SUBJECT TERMS
lncRNA, circRNA, biomarker

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Introduction

Circular RNAs (circRNAs) belong to a special group of long non-coding RNAs (lncRNAs). Although in some cases, circRNAs can code for protein, most of them lack the coding capacity. circRNAs are formed from lncRNAs or protein coding genes often through back splicing. There are five types of circRNA derived from: 1) exonic, 2) intronic, 3) antisense, 4) sense overlapping and 5) intergenic. "Exonic" represents circRNA arising from the exons of the linear transcript; "Intronic" represents the circRNA arising from an intron of the linear transcript; "antisense" represents circRNA whose gene locus overlap with the linear RNA, but transcribed from the opposite strand; "sense overlapping" represents circRNA transcribed from same gene locus as the linear transcript, but not classified into "exonic" and "intronic"; lastly, "intergenic" represents circRNA located outside known gene locus.

Despite different types of circRNAs, they all can play a regulatory role in gene expression through microRNA-mediated repression. Thus, we hypothesize that lung cancer may exploit this mechanism for its own advantage and as such lung cancer may display a very different circRNA pattern from normal lung cells Therefore, the major goal of this application is to determine whether we can identify differentially expressed circRNAs in lung cancer.

Body

Three major tasks were listed in SOW as below

Major Task 1: to determine whether lung cancer cells display different patterns of circRNAs from those of normal tissue.

Major Task 2: to determine whether differential expression of circRNAs can also be detected in cell culture models.

Major Task 3: to detect circRNAs in blood/serum samples from healthy individuals and lung cancer patients.

Results

Major Task 1: (complete)
Major Task 2: (complete)
Major Task 3: (complete)

We found that numerous number of circular RNAs are dysregulated in tumor cells as compared to normal tissues (Fig. 1).

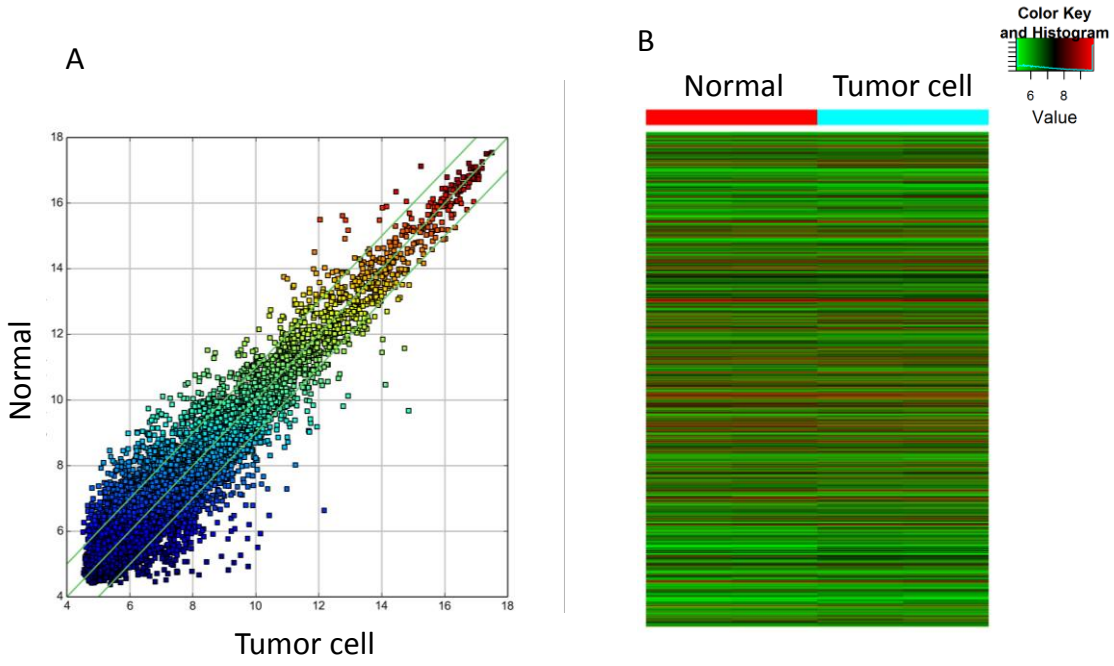

Fig. 1 Dysregulation of circular RNAs in tumor cells. A, Scatter plot analysis of microarray data. B, Heatmap of dysregulated circular RNAs.

For example, we found that >500 circular RNAs are upregulated and >300 circular RNAs are downregulated in tumor cells. Top 30 upregulated and top 30 downregulated circRNAs were listed in Table 1 and Table 2, respectively. For example, hsa_circRNA_400633 and

hsa_circRNA_101100 were upregulated with over an 8-fold increase in tumor vs normal. On the other hand, the expression level of hsa_circRNA_005054 and hsa_circRNA_001831 was 0.02 and 0.03, respectively, as compared to normal cells as 1. Several interesting findings from two tables are: 1) The source to generate circRNAs are very heterogeneous. Some circRNAs are derived from exons, and others are derived from introns. They can be in sense or antisense related to parental genes; 2) Although both coding genes and non-coding genes can lead to production of circRNAs, most of circRNAs are derived from coding genes; 3) Multiple microRNAs can interact with a given circRNA.

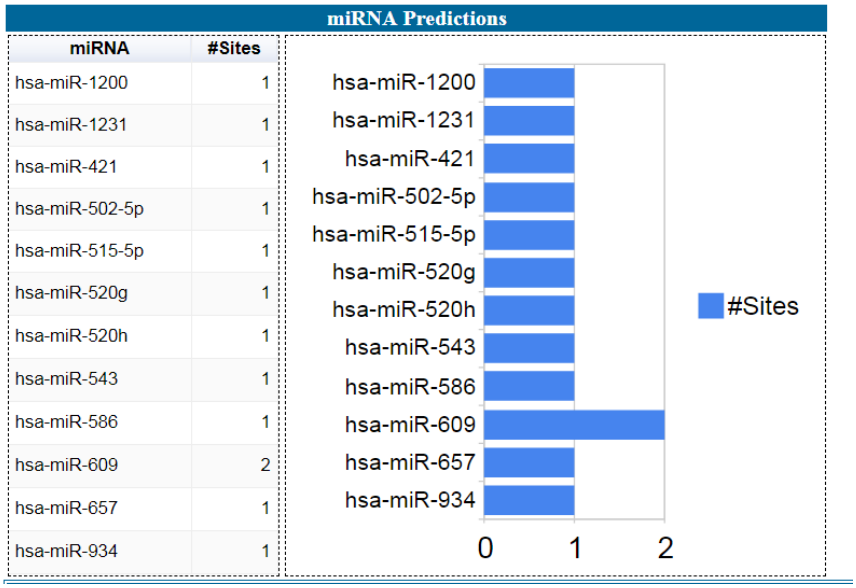

Fig. 2 MicroRNA binding sites for hsa_circ_0004788

aatgatgtctatgaatgggctcgtgaccaccgtgcccaccacaagttttcagaa
acacatgctgatcctcataattcccgacgtggctttttcttctctcacgtgggt
tggctgcttgtgcgcaaacacccagctgtcaaagagaaggggagtacgctagac
ttgtctgacctagaagctgagaaactggtgatgttccagaggag

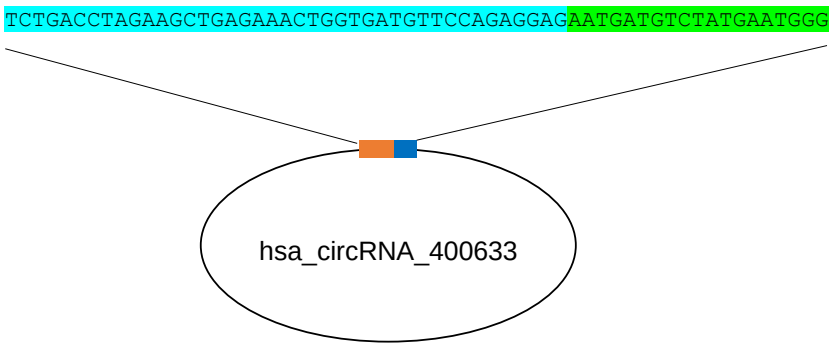

Fig. 3 DNA sequence of hsa_circRNA_400633. The junction of two ends is highlighted by red and blue, respectively.

To better elucidate this point, we listed hsa_circ_0004788 as an example. hsa_circ_0004788 can interact with 12 microRNAs (Fig. 2). Among them, there were 2 binding sites for miR-609, whereas the rest of microRNAs had one

binding site. We also provided the sequence for hsa_circRNA_400633 and hsa_circRNA_101100, as shown in Figs. 3 and 4, respectively to demonstrate how the circular form is formed. The top part is the actual sequence and the bottom part is when a circle is formed. Two ends at the junction were highlighted by green and blue, respectively.

gaagggaaatggatactgcaagaacgccattgagtgaagctgaattttgaagaaatcatgaataga
aatagggcaatctcaagcagtgctatttcgagagctgtgtctgatgccagtgctggtgattatgg
gagtgctattgagacactggtaactgcaatttctttaattaaacaatccaaagtatctgctgatg
atcgttgcaaagttcttattagttctttgcaagattgccttcatggaattgagtccaagtcttat
ggttctggatcaagacgtgaacgatcaagagagagggaccatagtagatcacgagaaaagagtcg
acgtcataaatcccgtagtagagaccgtcatgacgattattacagagagagaagcagagaacgag
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cgtta

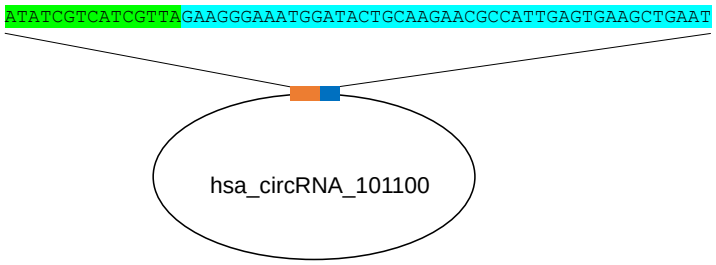

Fig. 4 DNA sequence of hsa_circRNA_101100. The junction of two ends is highlighted by blue and green, respectively.

To validate whether circRNAs can serve as sponges for microRNAs, we used RNAi approach to knockdown hsa_circRNA_101100. As shown in Fig. 5, we found that two microRNAs, miR-384 and miR-607, were upregulated after hsa_circRNA_101100 knockdown, suggesting that these microRNAs are potential targets for hsa_circRNA_101100.

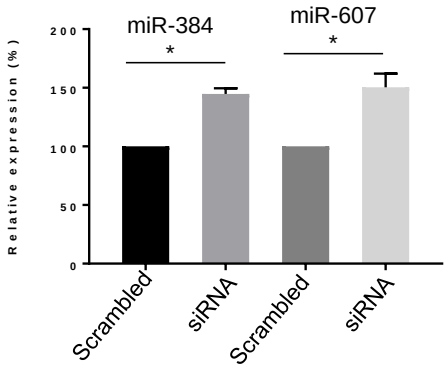

Fig. 5 Knockdown of hsa_circRNA_101100 upregulates miR-384 and miR-607. Values are means ± standard error. *, $p < 0.05$.

Finally, we selected three upregulated circRNAs (hsa_circRNA_400633, hsa_circRNA_101100, and hsa_circRNA_008817) and three downregulated circRNAs (hsa_circRNA_005054, hsa_circRNA_001831, and hsa_circRNA_104864) to examine their expression in clinical serum samples. Among 10 normal and 10 tumor serum samples, we found hsa_circRNA_101100 was slightly increased as compared to normal serum samples' for the downregulated group, we found that the level of hsa_circRNA_005054 was lower in tumor than normal serum, as expected, however, the difference was not statistically significant. It was not

detectable for the rest of 4 circRNAs, suggesting that overall, their expression is very low in serum samples.

Key Research Accomplishments

- We identified over 500 upregulated and >300 downregulated circRNAs from lung cancer cells through profiling.
- All of these identified circRNAs carry microRNA binding sites, through which they may regulate the level of endogenous microRNAs.
- Each circRNA carries multiple microRNA binding sites, suggest that they are potential targets for circRNAs
- Validation experiments with RNAi suggest that hsa_circRNA_101100 is a target for miR-384 and miR-607.
- Some circRNAs are detected in clinical serum samples; their clinical relevance needs further validation with large samples.

Reportable Outcomes

Not yet.

Conclusions

Microarray profiling has identified many dysregulated circRNAs from lung cancer cells. Most of them are derived from exonic regions of coding genes. Cell culture models demonstrated that circRNAs such as hsa_circRNA_101100 can negatively regulate miR-384 and miR-607. Future

work will determine whether a selected group of dysregulated circRNAs can be detected in a large number of clinical specimens.

Appendices
Table 1 and 2

Table 1 Upregulated circRNAs

circRNA	Alias	Fold change	circRNA_type
hsa_circRNA_400633		8.8717345	exonic
hsa_circRNA_101100	hsa_circ_0027506	8.5565076	exonic
hsa_circRNA_008817	hsa_circ_0008817	8.3475217	exonic
hsa_circRNA_100313	hsa_circ_0013737	8.2858994	exonic
hsa_circRNA_102710	hsa_circ_0054404	8.216709	exonic
hsa_circRNA_102759	hsa_circ_0055151	7.5807947	exonic
hsa_circRNA_101460	hsa_circ_0034067	7.2716958	exonic
hsa_circRNA_103417	hsa_circ_0004788	7.2709711	exonic
hsa_circRNA_405236		7.1481941	exonic
hsa_circRNA_103049	hsa_circ_0060158	6.8910635	exonic
hsa_circRNA_104686	hsa_circ_0085540	6.837951	exonic
hsa_circRNA_008849	hsa_circ_0008849	6.7378653	exonic
hsa_circRNA_101099	hsa_circ_0000417	6.7359531	exonic
hsa_circRNA_001354	hsa_circ_0001354	6.7097547	antisense
hsa_circRNA_049537	hsa_circ_0049537	6.6157519	exonic
hsa_circRNA_000006	hsa_circ_0001821	6.4885751	exonic
hsa_circRNA_008147	hsa_circ_0008147	6.4709223	intronic
hsa_circRNA_101488	hsa_circ_0000591	6.459583	exonic
hsa_circRNA_001379	hsa_circ_0000516	6.4593638	antisense
hsa_circRNA_054345	hsa_circ_0054345	6.4410606	exonic
hsa_circRNA_104333	hsa_circ_0001685	6.4307686	exonic
hsa_circRNA_402378		6.353686	exonic
hsa_circRNA_102737	hsa_circ_0001017	6.349647	exonic
hsa_circRNA_104518	hsa_circ_0005284	6.1885252	exonic
hsa_circRNA_001589	hsa_circ_0001589	6.0735159	sense overlapping
hsa_circRNA_006497	hsa_circ_0006497	5.9542017	exonic
hsa_circRNA_103091	hsa_circ_0060927	5.9138676	exonic
hsa_circRNA_400056	hsa_circ_0092297	5.911205	intronic
hsa_circRNA_000482	hsa_circ_0001829	5.8708066	exonic
hsa_circRNA_079614	hsa_circ_0079614	5.7385499	exonic

best_transcript	GeneSymbol	MRE1	MRE2	MRE3
NM_005063	SCD	hsa-miR-5589-5p	hsa-miR-1253	hsa-miR-3127-3p
NM_007007	CPSF6	hsa-miR-183-5p	hsa-miR-383-3p	hsa-miR-433-3p
NM_004902	RBM39	hsa-miR-6885-3p	hsa-miR-6809-3p	hsa-miR-6844
NM_006699	MAN1A2	hsa-miR-95-5p	hsa-miR-410-5p	hsa-miR-325
NM_133259	LRPPRC	hsa-miR-103a-2-5p	hsa-miR-589-5p	hsa-miR-22-5p
NM_014497	ZNF638	hsa-miR-19b-2-5p	hsa-miR-501-5p	hsa-miR-103a-2-5p
NM_014608	CYFIP1	hsa-miR-802	hsa-miR-586	hsa-miR-7-2-3p
NM_002941	ROBO1	hsa-miR-597-3p	hsa-miR-502-5p	hsa-miR-33a-5p
NM_004986	KTN1	hsa-miR-4639-3p	hsa-miR-335-3p	hsa-miR-135a-5p
NM_016436	PHF20	hsa-miR-627-3p	hsa-miR-374a-3p	hsa-miR-7-5p
uc003ysl.3	PVT1	hsa-miR-493-3p	hsa-miR-455-5p	hsa-miR-526b-5p
ENST00000522875	PVT1	hsa-miR-6773-3p	hsa-miR-1288-5p	hsa-miR-30c-1-3p
NM_007007	CPSF6	hsa-miR-665	hsa-miR-765	hsa-miR-328-5p
NM_015508	TIPARP	hsa-miR-922	hsa-miR-145-3p	hsa-miR-6810-5p
NM_016145	WDR83OS	hsa-miR-214-3p	hsa-miR-328-5p	hsa-miR-3619-5p
uc003ysl.3	PVT1	hsa-miR-526b-5p	hsa-miR-595	hsa-miR-181a-2-3p
ENST00000512617	PVT1	hsa-miR-3916	hsa-miR-153-5p	hsa-miR-1303
NM_001080541	MGA	hsa-miR-130b-3p	hsa-miR-182-5p	hsa-miR-205-3p
NR_002312	RPPH1	hsa-miR-18b-3p	hsa-miR-670-5p	hsa-miR-23a-5p
NM_133259	LRPPRC	hsa-miR-4307	hsa-miR-506-5p	hsa-miR-6719-3p
NM_016447	MPP6	hsa-miR-188-3p	hsa-miR-140-5p	hsa-miR-578
NM_052905	FMNL2	hsa-miR-301a-3p	hsa-miR-301b-3p	hsa-miR-454-3p
NM_003400	XPO1	hsa-miR-221-3p	hsa-miR-599	hsa-miR-145-5p
NM_001203248	EZH2	hsa-miR-495-3p	hsa-miR-30a-3p	hsa-miR-30e-3p
NM_005320	HIST1H1D	hsa-miR-6876-3p	hsa-miR-3922-3p	hsa-miR-6813-5p
NM_002093	GSK3B	hsa-miR-3140-5p	hsa-miR-6735-3p	hsa-miR-214-5p
NM_000782	CYP24A1	hsa-miR-224-3p	hsa-miR-29b-1-5p	hsa-miR-522-3p
ENST00000339679	SMPD4	hsa-miR-767-3p	hsa-miR-654-5p	hsa-miR-329-3p
NM_001286646	SLC45A4	hsa-miR-335-3p	hsa-miR-194-5p	hsa-miR-15a-5p
uc003swx.3	MPP6	hsa-miR-4659b-3p	hsa-miR-4659a-3p	hsa-miR-329-5p

MRE4	MRE5
hsa-miR-541-3p	hsa-miR-3691-3p
hsa-miR-607	hsa-miR-640
hsa-miR-942-5p	hsa-miR-3160-5p
hsa-miR-146a-3p	hsa-miR-494-5p
hsa-miR-202-5p	hsa-miR-601
hsa-miR-19b-1-5p	hsa-miR-429
hsa-miR-7-1-3p	hsa-miR-105-5p
hsa-miR-1185-1-3p	hsa-miR-657
hsa-miR-135b-5p	hsa-miR-6867-3p
hsa-miR-103a-2-5p	hsa-miR-127-3p
hsa-miR-595	hsa-miR-181a-2-3p
hsa-miR-4715-5p	hsa-miR-5582-3p
hsa-miR-323a-5p	hsa-miR-608
hsa-miR-548aq-5p	hsa-miR-26b-3p
hsa-miR-761	hsa-miR-6808-5p
hsa-miR-449b-3p	hsa-miR-30c-5p
hsa-miR-1273g-3p	hsa-miR-6782-5p
hsa-miR-492	hsa-miR-222-5p
hsa-miR-125a-3p	hsa-miR-125b-5p
hsa-miR-19b-1-5p	hsa-miR-19b-2-5p
hsa-miR-411-5p	hsa-miR-541-5p
hsa-miR-3912-3p	hsa-miR-4643
hsa-miR-23a-3p	hsa-miR-197-3p
hsa-miR-26a-1-3p	hsa-miR-30d-3p
hsa-miR-27a-5p	hsa-miR-6882-3p
hsa-miR-4705	hsa-miR-6753-3p
hsa-miR-661	hsa-miR-1264
hsa-miR-362-3p	hsa-miR-296-3p
hsa-miR-557	hsa-miR-548c-3p
hsa-miR-216b-5p	hsa-miR-4698

Table 2 Downregulated circRNAs

circRNA	Alias	fold change	circRNA_type	best_transcript
hsa_circRNA_005054	hsa_circ_0005054	0.021582688	exonic	NM_001103184
hsa_circRNA_001831	hsa_circ_0001831	0.027614555	antisense	NM_015356
hsa_circRNA_104864	hsa_circ_0003611	0.035251883	exonic	NM_057159
hsa_circRNA_100258	hsa_circ_0008433	0.042563402	exonic	NM_002600
hsa_circRNA_103729	hsa_circ_0002474	0.050452451	exonic	NM_001083
hsa_circRNA_005752	hsa_circ_0005752	0.052095151	intronic	uc011lwn.2
hsa_circRNA_104865	hsa_circ_0004928	0.05258166	exonic	uc010mub.3
hsa_circRNA_100833	hsa_circ_0022383	0.053792785	exonic	NM_004265
hsa_circRNA_101474	hsa_circ_0034510	0.064238291	exonic	NM_003246
hsa_circRNA_007444	hsa_circ_0007444	0.064899457	exonic	NM_014899
hsa_circRNA_104980	hsa_circ_0001910	0.07826109	exonic	NM_015691
hsa_circRNA_044097	hsa_circ_0044097	0.079673142	exonic	NM_004247
hsa_circRNA_101833	hsa_circ_0039908	0.083453687	exonic	NM_017803
hsa_circRNA_104863	hsa_circ_0002890	0.086761589	exonic	NM_001401
hsa_circRNA_101038	hsa_circ_0025768	0.096401254	exonic	NM_175861
hsa_circRNA_102673	hsa_circ_0053907	0.098118749	exonic	NM_000627
hsa_circRNA_403382		0.104427316	exonic	NM_006909
hsa_circRNA_000122	hsa_circ_0000122	0.106223219	intronic	NM_001039703
hsa_circRNA_089866	hsa_circ_0089866	0.107523664	exonic	NM_015691
hsa_circRNA_087964	hsa_circ_0087964	0.109297461	exonic	uc010mub.3
hsa_circRNA_091000	hsa_circ_0091000	0.118038672	exonic	uc004dzq.3
hsa_circRNA_100332	hsa_circ_0014130	0.128798327	exonic	NM_003557
hsa_circRNA_403044		0.135266466	exonic	NM_021627
hsa_circRNA_407249		0.140883369	intronic	ENST00000357304
hsa_circRNA_034537	hsa_circ_0034537	0.141487678	exonic	NM_003246
hsa_circRNA_103728	hsa_circ_0070805	0.147099786	exonic	NM_001083
hsa_circRNA_064335	hsa_circ_0064335	0.148638092	exonic	NM_138711
hsa_circRNA_010575	hsa_circ_0010575	0.149483639	exonic	NM_005529
hsa_circRNA_102674	hsa_circ_0053932	0.149872124	exonic	NM_000627
hsa_circRNA_008337	hsa_circ_0008337	0.151058775	exonic	NM_004318

GeneSymbol	MRE1	MRE2	MRE3	MRE4
FMN1	hsa-miR-612	hsa-miR-6515-3p	hsa-miR-4753-5p	hsa-miR-362-5p
SCRIB	hsa-miR-3151-5p	hsa-miR-6791-5p	hsa-miR-939-5p	hsa-miR-637
LPAR1	hsa-miR-7-5p	hsa-miR-588	hsa-miR-135a-3p	hsa-miR-608
PDE4B	hsa-miR-34c-5p	hsa-miR-34b-5p	hsa-miR-34a-5p	hsa-miR-449b-5p
PDE5A	hsa-miR-670-3p	hsa-miR-583	hsa-miR-455-3p	hsa-miR-510-3p
LPAR1	hsa-miR-153-5p	hsa-miR-3924	hsa-miR-3145-3p	hsa-miR-548az-5p
LPAR1	hsa-miR-135a-3p	hsa-miR-7-5p	hsa-miR-588	hsa-miR-383-5p
FADS2	hsa-miR-765	hsa-miR-495-3p	hsa-miR-665	hsa-miR-193b-5p
THBS1	hsa-miR-25-3p	hsa-miR-196a-5p	hsa-miR-597-3p	hsa-miR-196b-5p
RHOBTB3	hsa-miR-4778-3p	hsa-miR-4773	hsa-miR-6875-3p	hsa-miR-424-5p
WWC3	hsa-miR-26b-3p	hsa-miR-660-3p	hsa-miR-1298-3p	hsa-miR-596
EFTUD2	hsa-miR-1909-3p	hsa-miR-4711-5p	hsa-miR-6722-3p	hsa-miR-6735-5p
DUS2	hsa-miR-590-5p	hsa-miR-21-5p	hsa-miR-654-3p	hsa-miR-640
LPAR1	hsa-miR-588	hsa-miR-140-3p	hsa-miR-7-5p	hsa-miR-198
TMTC1	hsa-miR-449a	hsa-miR-449b-5p	hsa-miR-449c-5p	hsa-miR-34c-5p
LTBP1	hsa-miR-579-3p	hsa-miR-584-3p	hsa-miR-490-3p	hsa-miR-29b-2-5p
RASGRF2	hsa-miR-216a-3p	hsa-miR-764	hsa-miR-6804-5p	hsa-miR-5701
NBPF10	hsa-miR-627-3p	hsa-miR-510-5p	hsa-miR-552-3p	hsa-miR-4695-3p
WWC3	hsa-miR-1914-5p	hsa-miR-556-5p	hsa-miR-3692-5p	hsa-miR-4268
LPAR1	hsa-miR-4646-5p	hsa-miR-130b-5p	hsa-miR-4251	hsa-miR-6830-3p
NONO	hsa-miR-197-5p	hsa-miR-103a-2-5p	hsa-miR-4778-3p	hsa-miR-7851-3p
PIP5K1A	hsa-miR-892a	hsa-miR-216a-3p	hsa-miR-302c-3p	hsa-miR-493-5p
SENP2	hsa-miR-3121-5p	hsa-miR-3692-3p	hsa-miR-6504-3p	hsa-miR-1324
PRRC2B	hsa-miR-5008-5p	hsa-miR-6728-3p	hsa-miR-4741	hsa-miR-6828-3p
THBS1	hsa-miR-3613-3p	hsa-miR-198	hsa-miR-4668-5p	hsa-miR-6830-3p
PDE5A	hsa-miR-153-5p	hsa-miR-29b-1-5p	hsa-miR-670-3p	hsa-miR-199b-5p
PPARG	hsa-miR-3606-5p	hsa-miR-3160-3p	hsa-miR-3188	hsa-miR-3129-5p
HSPG2	hsa-miR-661	hsa-miR-4763-3p	hsa-miR-3620-5p	hsa-miR-6791-5p
LTBP1	hsa-miR-339-5p	hsa-miR-500a-3p	hsa-miR-503-3p	hsa-miR-491-3p
ASPH	hsa-miR-22-5p	hsa-miR-3692-5p	hsa-miR-670-3p	hsa-miR-384

MRE5

hsa-miR-450a-2-3p
hsa-miR-7974
hsa-miR-140-3p
hsa-miR-449a
hsa-miR-500a-5p
hsa-miR-8067
hsa-miR-620
hsa-miR-124-5p
hsa-miR-892a
hsa-miR-3978
hsa-miR-21-3p
hsa-miR-939-3p
hsa-miR-572
hsa-miR-584-3p
hsa-miR-629-3p
hsa-miR-665
hsa-miR-3126-3p
hsa-miR-503-3p
hsa-miR-4640-5p
hsa-miR-3124-3p
hsa-miR-4436b-5p
hsa-miR-200c-5p
hsa-miR-4436a
hsa-miR-661
hsa-miR-3916
hsa-miR-29a-5p
hsa-miR-5680
hsa-miR-939-5p
hsa-miR-764
hsa-miR-598-3p