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# Screening the key microRNAs and transcription factors in prostate cancer based on microRNA functional synergistic relationships

Fan Feng, MM, Jitao Wu, MD, Zhenli Gao, MM, Shengqiang Yu, MD, Yuanshan Cui, MM\*

#### Abstract

Prostate cancer (PC) is a common neoplasm, and metastatic PC remains incurable. The study aims to screen key microRNAs (miRNAs) and transcription factors (TFs) involved in PC.

The miRNA expression profile dataset (GSE45604) was downloaded from Gene Expression Omnibus database, including 50 PC and 10 normal specimens. Differentially expressed miRNAs (DEmiRNAs) were identified through limma package in R, and DEmiRNA–DEmiRNA co-regulation network was constructed based on the number of co-regulated target genes. Functional enrichment analysis of co-regulated target genes was performed using clusterProfiler package in R, and miRNA interactions sharing at least 1 functional term were used to construct a DEmiRNA–DEmiRNA functional synergistic network (MFSN). Based on Transcriptional Regulatory Element Database, cancer-related TFs which were co-regulated by DEmiRNAs were utilized to construct a DEmiRNA–TF regulation network.

A total of 66 DEmiRNAs were identified, including 7 up-regulated miRNAs with 18,642 target genes and 59 down-regulated miRNAs with 130,694 target genes. Then, the DEmiRNA–DEmiRNA co-regulation network was constructed, including 66 DEmiRNAs and 2024 co-regulation relationships. In MFSN, hsa-miR-1184, hsa-miR-1207-5p, and hsa-miR-24 had significant functional synergistic relationships. The DEmiRNA–TF network contained 6 up-regulated DEmiRNAs and 4 of them were highlighted, as hsa-miR-1184, hsa-miR-1207-5p, hsa-miR-182, and hsa-miR-183. In subnetwork of the 4 miRNAs, peroxisome proliferative activated receptor, alpha (PPARA) and cyclic AMP-responsive element modulator (CREM) were the critical regulated TFs.

Four up-regulated miRNAs (hsa-miR-1207-5p, hsa-miR-1184, hsa-miR-182, and hsa-miR-183) and 2 TFs (PPARA and CREM) were identified as key regulators in PC progression. The above 4 miRNAs might participate in PC progression by targeting PPARA and CREM.

**Abbreviations:** BP = biological process, COX2 = cyclooxygenase 2, CREM = cyclic AMP-responsive element modulator, DEmiRNA = differentially expressed miRNAs, DKK3 = dickkopf 3 homolog, FC = fold change, FDR = false discovery rate, GO = gene ontology, MFSN = DEmiRNA–DEmiRNA functional synergistic network, miRNAs = microRNAs, NFKB1 = nuclear factor of kappa light polypeptide, PC = prostate cancer, PPARA = peroxisome proliferative activated receptor, alpha, pT = pathological, RAS = p21 ras, SMAD4 = drosophila mothers against decapentaplegic family member 4, TF = transcription factor, TRED = Transcriptional Regulatory Element Database.

Keywords: differentially expressed microRNAs, functional enrichment analysis, functional synergistic network, prostate cancer, transcription factor

#### Editor: Maohua Xie.

FF and JW are the co-first authors.

Conceived and designed the experiments: YC and FF; acquired and analyzed the data: FF, JW, and ZG; drafted the manuscript: SY; and approved the manuscript: YC.

This study was funded by the Nature Science Foundation of Shandong Province (grant number ZR2015PH033) and the National Natural Science Foundation of China (grant number 81572835 and 81302234).

The authors have no conflicts of interest to disclose.

Department of Urological Surgery, Yantai Yuhuangding Hospital, Yantai, Shandong, China.

<sup>\*</sup> Correspondence: Yuanshan Cui, Department of Urological Surgery, Yantai Yuhuangding Hospital, Yuhuangding Dong Road 20, Yantai, Shandong 264000, China (e-mail: fengurology@126.com).

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Medicine (2017) 96:1(e5679)

Received: 21 September 2016 / Received in final form: 16 November 2016 / Accepted: 27 November 2016

http://dx.doi.org/10.1097/MD.000000000005679

#### 1. Introduction

Prostate cancer (PC) is a slowly developed malignancy among men that could become more aggressive in response to androgen blockade.<sup>[1]</sup> PC is the most prevalent nonskin cancer and the second leading cause of cancer-related deaths in men.<sup>[2]</sup> Although effective surgical and radiation treatments have been clinically utilized, metastatic PC remains incurable.<sup>[3]</sup> Better understanding of the molecular mechanism of PC is beneficial for development of novel therapeutic targets. Thus, several studies have been investigated to reveal the molecular mechanisms. For instance, frequent and large-scale genomic rearrangements have been identified in PC tissue.<sup>[4]</sup> Catechol-O-methyltransferase and glutathione reductase are less active in PC.<sup>[5]</sup> Sex-steroid hormone, androgens, and estrogens play regulatory roles in PC progression.<sup>[6]</sup> Testosterone is carcinogenic for rat prostate, as testosterone could be converted to reactive metabolites which adduct to DNA and potentially lead to mutations.<sup>[5]</sup> Estradiol and estrone are converted to estrogen semiquinones and estrogen quinones which adduct to DNA and redox cycling, producing reactive oxygen species and damaging DNA.<sup>[7]</sup> Therefore, androgen receptor, enzymes involved in androgens and estrogens metabolism, and DNA repair-related genes are critical for PC progression.<sup>[2,8–10]</sup>

In addition to hormone-related metabolites and genes, micro-RNAs (miRNAs) also play critical roles in PC progression. MiRNAs are small regulatory RNAs which post-transcriptionally repress the expression of target genes by binding to mRNA sequences and promoting mRNA degradation.<sup>[11]</sup> Widespread down-regulation of miR-125b, miR-145, and let-7c has been found in human PC tissue.<sup>[11]</sup> Moreover, it is reported that the target genes of these down-regulated miRNAs are up-regulated in PC tissue, including RAS (p21 ras), E2F transcription factor 3, Bcell lymphoma 2, and myeloid cell leukemia-1.<sup>[11]</sup> Therefore, screening abnormally expressed miRNAs should be highlighted in the understanding of PC mechanism. Moreover, miRNAs are highly related to the transcription factors (TFs) for the control of gene expressions. The TFs regulate gene expressions at transcriptional level, while the miRNAs at post-transcriptional level.<sup>[12]</sup> Interestingly, they could be regulated by each other: TF could modulate miRNA-mediated expression via certain pathways; and miRNAs could also regulate the TF-mediated issues to inactivate the target genes.<sup>[12]</sup> In PC, it is found the miRNAs coordinate with TFs to regulate genes in some transcriptional pathways.<sup>[13]</sup> However, the direct regulation between miRNAs and TFs are rarely reported. Therefore, we focused on the correlations between miRNAs and TFs in PC progression. In this study, differentially expressed miRNAs (DEmiRNAs) between PC and normal specimens were identified by using bioinformatics tools, and DEmiRNA-DEmiRNA co-regulation network was constructed. Then, DEmiRNA-DEmiRNA functional synergistic network (MFSN) was built based on gene ontology (GO) biological process (BP) functional categories that were enriched by the target genes of DEmiRNAs. Following that, a DEmiRNA-TF regulation network was constructed among the cancer-related TFs and their corresponding DEmiRNAs, and key DEmiRNAs and TFs were identified by analyzing these networks. This study might help researchers to understand the mechanism of PC at molecular level.

## 2. Materials and methods

#### 2.1. Microarray data

The miRNAs expression profile dataset GSE45604<sup>[14]</sup> was downloaded from Gene Expression Omnibus database (http://www.ncbi.nlm.nih.gov/geo/). The data derived from 60 specimens (10 normal persons and 50 PC patients before treatment) were available based on platform GPL14613 ([miRNA-2\_0] Affymetrix Multispecies miRNA-2\_0 Array, Affymetrix Inc, Santa Clara, CA). Based on Casanova's description, before tissue collection, the written informed consent was obtained from patients enrolled in the dataset of GSE45604. Additionally, this study was approved by the institutional ethics committee.<sup>[14]</sup>





#### 2.2. Data preprocessing

According to the annotation file of GPL14613, probe identifiers were converted into miRNA symbols. During this conversion, a probe was removed if it mapped to multiple miRNAs, while if multiple probes corresponded to the same miRNA, their values were averaged to calculate the miRNA expression. Furthermore, miRNAs expression values were normalized through median method.

## 2.3. DEmiRNAs screening

To screen the DEmiRNAs between normal and PC specimens, the Linear Models for Microarray Analysis (limma) package in R (available at http://www.bioconductor.org/packages/release/bioc/html/limma.html, version: 3.22.1) was utilized, which is the most popular method for differential expression analysis.<sup>[15,16]</sup> In the significance analysis, *P* value was adjusted as false discovery rate (FDR) by Benjamini and Hochberg method.<sup>[17]</sup> Only the miRNAs met with the criteria of |log<sub>2</sub> fold change (FC)| > 1 and FDR < 0.05 were defined as DEmiRNAs.

#### 2.4. DEmiRNA-target gene prediction

The target genes of DEmiRNAs were explored from 4 databases, including TargetScan (http://www.targetscan.org/),<sup>[18]</sup> PicTar (http://pictar.mdc-berlin.de/),<sup>[19]</sup> miRbase (http://www.mirbase. org/),<sup>[20]</sup> and DIANA-microT (http://diana.cslab.ece.ntua.gr/),<sup>[21]</sup> predicting potential DEmiRNA-target interactions.

# 2.5. Construction of DEmiRNA–DEmiRNA co-regulation network

DEmiRNAs co-regulating same target gene were identified, based on which a DEmiRNA–DEmiRNA co-regulation network was

Table	e 1

Details of 50 prostate cancer patients.						
Gleason score	No. of specimen	pT stage	No. of specimen	TMPRSS2-ERG status	No. of specimen	
≤6	15	≤pT2	35	Negative	15	
7	25	≥pT3	14	Positive	26	
8–10	10					

pT stage = pathological stage, TMPRSS2-ERG status = the specific TMPRSS2 and ERG rearrangement at 21q22.

Table 2

Differentially expressed miRNAs between prostate cancer and normal samples.

lb.seguittet         has-mi-305         10.4792         2.330         0.001887           h5 min 152         8.201505         0.000295         0.007193           h5 min 1527         8.201505         0.000295         0.007491           h5 min 1227         8.201505         0.000295         0.00244           h5 min 1227         1.027103         0.000736         0.002746           h5 min 1227         1.02805         0.000736         0.00144           h5 min 1228         1.02606         0.000736         0.00144           h5 min 1228         0.000736         0.00149         0.00149           h5 min 1228         0.00144         0.00149         0.00149           h5 min 1228         0.00149         0.00149         0.00149           h5 min 1228         0.00149         0.00149         0.00149           h5 min 1228         -1.3503         0.00149         0.00149           h5 min 1228         -1.4513         0.00149         0.00149           h5 min 1228         -1.4513         0.00149         0.00149           h5 min 1228         -1.4513         0.00149         0.00149           h5 min 1228         -2.4512         0.000156         0.000276         0.000276      <		miRNA name	Log <sub>2</sub> fold change	P value	Adjusted P value
has-mi-35         10.81401         1.9805         0.001703           has-mi-120.74p         7.44123         0.020230         0.071703           has-mi-120.74p         7.44123         0.020230         0.07183           has-mi-120.74p         7.44123         0.000890         0.029240           has-mi-120.74p         1.957133         0.000890         0.029240           has-mi-120.75p         -1.32080         0.00074         0.001591           has-mi-420.75p         -1.32080         0.000384         0.01733           has-mi-420.75p         -1.32080         0.000384         0.01733           has-mi-420.75p         -1.43013         0.001841         0.001842           has-mi-420.75p         -1.43013         0.001881         0.001842           has-mi-420.75p         -1.43013         0.001842         0.001842           has-mi-420.75p         -1.43013         0.001842         0.001842           has-mi-420.75p         -1.43013         0.001842         0.001842           has-mi-420.75p         -2.41080         0.001842         0.001842           has-mi-420.7         -2.210182         0.001842         0.001842           has-mi-420.7         -2.24066         0.000254         0.001874     <	Up-regulated	hsa-mir-200c	10.84792	2.33E-05	0.001988
has minitaz         8281905         0.00090         0.017101           has minitaz         0.001608         0.00284           has minitaz         1.0217101         0.001608         0.00284           has minitaz         1.0217101         0.00021         0.00157           has minitaz         1.02184         0.00021         0.00157           has minitaz         -1.12115         0.00044         0.01412           has minitaz         -1.12115         0.00044         0.01412           has minitaz         -1.12115         0.00044         0.01412           has minitaz         -1.12115         0.00044         0.01142           has minitaz         -1.33007         0.001421         0.001614           has minitaz         -1.33007         0.001421         0.001614           has minitaz         -1.05135         0.00038         0.001621           has minitaz         -1.95485         0.00122         0.001721         0.00181           has minitaz         -2.01650         0.00122         0.00072         0.00273           has minitaz         -2.0163         0.00013         0.00122         0.00274           has minitaz         -2.0163         0.00021         0.00013         0.		hsa-mir-375	10.81401	1.28E-05	0.001637
ma         nmi         200730         0.00443           bs=mi         158         1.57193         0.00096         0.002443           bs=mi         158         1.57193         0.00096         0.002443           bs=mi         128         1.08063         0.00276         0.00276           bs=mi         12815         0.00074         0.00276         0.00276           bs=mi         1.21215         0.00074         0.00276         0.00276           bs=mi         1.21215         0.00074         0.00276         0.00276           bs=mi         1.21215         0.00074         0.00134         0.001767           bs=mi         1.21215         0.001734         0.00134         0.001376           bs=mi         1.45798         5.547-05         0.001376         0.00237           bs=mi         1.45798         2.0112         0.00232         0.00237           bs=mi         1.45798         2.0112         0.00232         0.00237           bs=mi         1.4563         -2.1899         0.00223         0.00237           bs=mi         1.4579         -2.48961         0.00223         0.00237           bs=mi         1.4579         -2.49961         0.000		hsa-mir-182	8 281506	0.000589	0.017193
Name in 103         5.407391         0.001909         0.02443           Name in 138         1.37893         0.000291         0.03534           Name in 138         1.37893         0.000291         0.03534           Name in 1423         -1.12815         0.00044         0.04557           Namin 373a         -1.12815         0.00044         0.04123           Namin 373a         -1.12815         0.00044         0.04123           Namin 497.330         -1.5308         0.00048         0.04123           Namin 497.330         -1.5308         0.00048         0.03184           Namin 497.330         -1.5818         0.00048         0.03184           Namin 497.330         -1.5818         0.00036         0.01824           Namin 497.33         -1.5819         0.00036         0.01824           Namin 497.33         -1.5843         0.00036         0.01824           Namin 497.33         -2.5142         0.00036         0.01824           Namin 497.3         -2.5142         0.00036         0.01824           Namin 497.3         -2.2111         0.00044         0.01557           Namin 497.3         -2.40401         0.00044         0.01524           Namin 497.3         -2.51421		hsa-mir-1207-5n	7 /0/128	0.002539	0.047191
bear-rogulated bear-ri-134 bear-ri-238 bear-ri-134 bear-ri-238 bear-ri-134 bear-ri-238 bea		hea_mir_183	5 400361	0.001600	0.034443
Instrument 102         1701523         0.000021         0.000021           Decen-seguined         0.000021         0.000074         0.004077           Decen-seguined         11251         0.000074         0.004077           Decen-seguined         11251         0.000074         0.000074           Decen-seguined         -132030         0.002538         0.001344           Decen-seguined         -142013         0.001497         0.001588         0.001518           Decen-seguined         -14013         0.001497         0.001588         0.001518           Insami-S43         -14013         0.001497         0.001588         0.0015182           Insami-S43         -130532         0.000230         0.0012124         1.001417         0.001417         0.001417         0.0014124           Insami-S43         -130532         0.0000230         0.002237         0.001511         0.000230         0.002237           Insami-S43         -220191         0.000024         0.002237         0.000024         0.002237           Insami-S43         -220503         0.000024         0.002237         0.000131         0.00141           Insami-S43         -220504         0.000024         0.000237         0.000144         0.00024		hee mir 1229	1.057102	0.000099	0.034443
Down-regulated         Disk Hirt 1184         1.78823         0.00032         0.00032           Down-regulated         Disk Hirt 1184         -1.12870         0.00074         0.011470           Disk Hirt 11870         -1.12870         0.00074         0.011470           Disk Hirt 11870         -1.28080         0.00074         0.01184         0.01183           Disk Hirt 1187         -1.38007         0.00184         0.01183           Disk Hirt 1187         -1.48113         0.00184         0.00186         0.000870           Disk Hirt 1187         -1.48131         0.00184         0.00188         0.001826           Disk Hirt 1187         -1.5833         0.000184         0.001826         0.000877           Disk Hirt 1188         -2.21832         0.001887         0.0003787         0.003787           Disk Hirt 1485-38         -2.21832         0.0003873         0.020287         0.000377           Disk Hirt 1485-38         -2.24131         0.0003873         0.020377         Disk Hirt 1485-38         0.0003877         0.020377           Disk Hirt 1485-38         -3.24211         0.000377         0.000377         0.000377         0.000377           Disk Hirt 1485-38         -3.242471         0.0000181         0.000377         0		11sa-1111-1250	1.907195	0.000900	0.023034
Down - rogulated         Inst-mi - 2828         - 10808         0.002/35         0.004342           Inst-mi - 786         - 11275         0.00774         0.00773           Inst-mi - 786         - 12205         0.00774         0.00773           Inst-mi - 786         - 122056         0.00724         0.00774           Inst-mi - 757         - 13807         0.00734         0.00793           Inst-mi - 756         - 13759         5.554         0.00793           Inst-mi - 757         - 137598         5.554         0.00793           Inst-mi - 261         - 137598         5.554         0.0071493         0.001847           Inst-mi - 30c         - 139533         0.00053         0.00727         0.007377           Inst-mi - 30c         - 221052         0.00054         0.003757           Inst-mi - 428         - 221013         0.000654         0.003757           Inst-mi - 428         - 221013         0.000654         0.003757           Inst-mi - 428         - 2210132         0.000725         0.003757           Inst-mi - 428         - 24065         0.000725         0.003757           Inst-mi - 428         - 24065         0.000725         0.003757           Inst-mi - 428         - 24065		nsa-mir-1184	1.786823	0.000521	0.015575
hsamir 376a         -1.1213         0.000434         0.001423           hsamir 3200 3p         -1.22018         0.002288         0.00447           hsamir 342         -1.40019         0.001441         0.03194           hsamir 45         -1.40019         0.001447         0.001957           hsamir 54         -1.31979         0.001447         0.001957           hsamir 54         -2.01832         0.001447         0.001874           hsamir 54         -2.0111         0.000289         0.001377           hsamir 54         -2.21011         0.000281         0.002397           hsamir 387         -2.20111         0.000281         0.02286           hsamir 387         -2.20111         0.000281         0.02286           hsamir 387         -2.20111         0.000281         0.02286           hsamir 387         -2.20191         0.000216         0.08774           hsamir 387         -2.40741         0.000144         0.002397           hsamir 387         -2.40819<	Down-regulated	hsa-mir-4328	-1.08906	0.002736	0.049572
ha min 1980-1 - 1.14073 0.00074 0.202579 hss-min 2807 - 1.3208 0.0007378 0.011481 hss-min 2807-30 - 1.3208 0.0017481 0.03187 hss-min 2814 - 1.42013 0.011481 0.03187 hss-min 282 - 1.42013 0.011481 0.03187 hss-min 282 - 1.42013 0.001440 0.011484 hss-min 282 - 1.42013 0.001440 0.011484 hss-min 282 - 1.42013 0.000440 0.011484 hss-min 282 - 2.01532 0.000728 hss-min 282 - 2.01532 0.000728 hss-min 282 - 2.2011 0.000794 0.002387 hss-min 282 - 2.2013 0.000394 0.002387 hss-min 282 - 2.2016 0.000256 0.047191 hss-min 282 - 2.2016 0.000256 0.047191 hss-min 282 - 2.2016 0.000256 0.047191 hss-min 284 - 2.2017 0.000794 0.002387 hss-min 284 - 2.2017 0.000794 0.002387 hss-min 284 - 2.2018 0.000039 0.000374 hss-min 284 - 2.2018 0.000039 0.000374 hss-min 284 - 2.2018 0.000031 0.007419 hss-min 284 - 2.2017 0.000794 0.002387 hss-min 284 - 2.2017 0.000717 0.00774 hss-min 284 - 0.00013 0.007419 hss-min 284 - 0.00013 0.007419 hss-min 284 - 0.00081 0.000774 0.00774 hss-min 284 - 0.00081 0.000774 0.007754 hss-min 284 - 0.00081 0.000774 0.007754 hss-min 285 - 0.3176 0.000087 0.011228 hss-min 284 - 0.00087 0.01128 hss-min 285 - 0.3176 0.000183 0.00885 hss-min 284 - 0.00088 0.000187 0.00237 hss-min 284 - 0.00088 0.000187 0.00237 hss-min 284 - 0.00088 0.000187 0.00237 hss-min 285 - 0.77564 1.0167-06 0.00331 hss-min 285 - 0.72565 0.000282 0.000772 0.002684 hss-min 385 - 0.72764 0.000072 0.000784 hss-min 385 - 0.7286 0.000072 0.000784 hss-min 385 - 0.7286 0.000072 0.000784 hss-min 385 - 0.7288 0.000072 0.000		hsa-mir-376a	-1.12815	0.000434	0.014123
hss-mi-200-3p         -13288         0.00238         0.044767           hss-mi-876-3p         -13807         0.00134         0.05123           hss-mi-876-3p         -165189         0.001888         0.005162           hss-mi-876-3p         -165189         0.001888         0.001898           hss-mi-263         -185135         0.00038         0.001898           hss-mi-362-3p         -195433         0.001499         0.00187           hss-mi-362-3p         -195433         0.00028         0.00237           hss-mi-363-1         -195433         0.000284         0.00237           hss-mi-363-1         -21583         0.000284         0.00237           hss-mi-363-2p         -21632         0.000294         0.00237           hss-mi-363         -220113         0.002564         0.00237           hss-mi-663         -246961         0.0002564         0.00277           hss-mi-663         -249671         0.000131         0.002797           hss-mi-6763         -34987         0.000131         0.002797           hss-mi-6763         -34987         0.000131         0.002797           hss-mi-636         -34987         0.000137         0.00377           hss-mi-1611         -3		hsa-mir-199a-1	-1.14579	0.00074	0.020579
heamin 404         -1.43013         0.001491         0.015167           heamin 404         -1.43013         0.001491         0.015162           heamin 408         -1.67589         5.54E-05         0.003679           heamin 2023         -1.87589         5.54E-05         0.003679           heamin 2023         -1.9573         0.001437         0.051824           heamin 405         -1.95633         0.000430         0.01187           heamin 405         -2.1893         0.000430         0.01271           heamin 428         -2.21891         5.077-05         0.003737           heamin 428         -2.21893         0.000434         0.012824           heamin 4285         -2.24981         0.000181         0.003737           heamin 4287         -2.40881         0.000494         0.015805           heamin 4287         -2.4081         0.000181         0.003737           heamin 4284         -2.40817         0.000217         0.022918           heamin 428         -2.43741         0.000187         0.003737           heamin 427         -2.43741         0.000187         0.003737           heamin 421         -3.44219         0.000217         0.003737           heamin 421		hsa-mir-3200-3p	-1.32088	0.002358	0.044767
hsami-Asi         -1.43113         0.011481         0.003672           hsamir-2693-5;p         -1.65789         0.001868         0.003672           hsamir-244         -1.87938         5.545-05         0.00387           hsamir-243         -1.87633         0.001489         0.031847           hsamir-303-5;p         -1.95633         0.000139         0.01527           hsamir-303-5;p         -1.95633         0.000139         0.0228713           hsamir-468         -2.21132         0.000134         0.022867           hsamir-468         -2.20111         0.000284         0.022867           hsamir-4689         -2.20111         0.000284         0.022867           hsamir-4689         -2.20111         0.000284         0.022867           hsamir-4689         -2.20111         0.000284         0.022867           hsamir-424         -2.20111         0.000213         0.000217           hsamir-424         -2.20171         0.00013         0.000237           hsamir-424         -2.20171         0.00013         0.000337           hsamir-555         -3.41617         0.000217         0.00357           hsamir-556         -3.287         0.000217         0.00357           hsamir-138		hsa-mir-875-3p	-1.38307	0.001384	0.03123
hbar mir 603 Sp.         -1 65190         0.001808         0.001879           hbar mir 743         -1 8798         5.54805         0.001879           hbar mir 302-50         -1 31579         0.001437         0.018184           hbar mir 302-50         -1 31583         0.001437         0.018124           hbar mir 301-1         -1 45483         0.001437         0.01827           hbar mir 482         -2 1809         5.07705         0.00237           hbar mir 481         -2 25683         0.000233         0.02236           hbar mir 482         -2 43661         0.000544         0.01357           hbar mir 482         -2 43641         0.000144         0.01555           hbar mir 484         -2 43741         0.000181         0.003537           hbar mir 482         -2 43741         0.000181         0.003537           hbar mir 482         -2 43747         0.000181         0.00377           hbar mir 482         -3 40427         0.000181         0.003737           hbar mir 482         -3 40428         0.000231         0.000747           hbar mir 482         -3 40428         0.000231         0.000747           hbar mir 482         -3 40428         0.000187         0.000757 <t< td=""><td></td><td>hsa-mir-454</td><td>-1.43013</td><td>0.001491</td><td>0.031847</td></t<>		hsa-mir-454	-1.43013	0.001491	0.031847
issemi-34         -1.87288         5.64-05         0.003879           has-mi-543         -1.8818         0.000308         0.01886           has-mi-543         -1.9543         0.001489         0.031847           has-mi-645         -1.9543         0.001489         0.031847           has-mi-164         -2.9033         0.00038         0.0182           has-mi-164         -2.2063         0.00023         0.022867           has-mi-545         -2.2063         0.000266         0.022867           has-mi-646         -2.20648         0.000266         0.002787           has-mi-646         -2.20648         0.000266         0.000746           has-mi-546         -2.20642         0.00013         0.000741           has-mi-246         -2.6042         0.000266         0.000774           has-mi-247         -2.6042         0.000267         0.000774           has-mi-248         -3.404082         0.000217         0.000774           has-mi-249         -3.40402         0.000217         0.000774           has-mi-241         -3.40402         0.000217         0.000774           has-mi-242         -3.6787         0.000217         0.000774           has-mi-243         -3.6787 <td></td> <td>hsa-mir-509-3-5p</td> <td>-1.65189</td> <td>0.001868</td> <td>0.036162</td>		hsa-mir-509-3-5p	-1.65189	0.001868	0.036162
hsami-643		hsa-mir-24	-1 87598	5.54E-05	0.003679
har mir 302-3p-10157900014870.01877har mir 426-195330.0008390.01887har mir 428-2018220.0002390.01827har mir 428-2189 $5.97-65$ 0.00757har mir 438-22189 $5.97-65$ 0.00757har mir 439-228030.0008330.022896har mir 439-2280430.0008230.022896har mir 430-2280430.0008230.022896har mir 430-5p-2437410.00049440.01650har mir 431-2551470.0001810.00974har mir 432-2404230.0002050.00974har mir 44-3042190.00090110.029789har mir 44-3042190.0009110.00976har mir 453-3042190.0002370.00976har mir 454-348620.0012330.029799har mir 454-349820.0012330.029799har mir 454-349820.0012310.00976har mir 535-332780.0012310.00976har mir 535-33280.0018770.00231har mir 524-4452821.867-050.00133har mir 424-445291.867-050.00133har mir 525-33280.0001870.00133har mir 526-33280.001870.00133har mir 526-635689.36E-050.00138har mir 427-6434121.46E-050.00138har mir 526-6375120.0007710.00339har mi		hsa-mir-543	-1 88618	0.000308	0.010836
Insertin 200-1         — 19482         0.001409         0.001897           Insertin 465 Gp         — 194823         0.00020         0.0187           Insertin 465 Gp         — 201822         0.00297         0.029717           Insertin 485         — 210182         0.000304         0.02297           Insertin 485         — 220111         0.000304         0.02296           Insertin 485         — 220111         0.000304         0.02296           Insertin 465         — 240860         0.002565         0.041191           Insertin 465         — 240861         0.00013         0.007419           Insertin 465         — 240811         0.00013         0.007419           Insertin 204         — 24082         0.001206         0.00741           Insertin 204         — 24082         0.001216         0.00074           Insertin 455         — 34187         0.00011         0.02295           Insertin 455         — 34982         0.001217         0.00074           Insertin 424         — 34982         0.00137         0.01217           Insertin 425         — 34787         0.00017         0.01287           Insertin 424         — 34982         0.00137         0.01413           Insertin 42		hea_mir_362_3n	1 01570	0.001/37	0.031824
inst-min-85-5p         -1.95633         0.00169         0.031947           hss-min-62-5p         -2.01632         0.001722         0.0223773           hss-min-62         -2.01632         0.00054         0.022387           hss-min-628         -2.20111         0.00054         0.022387           hss-min-629         -2.240566         0.00054         0.022387           hss-min-620         -2.43741         0.00064         0.022387           hss-min-620         -2.43741         0.00013         0.07419           hss-min-620         -2.43741         0.00013         0.007419           hss-min-625         -3.41187         0.000217         0.002744           hss-min-635         -3.370824         0.000437         0.01233           hss-min-635-5p         -3.370824         0.00037         0.012837           hss-min-635-5p         -3.370824         0.00037         0.012837           hss-min-635-5p         -3.370824         0.00037         0.012837           hss-min-635-5p         -3.328         0.000367         0.012837           hss-min-635-5p         -3.328         0.00037         0.012837           hss-min-635-5p         -3.4282         1.066-05         0.001837           <		haa mir 20a 1	1 05492	0.001437	0.031024
m8amir 428-3p         −195033         0.00039         0.01221           hsamir 4284         −2.01892         9.57F~05         0.002777           hsamir 4284         −2.21899         9.57F~05         0.002323           hsamir 381         −2.225663         0.000243         0.022996           hsamir 342         −2.43741         0.000444         0.015555           hsamir 342         −2.43741         0.000131         0.000377           hsamir 342         −2.43741         0.000131         0.000377           hsamir 342         −2.43741         0.000131         0.000377           hsamir 342         −2.40891         0.00011         0.022918           hsamir 342         −2.40891         0.000011         0.0229718           hsamir 424         −3.04219         0.000011         0.02976           hsamir 424         −3.40824         0.000217         0.000377           hsamir 424         −3.40824         0.0001231         0.00976           hsamir 424         −3.40826         0.000377         0.00337           hsamir 424         −4.40388         0.000377         0.000377           hsamir 424         −4.40388         0.000377         0.000337           hsamir 424		IISa-IIIII-SUU-I	-1.95465	0.001469	0.031047
Iss.mir.194         −2.01832         0.019292         0.02377           Insa.mir.487         −2.20111         0.000954         0.02397           Insa.mir.487         −2.23011         0.000954         0.02296           Insa.mir.490-5p         −2.43561         0.000356         0.047191           Insa.mir.490-5p         −2.43741         0.00013         0.00744           Insa.mir.490-5p         −2.43741         0.00013         0.007974           Insa.mir.492         −2.6042         0.000216         0.009774           Insa.mir.495.5p         −3.41187         0.000217         0.009774           Insa.mir.495.5p         −3.4187         0.000125         0.029379           Insa.mir.424         −3.40882         0.00037         0.01257           Insa.mir.425         −3.3787         0.00037         0.01937           Insa.mir.636         −3.3782         0.000367         0.01153           Insa.mir.1910         −4.40058         0.000187         0.00337           Insa.mir.2024         −4.43382         1.66−05         0.001798           Insa.mir.2035         −4.43382         1.66−05         0.001837           Insa.mir.628-3p         −4.43386         1.305−06         0.000662		lisa-iiii-485-3p	- 1.90353	0.000639	0.01821
has mit 4288 — 2.21899 5.97 $-05$ 0.003757 has mit 4287 - 2.21893 0.000923 0.022986 has mit 452 - 2.40566 0.002565 0.0147191 has mit 452 - 2.43741 0.00014 0.015555 has mit 452, - 2.43741 0.00014 0.00037 has mit 7204 - 2.55147 0.000181 0.00037 has mit 724 - 2.6042 0.000206 0.002976 has mit 7181 - 3.04219 0.000091 0.022918 has mit 724 - 3.4882 0.000213 0.000976 has mit 7181 - 3.04219 0.000021 0.000976 has mit 724 - 3.4882 0.000213 0.000976 has mit 720 - 3.2787 0.000211 0.009766 has mit 730 - 3.7884 0.000231 0.009876 has mit 730 - 3.0882 0.00037 0.01153 has mit 730 - 4.40038 0.000187 0.011537 has mit 720 - 4.00382 0.000387 0.000337 has mit 720 - 4.400382 0.00037 0.000337 has mit 720 - 4.40038 0.000187 0.000337 has mit 720 - 4.40038 0.000187 0.000337 has mit 720 - 4.40038 0.000187 0.000337 has mit 721 - 4.40038 0.000187 0.000337 has mit 722 - 4.40038 0.000187 0.000337 has mit 723 - 6.74756 1.447 $-06$ 0.000321 has mit 721 - 5.280.30 4.677 $-05$ 0.0009283 has mit 731 - 6.4755 1.447 $-06$ 0.000321 has mit 737 - 6.24756 1.447 $-06$ 0.000321 has mit 737 - 6.74744 0.00032 0.000764 has mit 738 - 6.74754 0.000168 0.033399 has mit 731 - 6.74744 0.000168 0.033399 has mit 735 - 7.14077 0.00022 0.000764 has mit 736 - 6.74754 0.000168 0.033399 has mit 737 - 7.14077 0.00022 0.000764 has mit 739 - 7.74077 0.00022 0.000764 has mit 739 - 7.74077 0.00022 0.000764 has mit 730 - 7.74072 0.000168 0.033399 has mit 731 - 7.14077 0.00022 0.000764 has mit 732 - 7.8407 0.00168 0.033399 has mit 731 - 7.14077 0.00027 0.000283 has mit 732 - 7.8407 0.001757 0.03021 has mit 734 - 7.14077 0.00027 0.02268 has mit 735 - 7.8407 0.001757 0.03021 has mit 740 - 7.14077 0.00027 0.02268 has mit 740 - 7.44023 0.000775 0.03819 has mit 740 - 7.14077 0.00027 0.000277 has mit 740 - 7.14077 0.00027 0.000271 has mit 740 - 0.01081 8.00075 0.030839 has mit 740 - 0.010817 0.00075 0.030839 has mit 740 - 0.010817 0.00075 0.030811		hsa-mir-154	-2.01832	0.001292	0.029713
hsa-mi-361         -2.20111         0.000954         0.022965           hsa-mi-490-5p         -2.40566         0.000265         0.047191           hsa-mi-490-5p         -2.40561         0.00013         0.007419           hsa-mi-490-5p         -2.40991         0.00014         0.00037           hsa-mi-24-2         -2.40991         0.000206         0.00037           hsa-mi-45-5p         -3.4187         0.000216         0.00037           hsa-mi-455 <p< td="">         -3.4187         0.000217         0.00374           hsa-mi-455<p< td="">         -3.4182         0.000217         0.00374           hsa-mi-455         -3.370624         0.000217         0.00037           hsa-mi-455         -3.370624         0.000437         0.011252           hsa-mi-633         -3.370624         0.000167         0.00037           hsa-mi-633         -4.30368         0.000367         0.001637           hsa-mi-1334         -4.43026         0.000167         0.000637           hsa-mi-224         -4.45382         1.68205         0.000637           hsa-mi-1335         -4.43026         0.000167         0.000637           hsa-mi-1271         -5.2039         4.672-05         0.0000632           hsa-mi-138<!--</td--><td></td><td>hsa-mir-4288</td><td>-2.1899</td><td>5.97E—05</td><td>0.003757</td></p<></p<>		hsa-mir-4288	-2.1899	5.97E—05	0.003757
hsa-mi-381         -225863         0.009236         0.022966           hsa-mi-490-5p         -2.43741         0.000141         0.007419           hsa-mi-490-5p         -2.43741         0.000131         0.007419           hsa-mi-242         -2.63491         0.000131         0.007419           hsa-mi-242         -2.63421         0.000261         0.022918           hsa-mi-455         -3.41167         0.000217         0.009764           hsa-mi-453         -3.04219         0.000217         0.009764           hsa-mi-453         -3.07824         0.000231         0.009764           hsa-mi-505         -3.3787         0.000377         0.012523           hsa-mi-603         -4.40368         0.000187         0.000337           hsa-mi-781         -4.42522         1.37E-05         0.001778           hsa-mi-625-0p         -4.43632         1.65E-05         0.001788           hsa-mi-727         -5.28039         4.67E-05         0.000221           hsa-mi-137         -6.39568         3.32E-06         0.000622           hsa-mi-137         -6.39568         3.32E-06         0.000231           hsa-mi-137         -6.39568         3.32E-06         0.0000221           hsa-mi-137		hsa-mir-887	-2.20111	0.000954	0.023287
hsamin-492         -2.40566         0.002565         0.047191           hsamin-490-5p         -2.43891         0.00013         0.007419           hsamin-340-3p         -2.43891         0.000131         0.00337           hsamir-24-2         -2.6042         0.000206         0.003764           hsamir-24-2         -2.6042         0.000217         0.000764           hsamir-455-5p         -3.41817         0.000217         0.000774           hsamir-455         -3.4982         0.000367         0.01253         0.02373           hsamir-503         -3.70824         0.0002437         0.014123           hsamir-605         -3.928         0.000367         0.00187           hsamir-614         -4.00388         0.000187         0.00187           hsamir-615         -3.8737         0.000187         0.00187           hsamir-615         -3.828         0.000367         0.001873           hsamir-130         -4.403882         1.652-05         0.00187           hsamir-131         -6.441812         1.652-05         0.00187           hsamir-132         -6.14312         1.462-07         8.665-05           hsamir-132         -6.14721         0.463368         9.352-06         0.000321     <		hsa-mir-381	-2.25863	0.000923	0.022996
hsa-mir-400-5p         -2.43741         0.000494         0.01555           hsa-mir-204         -2.55147         0.000181         0.00937           hsa-mir-204         -2.50147         0.000206         0.009744           hsa-mir-181a         -3.04219         0.0002017         0.009376           hsa-mir-455-5p         -3.41187         0.000217         0.009764           hsa-mir-453         -3.70824         0.000231         0.009876           hsa-mir-338-5p         -3.37087         0.000231         0.009377           hsa-mir-284         -3.4252         1.65E-05         0.001782           hsa-mir-284         -4.42522         1.37E-05         0.001837           hsa-mir-284         -4.42522         1.65E-05         0.001837           hsa-mir-1814         -4.40388         0.000187         0.000821           hsa-mir-284         -4.42522         1.65E-05         0.001821           hsa-mir-1814         -4.40388         0.000187         0.00022           hsa-mir-284         -6.4312         1.46E-05         0.001821           hsa-mir-1814         -4.6382         1.65E-05         0.001821           hsa-mir-283         -6.73812         0.000022         0.00022		hsa-mir-452	-2.40566	0.002565	0.047191
hsa-mir-34c-2p         -2.43891         0.000131         0.007419           hsa-mir-244         -2.6042         0.000206         0.009764           hsa-mir-161a         -3.04219         0.000001         0.022318           hsa-mir-465-5p         -3.41187         0.000217         0.009764           hsa-mir-465-5p         -3.41187         0.000217         0.009764           hsa-mir-503         -3.3787         0.000367         0.012528           hsa-mir-605         -3.328         0.0000367         0.012528           hsa-mir-614         -4.40388         0.000187         0.00937           hsa-mir-628-3p         -4.40382         1.65E-05         0.001637           hsa-mir-628-3p         -4.40382         1.65E-05         0.001788           hsa-mir-628-3p         -4.40382         1.65E-05         0.00187           hsa-mir-637         -6.43082         1.65E-05         0.001892           hsa-mir-647         -6.43082         1.65E-05         0.00022           hsa-mir-628         -4.63882         1.65E-05         0.000218           hsa-mir-137         -6.24756         1.44E-06         0.00022           hsa-mir-137         -6.4782         0.001608         0.03329           <		hsa-mir-490-5p	-2.43741	0.000494	0.015555
hsa-mir-204         -2.5047         0.000181         0.00937           hsa-mir-24-2         -2.6042         0.000206         0.009764           hsa-mir-181a         -3.04219         0.000201         0.022318           hsa-mir-455-5p         -3.41187         0.000217         0.009764           hsa-mir-424         -3.49802         0.012523         0.023379           hsa-mir-505         -3.2082         0.000367         0.01528           hsa-mir-181d         -4.03088         0.000187         0.009377           hsa-mir-284         -4.42522         1.37E-05         0.001892           hsa-mir-181d         -4.03088         0.000187         0.009371           hsa-mir-224         -4.42522         1.37E-05         0.001892           hsa-mir-237         -4.63882         1.65E-05         0.001892           hsa-mir-247         -4.42522         1.37E-05         0.000521           hsa-mir-171         -5.2039         4.67E-05         0.000521           hsa-mir-187         -6.14312         1.44E-07         8.65E-05           hsa-mir-378         -6.73724         0.00168         0.000321           hsa-mir-378         -6.73724         0.000772         0.00262           hsa-mir-		hsa-mir-34c-3p	-2.49891	0.00013	0.007419
has-mir-24-2         -2.6042         0.000208         0.009764           has-mir-181a         -3.04219         0.000201         0.02218           has-mir-655-5p         -3.41187         0.000217         0.099764           has-mir-636         -3.49892         0.000233         0.029379           has-mir-505         -3.8787         0.000231         0.099764           has-mir-524         -4.400588         0.000167         0.099376           has-mir-224         -4.42522         1.37E-05         0.011837           has-mir-224         -4.42522         1.37E-05         0.001982           has-mir-1230         -4.63882         1.68E-05         0.001982           has-mir-1230         -4.63882         1.68E-05         0.001982           has-mir-1230         -4.63864         1.90E-05         0.001982           has-mir-1271         -5.29039         4.67E-05         0.00323           has-mir-1376         -6.44712         1.44E-06         0.000321           has-mir-1378c         -6.39558         9.35E-06         0.003389           has-mir-1378c         -6.74764         1.61E-06         0.00322           has-mir-138         -7.14977         0.00022         0.009774 <t< td=""><td></td><td>hsa-mir-204</td><td>-2 55147</td><td>0.000181</td><td>0 009337</td></t<>		hsa-mir-204	-2 55147	0.000181	0 009337
Inst.LLDD <td></td> <td>hsa-mir-24-2</td> <td>-2 6042</td> <td>0.000206</td> <td>0.009764</td>		hsa-mir-24-2	-2 6042	0.000206	0.009764
hsar.mir.455-5p         -3.41187         0.000217         0.009764           hsar.mir.455-5p         -3.41187         0.000217         0.009774           hsar.mir.436-5p         -3.49922         0.000233         0.099764           hsar.mir.503         -3.70824         0.000237         0.014123           hsar.mir.505         -3.8787         0.000231         0.099764           hsar.mir.505         -3.928         0.000187         0.099337           hsar.mir.628-3p         -4.63882         1.65E-05         0.011936           hsar.mir.628-3p         -4.63882         1.65E-05         0.011937           hsar.mir.629-3p         -4.63882         1.65E-05         0.011982           hsar.mir.421         -4.42522         1.37E-05         0.011982           hsar.mir.423         -4.63862         1.65E-05         0.003823           hsar.mir.421         -5.28039         4.67E-05         0.03283           hsar.mir.63         -6.4312         1.45E-06         0.00322           hsar.mir.63         -6.7372         0.000168         0.033389           hsar.mir.63         -6.7374         0.000322         0.01974           hsar.mir.63         -7.716942         0.00072         0.00974		hea_mir_181a	-3 0/210	0.000200	0.022018
inserniti-424         -3.49992         0.001253         0.029769           hsarmir-326         -3.49992         0.000237         0.014123           hsarmir-338.50         -3.8787         0.000237         0.01253           hsarmir-386.50         -3.8787         0.000237         0.01253           hsarmir-505         -3.928         0.000367         0.01253           hsarmir-244         -4.42522         1.37E-05         0.001637           hsarmir-245         -4.42552         1.37E-05         0.001637           hsarmir-245         -4.42552         1.37E-05         0.001637           hsarmir-242         -4.42552         1.37E-05         0.001637           hsarmir-1310         -4.6346         1.90E-05         0.001892           hsarmir-1271         -5.243182         1.46E-07         0.65E-05           hsarmir-132         -6.43122         1.46E-07         0.65E-05           hsarmir-1378c         -6.39558         9.35E-06         0.001338           hsarmir-1378         -6.73724         0.000163         0.008855           hsarmir-1395         -6.74744         0.000022         0.000772         0.020654           hsarmir-1395         -7.16977         0.00022         0.000772		hee mir 455 5p	2 /1107	0.000301	0.022510
Insertim -24         -3.4982         0.001233         0.012937           Issemir-503         -3.70824         0.00037         0.014123           Issemir-505         -3.928         0.000387         0.012828           Issemir-505         -3.928         0.000187         0.009837           Issemir-505         -3.928         0.000187         0.009837           Issemir-628.3p         -4.45382         1.65E-05         0.0011798           Issemir-7330         -4.80346         1.90E-05         0.000822           Issemir-1271         -5.28039         4.67E-05         0.000821           Issemir-1271         -5.28039         4.67E-05         0.000821           Issemir-1271         -5.28039         4.67E-05         0.0003283           Issemir-1378         -6.613956         9.35E-06         0.000822           Issemir-378         -6.73812         0.000168         0.0003283           Issemir-139.5p         -6.74764         0.00022         0.009764           Issemir-139.5p         -7.74972         0.000022         0.009764           Issemir-139.5p         -7.74974         0.00022         0.009764           Issemir-139.5p         -7.74972         0.000022         0.009764		haa mir 404	-3.41187	0.000217	0.009704
Inst-mir-303 $-3,702/4$ $0.00043/$ $0.014123$ hsa-mir-505 $-3.8787$ $0.000231$ $0.009876$ hsa-mir-505 $-3.928$ $0.0001877$ $0.09237$ hsa-mir-181d $-4.00388$ $0.000187$ $0.00937$ hsa-mir-224 $-4.42522$ $1.37E-05$ $0.001187$ hsa-mir-130 $-4.80346$ $1.90E-05$ $0.001892$ hsa-mir-131 $-4.80346$ $3.52E-06$ $0.0002823$ hsa-mir-421 $-4.84186$ $3.52E-06$ $0.0002823$ hsa-mir-421 $-6.14312$ $1.46E-07$ $8.66E-05$ hsa-mir-422 $-6.14312$ $1.46E-07$ $8.66E-05$ hsa-mir-378 $-6.24756$ $1.44E-06$ $0.003283$ hsa-mir-38 $-6.4792$ $0.001608$ $0.03369$ hsa-mir-395 $-6.7474$ $0.000302$ $0.009764$ hsa-mir-131a $-7.14977$ $0.00022$ $0.009764$ hsa-mir-135b $-7.16942$ $0.000772$ $0.020654$ hsa-mir-161b $-7.14977$ $0.00022$ $0.009764$ hsa-mir-173 $-8.02489$ $4.00E-05$ $0.003283$ hsa-mir-181b $-7.16942$ $0.000777$ $0.200654$ hsa-mir-193 $-7.81912$ $2.15E-05$ $0.000281$ hsa-mir-193 $-7.81912$ $0.000777$ $0.000261$ hsa-mir-193 $-9.16873$ $0.000775$ $0.020651$ hsa-mir-193 $-9.16873$ $0.000281$ $0.01818$ hsa-mir-193 $-9.16873$ $0.000795$ $0.00261$ hsa-mir-193 $-9.16873$ $0.000275$ <		IISa-IIII-424	-3.49982	0.001253	0.029379
Insa-mir-334-5p       -3.8787       0.000231       0.000237         hsa-mir-505       -3.928       0.000387       0.012528         hsa-mir-181d       -4.0368       0.000187       0.00937         hsa-mir-224       -4.63882       1.56E-05       0.00187         hsa-mir-133b       -4.80346       1.90E-05       0.00192         hsa-mir-421       -4.84186       3.52E-06       0.000602         hsa-mir-4271       -5.29039       4.67E-05       0.003283         hsa-mir-422a       -6.14312       1.48E-07       8.66E-05         hsa-mir-187       -6.24756       1.44E-06       0.00021         hsa-mir-378       -6.73912       0.001608       0.03389         hsa-mir-378       -6.73724       0.000163       0.00855         hsa-mir-139-5p       -6.74784       0.00022       0.009764         hsa-mir-139-5p       -7.2555       0.00022       0.009764         hsa-mir-187       -7.14977       0.00022       0.00964         hsa-mir-180       -7.14977       0.00022       0.009764         hsa-mir-130       -7.42023       0.000772       0.00051         hsa-mir-130       -7.2555       0.000222       0.001682         hsa-mir-130 </td <td></td> <td>nsa-mir-503</td> <td>-3.70824</td> <td>0.000437</td> <td>0.014123</td>		nsa-mir-503	-3.70824	0.000437	0.014123
hsa-mir-305       -3.928       0.000367       0.00337         hsa-mir-181d       -4.00368       0.000167       0.00337         hsa-mir-224       -4.42522       1.37E-05       0.001637         hsa-mir-130       -4.60346       1.90E-05       0.001892         hsa-mir-1271       -5.60312       1.66E-05       0.001892         hsa-mir-421       -4.8146       3.52E-06       0.003283         hsa-mir-1271       -5.61312       1.46E-07       8.6E-05         hsa-mir-376       -6.24756       1.44E-06       0.000321         hsa-mir-378       -6.73812       0.001608       0.003369         hsa-mir-378       -6.73812       0.001608       0.003369         hsa-mir-133a       -7.05564       1.61E-06       0.000321         hsa-mir-133a       -7.05564       1.61E-06       0.000321         hsa-mir-133a       -7.05564       1.61E-06       0.00326         hsa-mir-133a       -7.05564       1.61E-06       0.003283         hsa-mir-140       -7.14977       0.00022       0.009764         hsa-mir-28-3p       -7.2595       0.000262       0.010777         hsa-mir-28-3p       -7.47102       0.0001618       0.03369         hsa-mir		hsa-mir-338-5p	-3.8787	0.000231	0.009876
hsa-mir-181d       -4.40388       0.000187       0.00937         hsa-mir-224       -4.40382       1.85E-05       0.001798         hsa-mir-628-3p       -4.63882       1.65E-05       0.001892         hsa-mir-133b       -4.80346       1.90E-05       0.000802         hsa-mir-1271       -5.28039       4.67E-05       0.0003283         hsa-mir-1271       -5.28039       4.67E-06       0.000321         hsa-mir-378       -6.14312       1.45E-07       8.65E-05         hsa-mir-378       -6.24756       1.44E-06       0.000321         hsa-mir-378       -6.73812       0.001608       0.03389         hsa-mir-378       -6.74764       1.61E-06       0.000321         hsa-mir-378       -6.74764       0.00022       0.00964         hsa-mir-139-5p       -7.16972       0.00022       0.009764         hsa-mir-139       -7.16972       0.00022       0.009772       0.020654         hsa-mir-181b       -7.16972       0.00022       0.009772       0.020654         hsa-mir-190       -7.44023       0.000777       0.020654         hsa-mir-190       -7.44023       0.000777       0.020654         hsa-mir-152       -7.81912       2.15E-05 <td< td=""><td></td><td>hsa-mir-505</td><td>-3.928</td><td>0.000367</td><td>0.012528</td></td<>		hsa-mir-505	-3.928	0.000367	0.012528
hsa-mir-224       -4.42522       1.37E-05       0.001637         hsa-mir-223       -4.63822       1.68E-05       0.001892         hsa-mir-133b       -4.80346       1.90E-05       0.001892         hsa-mir-421       -4.84186       3.52E-06       0.00023         hsa-mir-427       -5.28039       4.67E-05       0.0003283         hsa-mir-187       -6.24756       1.44E-06       0.000321         hsa-mir-378       -6.73812       0.001608       0.03389         hsa-mir-378       -6.73812       0.001608       0.03389         hsa-mir-378       -6.73812       0.001608       0.00321         hsa-mir-378       -6.7784       0.00022       0.00774         hsa-mir-139-5p       -6.7474       0.00022       0.009764         hsa-mir-133       -7.14977       0.00022       0.009764         hsa-mir-100       -7.44023       0.000772       0.020654         hsa-mir-30c       -8.74333       0.000777       0.020654         hsa-mir-30c       -8.74333       0.000775       0.003883         hsa-mir-28-5p       -9.15993       7.27E-07       0.001818         hsa-mir-28-5p       -9.15993       7.27E-07       0.000217         hsa-mir-27		hsa-mir-181d	-4.00368	0.000187	0.009337
hsa-mir-628-3p       -4.63882       1.65E-05       0.001798         hsa-mir-133b       -4.80346       1.90E-05       0.001892         hsa-mir-421       -4.84186       3.52E-06       0.000202         hsa-mir-1271       -5.28039       4.67E-05       0.003283         hsa-mir-1422a       -6.14312       1.45E-07       8.65E-05         hsa-mir-378c       -6.39558       9.35E-06       0.003316         hsa-mir-378       -6.73812       0.001608       0.033369         hsa-mir-379       -6.73812       0.000163       0.000321         hsa-mir-133a       -7.05564       1.61E-06       0.000321         hsa-mir-131b       -7.14977       0.00022       0.00776         hsa-mir-131b       -7.15942       0.000772       0.020654         hsa-mir-132       -7.2595       0.000262       0.10777         hsa-mir-28-3p       -7.47102       0.001618       0.033369         hsa-mir-28-5p       -8.02489       4.06E-05       0.003283         hsa-mir-152       -7.81912       2.15E-05       0.001982         hsa-mir-28-5p       -8.02489       4.00E-05       0.003283         hsa-mir-295       -8.02489       4.00E-05       0.003283		hsa-mir-224	-4.42522	1.37E-05	0.001637
hsa-mir-133b         -4.80346         1.90E-05         0.001892           hsa-mir-421         -4.84186         3.52E-06         0.000602           hsa-mir-1271         -5.28039         4.67E-05         0.003283           hsa-mir-1271         -6.24756         1.44E-06         0.000321           hsa-mir-1378         -6.24756         1.44E-06         0.00033169           hsa-mir-378         -6.73812         0.001608         0.033369           hsa-mir-378         -6.73812         0.0001603         0.008855           hsa-mir-139-5p         -6.74784         0.000321         0.00321           hsa-mir-139-5p         -7.05564         1.61E-06         0.000321           hsa-mir-131         -7.16972         0.000772         0.020654           hsa-mir-139         -7.2595         0.000772         0.020654           hsa-mir-28-3p         -7.2595         0.000777         0.022654           hsa-mir-28-5p         -8.02499         4.40E-05         0.003289           hsa-mir-28-5p         -8.02499         4.00E-05         0.003283           hsa-mir-28-5p         -8.02499         4.00E-05         0.003283           hsa-mir-28-5p         -8.02499         4.00E-05         0.003283		hsa-mir-628-3p	-4.63882	1.65E-05	0.001798
hsa-mir-421         -4.84186         3.52E06         0.000602           hsa-mir-1271         -5.28039         4.67E05         0.003283           hsa-mir-422a         -6.14312         1.45E07         8.65E05           hsa-mir-187         -6.24756         1.44E06         0.00321           hsa-mir-378         -6.39558         9.35E06         0.001380           hsa-mir-378         -6.73812         0.001608         0.033369           hsa-mir-133         -7.05564         1.61E06         0.000321           hsa-mir-181b         -7.14977         0.00022         0.009764           hsa-mir-181b         -7.14977         0.00022         0.009764           hsa-mir-190         -7.44023         0.000777         0.020654           hsa-mir-100         -7.44023         0.000777         0.020654           hsa-mir-28-3p         -7.2595         0.000282         0.001777           hsa-mir-28-5p         -8.02489         4.40E05         0.003283           hsa-mir-28-5p         -8.02489         4.40E05         0.003283           hsa-mir-28-5p         -8.02489         4.00E05         0.003283           hsa-mir-30c         -8.74333         0.000278         0.000217		hsa-mir-133b	-4.80346	1.90E-05	0.001892
hsa-mir-1271       -5.28039       4.67E-05       0.003283         hsa-mir-422a       -6.14312       1.45E-07       8.65E-05         hsa-mir-378c       -6.39558       9.35E-06       0.001398         hsa-mir-378c       -6.39558       9.35E-06       0.003283         hsa-mir-378       -6.73812       0.001608       0.033369         hsa-mir-139-5p       -6.74784       0.000322       0.009855         hsa-mir-133a       -7.05564       1.61E-06       0.000321         hsa-mir-181b       -7.16942       0.000772       0.020654         hsa-mir-28-3p       -7.22595       0.000282       0.010777         hsa-mir-28-5p       -8.02498       4.06-05       0.003283         hsa-mir-28-5p       -8.02498       4.06-05       0.003283         hsa-mir-28-5p       -8.02498       4.06-05       0.003283         hsa-mir-28-5p       -8.02498       4.06-05       0.002823         hsa-mir-28-5p       -8.02498       4.06-05       0.002823         hsa-mir-28-5p       -8.02498       4.06-05       0.002823         hsa-mir-28-5p       -8.02498       4.06-05       0.002824         hsa-mir-28-5p       -8.02498       4.06-05       0.00217		hsa-mir-421	-4.84186	3.52E-06	0.000602
hsa-mir-422a       -6.14312       1.45E-07       8.65E-05         hsa-mir-187       -6.24756       1.44E-06       0.000321         hsa-mir-378c       -6.39558       9.35E-06       0.001398         hsa-mir-378       -6.74792       0.001608       0.033369         hsa-mir-378       -6.74784       0.000302       0.01885         hsa-mir-133a       -7.05564       1.61E-06       0.000321         hsa-mir-181b       -7.14977       0.00022       0.009764         hsa-mir-181b       -7.12942       0.000772       0.0220554         hsa-mir-181b       -7.44023       0.000777       0.0220564         hsa-mir-190       -7.44023       0.000777       0.020564         hsa-mir-182       -7.81912       2.15E-05       0.001982         hsa-mir-205       -8.02489       4.0E-05       0.003283         hsa-mir-205       -8.02489       4.0E-05       0.003283         hsa-mir-205       -9.14667       0.001875       0.020681         hsa-mir-205       -9.14687       0.001875       0.02081         hsa-mir-205       -9.14687       0.001875       0.02081         hsa-mir-205       -9.14687       0.00051       0.015575         hsa-mir-		hsa-mir-1271	-5.28039	4.67E-05	0.003283
hsa-mir-187         -6.24756         1.44E-06         0.000321           hsa-mir-378c         -6.39558         9.35E-06         0.001398           hsa-mir-378c         -6.4792         0.001608         0.033369           hsa-mir-378         -6.73812         0.00163         0.008855           hsa-mir-139-5p         -6.74784         0.000302         0.01083           hsa-mir-133a         -7.05564         1.61E-06         0.000321           hsa-mir-1         -7.14977         0.00022         0.009764           hsa-mir-181b         -7.16942         0.000772         0.020654           hsa-mir-190         -7.44023         0.000777         0.020654           hsa-mir-28-3p         -7.47102         0.001618         0.033369           hsa-mir-30c         -7.44023         0.000777         0.020654           hsa-mir-28-5p         -7.4102         0.001618         0.033369           hsa-mir-28-5p         -7.41023         0.000777         0.020654           hsa-mir-28-5p         -8.02489         4.40E-05         0.003283           hsa-mir-205         -9.16487         0.001875         0.002264           hsa-mir-205         -9.16487         0.000175         0.002027 <td< td=""><td></td><td>hsa-mir-422a</td><td>-6.14312</td><td>1.45E-07</td><td>8.65E-05</td></td<>		hsa-mir-422a	-6.14312	1.45E-07	8.65E-05
Inamir-376c         -6.39558         9.35E-06         0.00138           hsa-mir-376c         -6.39558         9.35E-06         0.00138           hsa-mir-378         -6.73812         0.000302         0.010836           hsa-mir-139-5p         -6.74784         0.000302         0.010836           hsa-mir-133a         -7.05564         1.61E-06         0.000321           hsa-mir-13         -7.14977         0.00022         0.009764           hsa-mir-181b         -7.14977         0.00022         0.00064           hsa-mir-28-3p         -7.22595         0.000772         0.020654           hsa-mir-28-3p         -7.47102         0.001618         0.033369           hsa-mir-28-3p         -7.47102         0.001618         0.033369           hsa-mir-28-5p         -8.02489         4.40E-05         0.002823           hsa-mir-28-5p         -8.02489         4.40E-05         0.002833           hsa-mir-205         -9.16872         0.001875         0.036162           hsa-mir-225         -9.63879         6.73E-07         0.000217           hsa-mir-224         -9.63879         6.73E-07         0.000217           hsa-mir-225         -9.63879         6.73E-07         0.000217		hsa-mir-187	-6.24756	1 44E-06	0.000321
Inde min 0700         0.64792         0.001608         0.033369           hsa-mir-37         -6.4792         0.00163         0.008855           hsa-mir-139-5p         -6.74784         0.000302         0.010336           hsa-mir-139         -7.05564         1.61E-06         0.000321           hsa-mir-133         -7.14977         0.00022         0.009764           hsa-mir-181b         -7.16942         0.000772         0.020654           hsa-mir-28-3p         -7.2595         0.000262         0.010777           hsa-mir-28-5p         -7.47102         0.000777         0.020654           hsa-mir-152         -7.47102         0.000777         0.020654           hsa-mir-28-5p         -7.47102         0.000777         0.020654           hsa-mir-152         -7.81912         2.15E-05         0.003369           hsa-mir-28-5p         -8.02489         4.40E-05         0.003283           hsa-mir-28-5p         -8.97619         0.000795         0.020618           hsa-mir-205         -9.14687         0.001875         0.02081           hsa-mir-27b         -9.15993         7.27E-07         0.000217           hsa-mir-145         -9.06879         6.73E-07         0.000217 <t< td=""><td></td><td>hsa-mir-378c</td><td>-6 39558</td><td>9 35E_06</td><td>0.001398</td></t<>		hsa-mir-378c	-6 39558	9 35E_06	0.001398
Insa-mir-378         -6.78312         0.001063         0.008855           hsa-mir-139-5p         -6.74784         0.000302         0.010836           hsa-mir-133-3a         -7.05564         1.61E06         0.000321           hsa-mir-11         -7.14977         0.00022         0.009764           hsa-mir-181b         -7.14977         0.00022         0.010777           hsa-mir-181b         -7.42595         0.000772         0.020654           hsa-mir-190         -7.47102         0.001618         0.033892           hsa-mir-152         -7.81912         2.15E05         0.001982           hsa-mir-30c         -8.74333         0.000284         0.010818           hsa-mir-205         -9.14687         0.001875         0.038162           hsa-mir-205         -9.14687         0.001875         0.038162           hsa-mir-27b         -9.14993         7.27E-07         0.000217           hsa-mir-27b         -9.1693         7.27E-07         0.000217           hsa-mir-143         -10.1044         8.01E-05         0.002633           hsa-mir-225         -9.61812         0.00051         0.015575           hsa-mir-143         -10.2596         3.30E-05         0.002633           h		bea_mir_31	6.4702	0.001608	0.033360
Isa-mir-139-5p         -6.74784         0.000302         0.00836           hsa-mir-133a         -7.05564         1.61E-06         0.000321           hsa-mir-1         -7.14977         0.00022         0.09764           hsa-mir-181b         -7.16942         0.000772         0.020654           hsa-mir-181b         -7.16942         0.000772         0.020654           hsa-mir-190         -7.44023         0.000777         0.020654           hsa-mir-100         -7.44023         0.000777         0.020654           hsa-mir-152         -7.81912         2.15E-05         0.001982           hsa-mir-152         -7.81912         2.15E-05         0.001982           hsa-mir-455-3p         -8.02489         4.0E-05         0.00283           hsa-mir-205         -9.14687         0.001875         0.020661           hsa-mir-205         -9.14687         0.001875         0.00217           hsa-mir-205         -9.14687         0.001875         0.00217           hsa-mir-220         -9.61812         0.00051         0.01575           hsa-mir-221         -9.01993         7.27E-07         0.000217           hsa-mir-23b         -10.2908         1.20E-10         1.44E-07           hsa-mir-2		hoo mir 279	6 72010	0.00162	0.000000
Isa-mir-133a       -0.74744       0.000302       0.010330         hsa-mir-133a       -7.05564       1.61E-06       0.000321         hsa-mir-1       -7.14977       0.00022       0.009764         hsa-mir-181b       -7.16942       0.000772       0.020654         hsa-mir-28-3p       -7.2595       0.000262       0.010777         hsa-mir-100       -7.44023       0.000777       0.020654         hsa-mir-152       -7.81912       2.15E-05       0.001882         hsa-mir-152       -7.81912       2.15E-05       0.001882         hsa-mir-28-5p       -8.02489       4.40E-05       0.003283         hsa-mir-28-5p       -8.02489       4.00E-05       0.003283         hsa-mir-205       -9.14687       0.001875       0.00261         hsa-mir-205       -9.14687       0.001875       0.00217         hsa-mir-205       -9.14933       7.27E-07       0.000217         hsa-mir-210       -9.63879       6.73E-07       0.00217         hsa-mir-221       -9.0388       0.0051       0.015575         hsa-mir-23b       -10.2908       1.20E-10       1.44E-07         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-19		IISd-IIIII-370	-0.73012	0.000103	0.000000
Insa-mir-133a       -7.0504       1.61E-06       0.00024         hsa-mir-131       -7.14977       0.00022       0.009764         hsa-mir-181b       -7.16942       0.000772       0.20654         hsa-mir-28-3p       -7.2595       0.000262       0.010777         hsa-mir-90b       -7.44023       0.000777       0.020654         hsa-mir-92b       -7.47102       0.001618       0.03389         hsa-mir-252       -7.81912       2.15E-05       0.001982         hsa-mir-28-5p       -8.02489       4.40E-05       0.002833         hsa-mir-30c       -8.74333       0.000284       0.010818         hsa-mir-205       -9.14687       0.001875       0.020681         hsa-mir-27b       -9.15993       7.27E-07       0.000217         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-224       -9.63879       6.73E-07       0.00217         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-23b       -10.2563       0.001784       0.035561         hsa-mir-2		lisa-IIII-139-5p	-0.74704	0.000302	0.010630
hsa-mir-1       -/.149//       0.00022       0.009/64         hsa-mir-181b       -7.16942       0.000772       0.020654         hsa-mir-100       -7.44023       0.000777       0.020654         hsa-mir-100       -7.44023       0.000777       0.020654         hsa-mir-152       -7.81912       2.15E-05       0.001982         hsa-mir-28-5p       -8.02489       4.40E-05       0.00283         hsa-mir-30c       -8.74333       0.000284       0.00261         hsa-mir-27b       -9.14687       0.001875       0.00261         hsa-mir-27b       -9.15993       7.27E-07       0.000217         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-223       -9.63879       6.73E-07       0.000217         hsa-mir-23b       -10.1044       8.01E-05       0.002633         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-245       -10.2596       3.30E-05       0.002633         hsa-mir-25a       -10.2596       3.30E-05       0.002633         hsa-mir-145a       -10.2596       3.30E-05       0.002633         hsa-mir-145a       -10.2596       3.30E-05       0.002633         hsa-mir-12		nsa-mir-133a	-7.05564	1.61E—06	0.000321
hsa-mir-181b       -7.16942       0.000772       0.020654         hsa-mir-28-3p       -7.2595       0.000262       0.010777         hsa-mir-100       -7.44023       0.000777       0.020654         hsa-mir-99b       -7.47102       0.001618       0.033369         hsa-mir-99b       -7.81912       2.15E-05       0.001982         hsa-mir-28-5p       -8.02489       4.40E-05       0.003283         hsa-mir-30c       -8.74333       0.000284       0.010818         hsa-mir-455-3p       -8.97619       0.001875       0.020681         hsa-mir-20c       -9.14687       0.001875       0.020217         hsa-mir-27b       -9.15993       7.27E-07       0.000217         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-143       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818 <t< td=""><td></td><td>hsa-mir-1</td><td>-7.14977</td><td>0.00022</td><td>0.009764</td></t<>		hsa-mir-1	-7.14977	0.00022	0.009764
hsa-mir-28-3p-7.225950.0002620.010777hsa-mir-100-7.440230.0007770.020654hsa-mir-99b-7.471020.0016180.03369hsa-mir-152-7.819122.15E-050.001982hsa-mir-28-5p-8.024894.40E-050.00284hsa-mir-30c-8.743330.0002840.010818hsa-mir-205-9.146870.0018750.020681hsa-mir-27b-9.159937.27E-070.000217hsa-mir-222-9.618120.000510.015575hsa-mir-23b-10.25963.30E-050.00217hsa-mir-221-10.29081.20E-1101.44E-07hsa-mir-295-10.36380.0002890.010818hsa-mir-199a-3p-10.36330.0017840.03561hsa-mir-145-10.61030.00270.010777		hsa-mir-181b	-7.16942	0.000772	0.020654
hsa-mir-100       -7.44023       0.000777       0.020654         hsa-mir-99b       -7.47102       0.001618       0.03369         hsa-mir-152       -7.81912       2.15E-05       0.001982         hsa-mir-28-5p       -8.02489       4.40E-05       0.003283         hsa-mir-30c       -8.74333       0.000284       0.010818         hsa-mir-455-3p       -8.97619       0.001795       0.020681         hsa-mir-205       -9.14687       0.001875       0.030127         hsa-mir-205       -9.14687       0.001875       0.000217         hsa-mir-205       -9.15993       7.27E-07       0.000217         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-143       -10.1044       8.01E-05       0.00217         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-221       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-125a-5p       -10.5363       0.001784       0.035561         hsa-mir-145       -10.6103       0.00027       0.010777		hsa-mir-28-3p	-7.22595	0.000262	0.010777
hsa-mir-99b-7.471020.0016180.03369hsa-mir-152-7.819122.15E-050.001982hsa-mir-28-5p-8.024894.40E-050.003283hsa-mir-30c-8.743330.0002840.010818hsa-mir-455-3p-8.976190.0007950.020681hsa-mir-205-9.146870.0018750.036162hsa-mir-27b-9.159937.27E-070.000217hsa-mir-27b-9.618120.000510.015575hsa-mir-222-9.638796.73E-070.000217hsa-mir-143-10.10448.01E-050.004791hsa-mir-23b-10.25963.30E-050.02633hsa-mir-221-10.29081.20E-101.44E-07hsa-mir-199a-3p-10.36380.0002890.010818hsa-mir-145-10.53630.0017840.035561hsa-mir-145-10.61030.000270.010777		hsa-mir-100	-7.44023	0.000777	0.020654
hsa-mir-152-7.819122.15E-050.001982hsa-mir-28-5p-8.024894.40E-050.003283hsa-mir-30c-8.743330.0002840.010818hsa-mir-455-3p-8.976190.0007950.020681hsa-mir-205-9.146870.0018750.036162hsa-mir-27b-9.159937.27E-070.000217hsa-mir-222-9.618120.000510.015575hsa-mir-143-10.10448.01E-050.0002191hsa-mir-23b-10.25963.30E-050.002633hsa-mir-221-10.29081.20E-101.44E-07hsa-mir-199a-3p-10.36380.0002890.010818hsa-mir-145-10.61030.00270.010777		hsa-mir-99b	-7.47102	0.001618	0.033369
hsa-mir-28-5p       -8.02489       4.40E-05       0.003283         hsa-mir-30c       -8.74333       0.000284       0.010818         hsa-mir-455-3p       -8.97619       0.000795       0.020681         hsa-mir-205       -9.14687       0.001875       0.030162         hsa-mir-27b       -9.15993       7.27E-07       0.000217         hsa-mir-27b       -9.61812       0.00051       0.015575         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-143       -10.1044       8.01E-05       0.000217         hsa-mir-22b       -9.63879       6.73E-07       0.000217         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-24       -10.2596       3.05E-05       0.002633         hsa-mir-25       -10.3638       0.000289       0.010818         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-125a-5p       -10.5363       0.001784       0.035561         hsa-mir-145       -10.6103       0.00027       0.010777		hsa-mir-152	-7.81912	2.15E-05	0.001982
hsa-mir-30.       -8.74333       0.000284       0.010818         hsa-mir-455-3p       -8.97619       0.000795       0.020681         hsa-mir-205       -9.14687       0.001875       0.036162         hsa-mir-27b       -9.15993       7.27E-07       0.000217         hsa-let-7c       -9.61812       0.00051       0.015575         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-230       -10.1044       8.01E-05       0.004791         hsa-mir-241       -10.2596       3.30E-05       0.002633         hsa-mir-221       -10.2908       1.20E-10       1.44E-07         hsa-mir-19a-3p       -10.3638       0.000289       0.010818         hsa-mir-145       -10.5363       0.001784       0.035561		hsa-mir-28-5p	-8.02489	4.40E-05	0.003283
hsa-mir-455-3p       -8.97619       0.000795       0.020681         hsa-mir-205       -9.14687       0.001875       0.036162         hsa-mir-27b       -9.15993       7.27E-07       0.000217         hsa-let-7c       -9.61812       0.00051       0.015575         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-143       -10.1044       8.01E-05       0.004791         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-221       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-145       -10.6103       0.0027       0.010777		hsa-mir-30c	-8.74333	0.000284	0.010818
had min 100 op       0.01875       0.001875       0.036162         hsa-mir-27b       -9.14687       0.001875       0.030612         hsa-mir-27b       -9.15993       7.27E-07       0.000217         hsa-let-7c       -9.61812       0.00051       0.015575         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-143       -10.1044       8.01E-05       0.004791         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-221       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-145       -10.6103       0.0027       0.010777		hsa-mir-455-3n	-8 97619	0.000795	0.020681
had mir 20b       -9.15993       7.27E-07       0.000217         hsa-mir-27b       -9.61812       0.00051       0.01575         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-143       -10.1044       8.01E-05       0.004791         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-21       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-145       -10.6103       0.00027       0.010777		hsa-mir-205	_9 14687	0.001875	0.036162
had him 210       -9.0303       1.212-01       0.000217         hsa-let-7c       -9.61812       0.00051       0.015575         hsa-mir-222       -9.63879       6.73E-07       0.000217         hsa-mir-143       -10.1044       8.01E-05       0.002633         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-221       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-125a-5p       -10.5363       0.001784       0.035561         hsa-mir-145       -10.6103       0.00027       0.010777		hsa-mir-27b	0 15003	7.27E_07	0.000102
hsa-mir-122     -9.63879     6.73E-07     0.000217       hsa-mir-143     -10.1044     8.01E-05     0.002633       hsa-mir-23b     -10.2596     3.30E-05     0.002633       hsa-mir-221     -10.2908     1.20E-10     1.44E-07       hsa-mir-199a-3p     -10.3638     0.000289     0.010818       hsa-mir-125a-5p     -10.5363     0.001784     0.035561       hsa-mir-145     -10.6103     0.00027     0.010777		hea_lat_70	-0.61910	0.00051	0.000217
H38-HIII-222       -9.63879       6.73E-07       0.000217         hsa-mir-143       -10.1044       8.01E-05       0.004791         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-221       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-125a-5p       -10.5363       0.001784       0.035561         hsa-mir-145       -10.6103       0.00027       0.010777		Hoa-Hel-/6	-3.01012		0.000017
hsa-mir-143       -10.1044       8.01E-05       0.004791         hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-221       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-125a-5p       -10.5363       0.001784       0.035561         hsa-mir-145       -10.6103       0.00027       0.010777		nsa-mir-222	-9.638/9	0./3E-U/	0.000217
hsa-mir-23b       -10.2596       3.30E-05       0.002633         hsa-mir-221       -10.2908       1.20E-10       1.44E-07         hsa-mir-199a-3p       -10.3638       0.000289       0.010818         hsa-mir-125a-5p       -10.5363       0.001784       0.035561         hsa-mir-145       -10.6103       0.00027       0.010777		hsa-mir-143	-10.1044	8.01E-05	0.004791
hsa-mir-221-10.29081.20E-101.44E-07hsa-mir-199a-3p-10.36380.0002890.010818hsa-mir-125a-5p-10.53630.0017840.035561hsa-mir-145-10.61030.000270.010777		hsa-mir-23b	-10.2596	3.30E-05	0.002633
hsa-mir-199a-3p-10.36380.0002890.010818hsa-mir-125a-5p-10.53630.0017840.035561hsa-mir-145-10.61030.000270.010777		hsa-mir-221	-10.2908	1.20E-10	1.44E-07
hsa-mir-125a-5p-10.53630.0017840.035561hsa-mir-145-10.61030.000270.010777		hsa-mir-199a-3p	-10.3638	0.000289	0.010818
hsa-mir-145 –10.6103 0.00027 0.010777		hsa-mir-125a-5p	-10.5363	0.001784	0.035561
		hsa-mir-145	-10.6103	0.00027	0.010777

constructed and visualized through Cytoscape software (available at http://www.cytoscape.org/, version: 3.2.0).<sup>[22]</sup>

# 2.6. Construction of MFSN

GO enrichment analysis is a common approach for functional annotation.<sup>[23]</sup> If co-regulated target genes of 2 (or more) DEmi-RNAs were significantly enriched in 1 (or more) GO BP functional term, it is defined that functional synergistic relationships exist between the corresponding DEmiRNAs. To construct an MFSN, DEmiRNA interactions in DEmiRNA–DEmiRNA co-regulation network were ranked according to the numbers of their co-regulated target genes. Thereafter, the target genes co-regulated by the top 30 DEmiRNA pairs were put through GO BP functional enrichment analysis by clusterProfiler package in R (available at http://bioconductor.org/packages/release/bioc/html/clusterProfiler.html,

version: 2.0.0),<sup>[24]</sup> and the criteria for significant BP terms were P < 0.05 and q < 0.05. Moreover, based on functional enrichment results, DEmiRNA interactions sharing 1 (or more) GO BP functional term were utilized to construct MSFN, which was further visualized through Cytoscape software.

## 2.7. Construction of DEmiRNA–TF regulation network and subnetwork

Comprising of eukaryotic TFs, TFs target genes, and regulatory binding sites, the TRANSFAC database (http://www.generegulation.com/index2) has been established and well developed.<sup>[25]</sup> According to TRANSFAC database and Transcriptional Regulatory Element Database (TRED, https://cb.utdallas.edu/ cgi-bin/TRED/tred.cgi?process=home),<sup>[26]</sup> cancer-related TFs were screened out to build DEmiRNA–TF regulation network,



Figure 2. DEmiRNA–DEmiRNA co-regulation network. Edges represent the target genes co-regulated by a pair of miRNAs. Edge thickness represents the number of co-regulated target genes. Red nodes represent up-regulated DEmiRNAs, and yellow nodes represent down-regulated DEmiRNAs.

which was further visualized by Cytoscape software. Then, the node degrees of TFs in this network were analyzed, and subnetworks were mined.

### 3. Results

The process of analyses in our study is presented in Fig. 1.

# 3.1. Data preprocessing, DEmiRNAs screening, and DEmiRNA-target gene interaction constructing

The clinical details of 50 PC patients in the dataset of GSE45604 were listed in Table 1. After data preprocessing, expression information of 1196 miRNAs corresponding to 20,643 probes was available. Under the predefined criteria for DEmiRNAs and target genes screening ( $|\log_2 FC| > 1$ , FDR < 0.05), 66 significant DEmiRNAs were identified between PC patients and normal controls, including 7 up-regulated miRNAs with 18,642 target genes and 59 down-regulated miRNAs with 130,694 target genes. The 66 DEmiRNAs are listed in Table 2.

# 3.2. Construction of DEmiRNA–DEmiRNA co-regulation network

Based on the numbers of co-regulated target genes, a DEmiRNA–DEmiRNA co-regulation network was constructed, involving 66 nodes (DEmiRNAs), 2024 edges (co-regulation relationships), and 11,086 co-regulated target genes (Fig. 2). In this network, there were strong relationships between hsa-miR-875-3p, hsa-miR-4328, hsa-miR-24, and hsa-miR-31; hsa-miR-338-5p and hsa-miR-543; hsa-miR-24 and hsa-miR-1184; hsa-miR-24 and hsa-miR-1207-5p; etc. Especially, hsa-miR-24 was down-regulated, whereas hsa-miR-1184 and hsa-miR-1207-5p were up-regulated, which shared 1321 and 1230 target genes with hsa-miR-24, respectively. Additionally, hsa-mir-875-3p was

tightly linked to hsa-mir-4328 in the network, and both of them were down-regulated (Fig. 2).

# 3.3. Construction of DEmiRNA–DEmiRNA functional synergistic network

After GO BP functional enrichment analysis with the aforementioned criteria (P < 0.05, q < 0.05), significant functional synergistic relationships were identified among the top 30 DEmiRNA interactions with most co-regulated target genes in Fig. 2. Then, MFSN was constructed (Fig. 3). In addition, 693 significant GO BP terms were enriched by the co-regulated target genes of hsa-miR-1207-5p and hsa-miR-24, and 862 significant BP terms were enriched by the co-regulated target genes of hsamiR-1184 and hsa-miR-24. Apparently, hsa-miR-1184, hsamiR-1207-5p, and hsa-miR-24 had significant functional synergistic relationships.

# 3.4. Construction of DEmiRNA–TF regulation network and subnetwork

Using the information in TRANSFAC database, 331 TFs were predicted to regulate the 11,086 co-regulated target genes. Further, according to the information of 36 cancer-related TF families in TRED database, 52 of the 331 TFs belonged to 28 cancer-related TF families (Table 3). Then, regulation network was constructed between the 52 cancer-related TFs and their corresponding DEmiRNAs (Fig. 4). Considering miRNAs often suppress gene or TF expressions by targeting them, increased miRNAs might have more important roles in cancer development. Therefore, we mainly focused on the up-regulated DEmiRNAs. Among the 7 identified DEmiRNAs, 6 were exhibited in this network. As hsa-miR-1207-5p and hsa-miR-1184 both had the co-regulation relationship with the



Figure 3. DEmiRNA–DEmiRNA functional synergistic network. Edge thickness represents the number of GO BP terms enriched by co-regulated target genes. Red nodes represent up-regulated DEmiRNAs, and yellow nodes represent down-regulated DEmiRNAs. BP=biological process, GO=gene ontology.

#### Table 3

The 52 cancer-related transcription factors regulated by differentially expressed miRNAs.

APRT         H/F         Hypel-induction factor         14           AFF3         A/F         Activatory transcription factor         5           AFF7         A/F         Activatory transcription factor         20           BDL5         BC         BC         BC         BC         BC           BFCA         BFCA         BFCA         BFCA         BFCA         BFCA           BFCA         BFCA         BFCA         BFCA         BFCA         BFCA           BFCA	Transcription factor	Family	Full name	Degree
ATF3ATFActivating transcription factor5ATF7ATFActivating transcription factor20BCL6BDLBredt CLL/mythoma10BRCA1BRGABreast cancer susceptibility protein11BRCA2BRGABreast cancer susceptibility protein27CREMCREBCAMP responsive element binding protein27CREMCREBCAMP responsive element binding protein27CREMCREBCAMP responsive element binding protein27CREMCREBCAMP responsive element binding protein15ERGERGEarly growth response protein16ELK1ELKMenter of ES encogene family2ERGERGEstrogan response protein28ERGERGEstrogan response protein16ELK1ELKMenter of ES encogene family2ERGERGEstrogan response protein16ERGETSEstrogan response protein16GL1GL1Gliama-essociated ancogene homolog15GL3GL1Gliama-essociated ancogene homolog15GL3GL1Gliama-essociated ancogene homolog15GL3GL1HilfHypotal-inductof factor24MFANRNuclear factor / CAAI-Hynding transcription factor24MFANRNuclear factor / CAAI-Hynding transcription factor26GL3GL1Gliama factor (CAAI-Hynding transcription factor26MFANRA <td>ARNT</td> <td>HIF</td> <td>Hypoxia-inducible factor</td> <td>14</td>	ARNT	HIF	Hypoxia-inducible factor	14
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Degree represented the number of corresponding DEmiRNAs.

down-regulated hsa-miR-24 (Fig. 3); and hsa-miR-182 and hsamiR-183 had been implicated in PC or other cancer types,<sup>[14,27,28]</sup> the 4 DEmiRNAs were further extracted to construct subnetwork (Fig. 5). It is found that the TFs of peroxisome proliferative activated receptor, alpha (PPARA) and cyclic AMP-responsive element modulator (CREM) were 2 critical nodes with the highest degree (=4), which indicated both of them were interplayed with the 4 up-regulated DEmiRNAs.

# 4. Discussion

PC is a prevalent cancer, whose occurrence and development is a complex process. Comprehensive analysis of miRNAs and TFs related to PC will help us to understand the molecular mechanism of PC and develop novel therapeutic targets for its treatment. In this study, we identified 66 significant DEmiRNAs between normal and PC specimens and their coregulated cancer-related TFs through bioinformatics analysis. It



Figure 4. Regulation networks between 52 cancer-related TFs and the corresponding DEmiRNAs. Yellow triangles represent cancer-related TFs. Red nodes represent up-regulated DEmiRNAs. Purple nodes represent down-regulated DEmiRNAs. TFs = transcription factors.

was predicted that 4 up-regulated DEmiRNAs (hsa-miR-1207-5p, hsa-miR-1184, hsa-miR-182, and hsa-miR-183) and 2 of their co-regulated target TFs (PPARA and CREM) might participate in PC. In addition, 2 down-regulated DEmiRNAs, hsa-mir-875-3p and hsa-mir-4328 were also important for their strong relationships in the co-regulation network.

Among these DEmiRNAs, hsa-miR-1207-5p and hsa-miR-1184 shared more than 1200 target genes with hsa-miR-24, which enhances breast tumor metastasis and invasion by targeting PTPN9 and PTPRF, and promoting EGF signaling.<sup>[29]</sup> In addition, miRNA-24 is one of the most abundant miRNAs in cervical cancer cells, and it is reported to be up-regulated in solid stomach cancers.<sup>[29]</sup> It seems like hsa-miR-24 plays vital roles in various cancers. In PC, miR-24 is found to modulate apoptosis in the DU-145 cell lines, via targeting to the coding sequence region of fas associated factor 1.<sup>[30]</sup> Therefore, we speculated that it may

be involved in PC progression. As large amount of target genes and GO BP terms were shared by hsa-miR-1184 and hsa-miR-1207-5p with hsa-miR-24, hsa-miR-1184 and hsa-miR-1207-5p might also play a role in the development of PC, and they might be used as potential targets for the treatment of PC. In addition, it is reported that hsa-miR-182-5p promotes cell proliferation, migration, and invasion by down regulating forkhead box F2, reversion-inducing cysteine-rich protein with Kazal motifs, and metastasis suppressor 1 in human PC, and the knock-down of miR-182-5p with its inhibitor significantly decreased prostate tumor growth.<sup>[31]</sup> Moreover, hsa-miR-183 is an oncogenic miRNA targeting dickkopf 3 homolog (DKK3) and drosophila mothers against decapentaplegic family member 4 (SMAD4) in PC.<sup>[27]</sup> The high expression of hsa-miR-183 was correlated with high pathological (pT) stage and short overall survival time of PC patients, and the knockdown of hsa-miR-183 significantly



Figure 5. Regulation subnetworks between cancer-related TFs and the corresponding DEmiRNAs. Yellow triangles represent cancer-related TFs. Red nodes represent up-regulated DEmiRNAs. The 2 aggravated yellow triangles represent the TFs co-regulated by 4 DEmiRNAs. TFs=transcription factors.

decreased cell proliferation, motility, and prostate tumor growth.<sup>[27]</sup> In this study, hsa-miR-182 and hsa-miR-183 were significantly up-regulated in PC tissue, coinciding with previous studies. Therefore, these DEmiRNAs might be key regulators in PC progression, and they might be used as potential targets for the treatment of PC.

Regarding to the down-regulated DEmiRNAs, hsa-miR-875-5p is predicted to be associated with different PC tumor status.<sup>[32]</sup> Inconsistent with our findings in PC, in other cancer types such as intrahepatic cholangiocarcinoma and esophageal cancer, expression of hsa-miR-875-3p is increased in tumor groups compared with normal control.<sup>[33,34]</sup> This prompts us the down-regulation of hsa-miR-875-3p might be specific in PC, and could be used as a novel indicator for the disease progression. However, its detailed functions should be investigated by further studies. Currently, only a few studies reported the alteration of hsa-mir-4328 in cancers. In mucinous cystadenocarcinoma, hsa-mir-4328 is significantly decreased compared with the mucinous cystadenoma.<sup>[35]</sup> In addition, it is also down-regulated in keloid fibroblasts.<sup>[36]</sup> Nevertheless, dysregulation of this miRNA has not been reported in PC yet. Thus, based on our study, it might be inferred down-regulation of hsa-mir-4328 may be a novel biomarker for PC progression.

The DEmiRNA–TF regulation network displayed that PPARA and CREM were co-regulated by 4 up-regulated DEmiRNAs. CREM can bind to c-fos CRE and heterodimerize with CREbinding protein, which could block cAMP induction and cAMPinduced apoptosis of germ cells.<sup>[27]</sup> In this study, CREM was found to be co-regulated by 4 DEmiRNAs, which might influence apoptosis and carcinogenesis in PC cells. However, no current studies have reported the regulation between this gene and the 4 miRNAs. PPARA is a peroxisome proliferator-activated receptor, which regulates key genes involved in fatty acid oxidation, extracellular lipid metabolism, hemostasis, and inflammation.<sup>[37]</sup> It is demonstrated that the up-regulation of PPARA and its downstream targets leads to increased lipogenesis, which slows cell growth and tumor progression.<sup>[38]</sup> In this study, the significant upregulation of 4 DEmiRNAs might collectively decrease PPARA mRNA, promoting cell growth and tumor progression. However, these targeting relationships need to be further validated.

What is more, conflicts between DEmiRNAs co-regulating the same gene also exist. Nuclear factor of kappa light polypeptide (NFKB1) was presented in DEmiRNA-TF regulation subnetwork. NFKB1 is associated with colorectal cancer.<sup>[39]</sup> Constitutive NFKB activation was observed in 40% of colorectal cancer tissues.<sup>[40]</sup> In this study, NFKB1 was co-regulated by hsa-miR-183 and hsa-miR-338-5p, which were significantly up-regulated and down-regulated in PC tissue, respectively. Therefore, it is predicted that the balance between hsa-miR-183 and hsa-miR-338-5p might play a role in PC through co-regulating NFKB1. Moreover, cyclooxygenase 2 (COX2) is a key enzyme in the biosynthesis of prostaglandins, which promote inflammation.<sup>[41]</sup> Additionally, COX2 promotes cell proliferation and growth, and its overexpression is often found in tumor tissues.<sup>[42]</sup> The activation of P2Y2/Src/p38/COX2 pathway induces resistance to apoptosis in PC cells.<sup>[42]</sup> It is reported that miR-101 could inhibit COX2 expression post-transcriptionally, and exogenous miR-101 could effectively suppress PC cells growth, providing a new therapy for PC treatment.<sup>[43]</sup> In this study, COX2 is co-regulated by both up-regulated and down-regulated DEmiRNAs, like hsamiR-490-5p, hsa-miR-509-3-5p, hsa-miR-143, hsa-miR-628-3p, hsa-miR-182, and hsa-miR-183, indicating that the balance between these DEmiRNAs might play a role in PC through coregulating COX2.

Researches on miRNAs and TFs are fascinating for human to understand and recognize the mechanism of cancers and further develop new therapeutic strategies for cancers. The miRNAs and TFs found in our research might co-regulate PC and thus serve as new therapeutic targets for PC treatment. But more in vivo researches are needed, and we plan to validate the results of this study by using real-time PCR and dual-luciferase reporter assay in the future study. In addition, it will be useful to further analyze the dynamic changes of miRNA expression along the progression of PC using specimens from patients with different pT stage or Gleason score, and we plan to perform this analysis in the future.

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