Supplementary Material

Identification of potential biomarkers for idiopathic pulmonary fibrosis and validation of TDO2 as a potential therapeutic target

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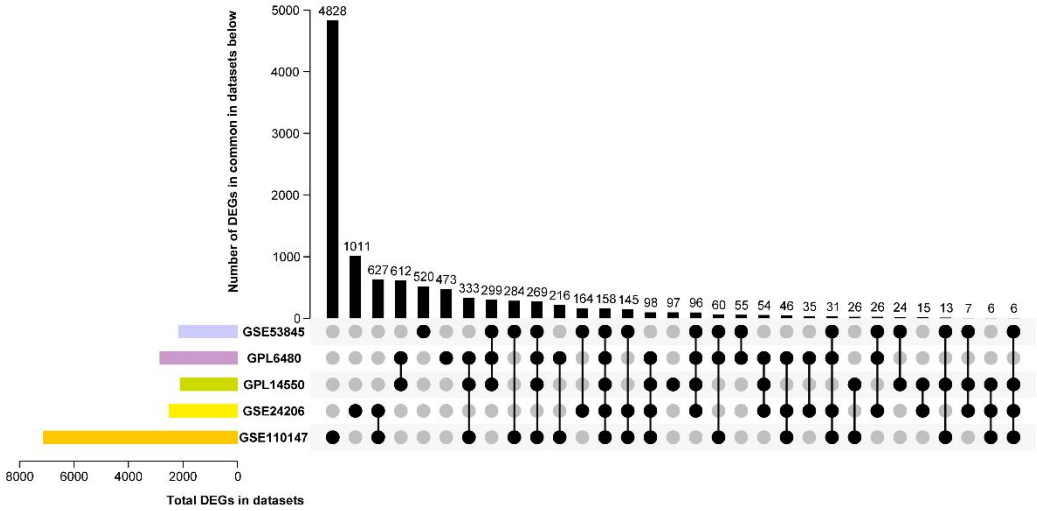
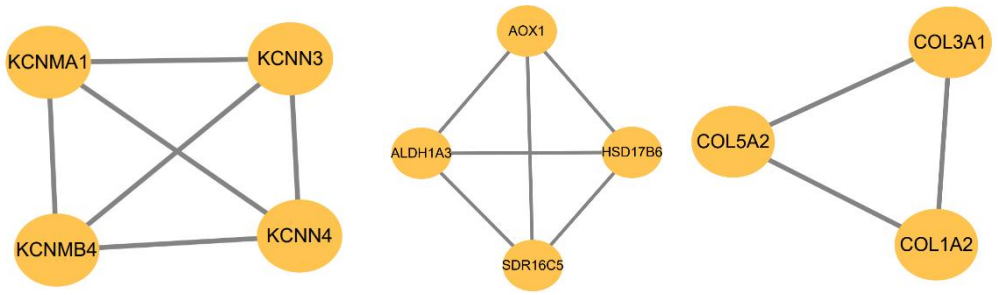
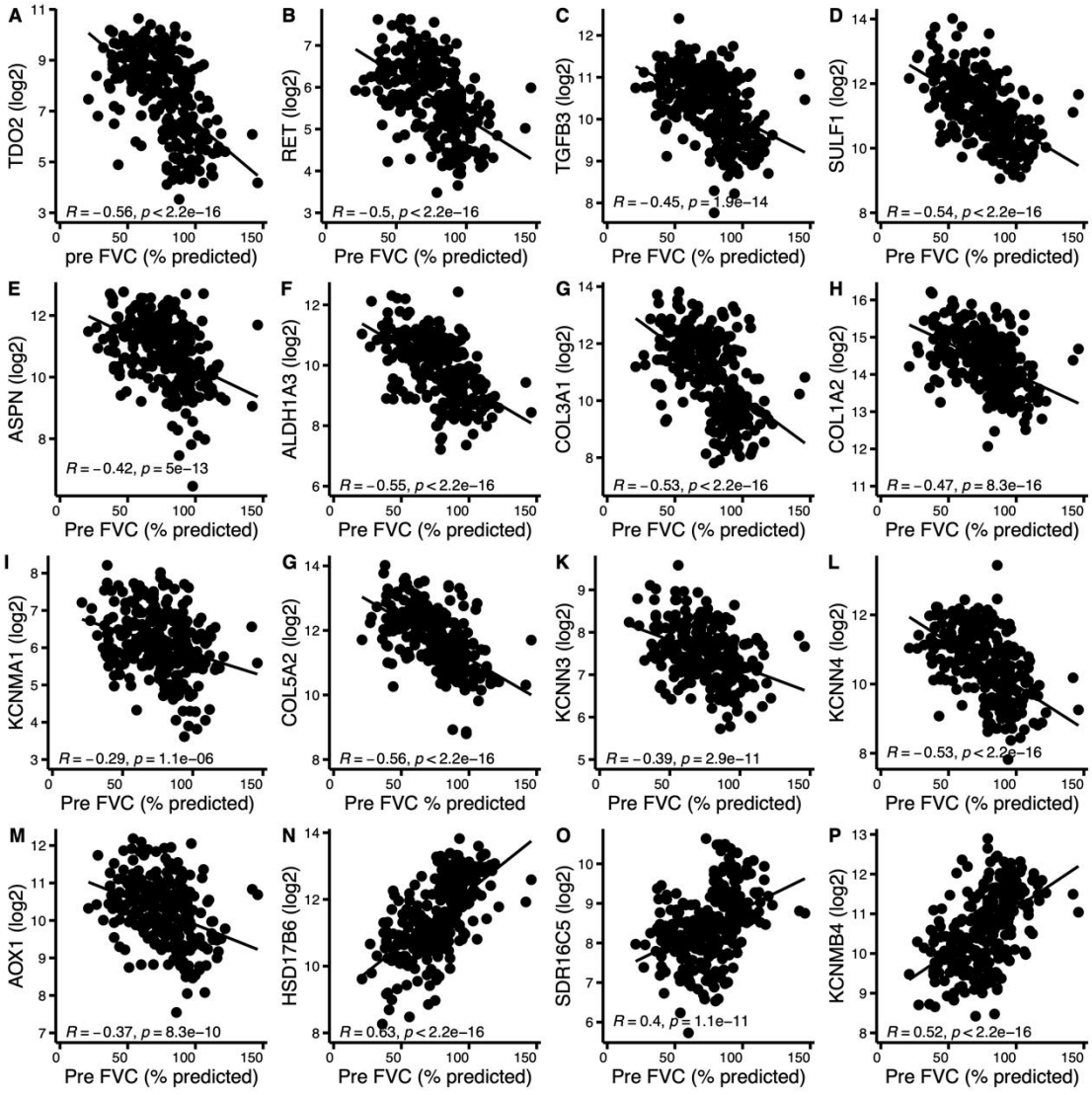
Supplementary Figures



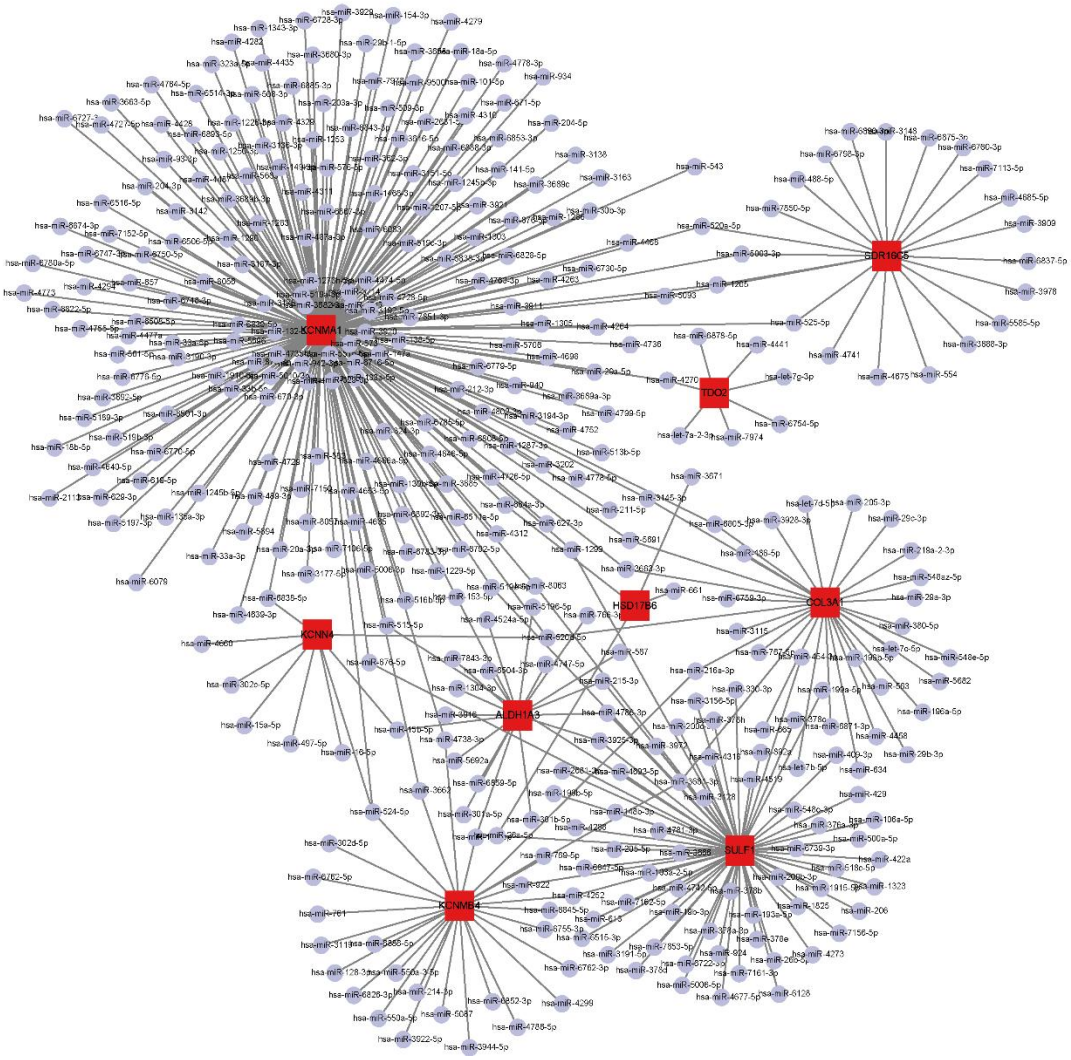
Supplementary Figure 1 UpSet plot of differentially expressed genes. Graph of total number of differentially expressed genes (DEGs) (X axis) in each dataset (Y axis). Intersection of sets of genes at multiple datasets. Each column corresponds to a dataset or set of datasets (dots connected by lines below the X axis) containing the same DEGs. The number of genes in each set appears above the column, while the dataset shared are indicated in the graphic below the column, with the dataset on the left. The consistency between DEGs of GSE110147 and other data sets was less than 50%. Therefore, GSE110147 was discarded in subsequent analyses.



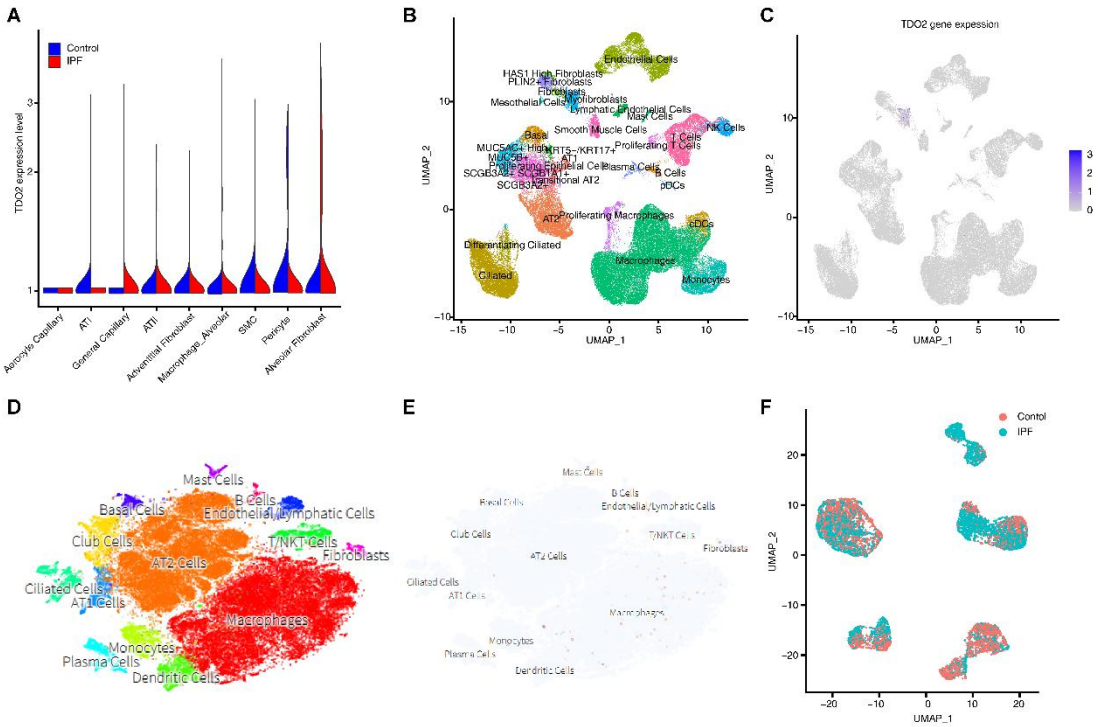
Supplementary Figure 2 Identified three modules with the MCODE plugin. Cluster 1 (score: 4.000, 4 nodes and 6 edges), followed by cluster 2 (score: 4.000, 4 nodes and 6 edges), cluster 3 (score: 3.000, 3 nodes and 3 edges).



Supplementary Figure 3 Correlation with the lung functions of idiopathic pulmonary fibrosis patients. *TDO2, RET, TGFB3, SULF1, ASPN, ALDH1A3, COL3A1, COL1A2, KCNMA1, COL5A2, KCNN3, KCNN4* and *AOX1* expression was negatively correlated with forced vital capacity (FVC), while HSD17B6, SDR16C5, KCNMB4 were significantly positively correlated with FVC. The Pearson correlation metric was computed by using the 'stat_cor' function in R.



Supplementary Figure 4 The co-expressed network of messenger RNAs and target microRNAs.



Supplementary Figure 5 Single-cell landscape of pulmonary fibrosis and normal lungs. A: *TDO2* gene expression in each cluster in GSE136831; B: Uniform Manifold Approximation and Projection (UMAP) analyzed single-cell transcriptomes from GSE135893 and annotated by cell type; C: Expression of *TDO2* gene in GSE135893; D and E: (D) Cell cluster analysis and (E) gene expression of *TDO2* in GSE122960; F: UMAP with cells labeled by disease identity in GSE136831.

Supplementary Tables

Supplementary Table 1 IPF data used in this study

GEO Dataset	Platform	Control	IPF
GSE110147	Affymetrix GPL6244	11	22
	Agilent microarray		
GSE53845	GPL6480	8	40
	Agilent GPL6480	17	38
GSE47460	Agilent GPL14550	91	122
GSE24206	Affymetrix GPL570	6	17

Supplementary Table 2 The top 30 genes ranked by MCC method

Rank	Name	Score
1	*ALDH1A3*	7
2	*HSD17B6*	6
2	*KCNMA1*	6
2	*KCNMB4*	6
2	*KCNN4*	6
2	*KCNN3*	6
2	*SDR16C5*	6
2	*AOX1*	6
9	*TGFB3*	5
10	*ASPN*	4
10	*COL3A1*	4
10	*IGF1*	4
10	*MMP7*	4
14	*FBLN2*	3
14	*COL18A1*	3
14	*COL1A2*	3
17	*FZD5*	2
17	*RET*	2
17	*EPHA3*	2
17	*MATN3*	2
17	*CLU*	2
17	*LDLR*	2
17	*IRS2*	2
17	*COL15A1*	2
17	*ALDH18A1*	2
17	*COL5A2*	2
27	*TIMP3*	1
27	*SULF1*	1

27	*MT1E*	1
27	*MT1M*	1

Supplementary Table 3 Top 30 genes ranked by DMNC method

Rank	Name	Score
1	*HSD17B6*	0.463463057
1	*KCNMA1*	0.463463057
1	*KCNMB4*	0.463463057
1	*KCNN4*	0.463463057
1	*KCNN3*	0.463463057
1	*ALDH1A3*	0.463463057
1	*SDR16C5*	0.463463057
1	*AOX1*	0.463463057
9	*COL3A1*	0.307786103
9	*COL1A2*	0.307786103
9	*COL5A2*	0.307786103
12	*TIMP3*	0
12	*SULF1*	0
12	*MT1E*	0
12	*MT1M*	0
12	*COMP*	0
12	*NEDD4L*	0
12	*ARHGAP6*	0
12	*CTHRC1*	0
12	*KDELR3*	0
12	*FZD5*	0
12	*SCG2*	0
12	*SCG5*	0
12	*ASPN*	0
12	*DOK5*	0
12	*TGFB3*	0
12	*RET*	0
12	*OGN*	0

12	*EFNA4*	0
12	*EPHA3*	0

Supplementary Table 4 Top 30 genes ranked by MNC method

Rank	Name	Score
1	*HSD17B6*	3
1	*KCNMA1*	3
1	*KCNMB4*	3
1	*KCNN4*	3
1	*KCNN3*	3
1	*ALDH1A3*	3
1	*SDR16C5*	3
1	*AOX1*	3
9	*COL3A1*	2
9	*COL1A2*	2
9	*COL5A2*	2
12	*TIMP3*	1
12	*SULF1*	1
12	*MT1E*	1
12	*MT1M*	1
12	*COMP*	1
12	*NEDD4L*	1
12	*ARHGAP6*	1
12	*CTHRC1*	1
12	*KDELR3*	1
12	*FZD5*	1
12	*SCG2*	1
12	*SCG5*	1
12	*ASPN*	1
12	*DOK5*	1
12	*TGFB3*	1
12	*RET*	1
12	*OGN*	1

12	*EFNA4*	1
12	*EPHA3*	1

Supplementary Table 5 Top 30 genes by Degree method

Rank	Name	Score
1	*TGFB3*	5
2	*ASPN*	4
2	*COL3A1*	4
2	*IGF1*	4
2	*MMP7*	4
2	*ALDH1A3*	4
7	*HSD17B6*	3
7	*KCNMA1*	3
7	*KCNMB4*	3
7	*KCNN4*	3
7	*FBLN2*	3
7	*KCNN3*	3
7	*COL18A1*	3
7	*COL1A2*	3
7	*SDR16C5*	3
7	*AOX1*	3
17	*FZD5*	2
17	*RET*	2
17	*EPHA3*	2
17	*MATN3*	2
17	*CLU*	2
17	*LDLR*	2
17	*IRS2*	2
17	*COL15A1*	2
17	*ALDH18A1*	2
17	*COL5A2*	2
27	*TIMP3*	1
27	*SULF1*	1

27	*MT1E*	1
27	*MT1M*	1

Supplementary Table 6 Top 30 genes ranked by EPC method

Rank	Name	Score
1	*TGFB3*	4.399
2	*ASPN*	4.349
3	*COL3A1*	3.99
4	*IGF1*	3.709
5	*ALDH1A3*	3.396
6	*COL1A2*	3.284
7	*HSD17B6*	3.225
8	*SDR16C5*	3.215
9	*AOX1*	3.203
10	*MMP7*	3.198
11	*COL5A2*	3.053
12	*COL18A1*	3.001
13	*MATN3*	2.959
14	*FBLN2*	2.901
15	*KCNN3*	2.824
16	*KCNMB4*	2.811
17	*KCNMA1*	2.805
18	*COL15A1*	2.769
19	*KCNN4*	2.754
20	*IRS2*	2.747
21	*LTBP1*	2.692
22	*OGN*	2.658
23	*ITGB8*	2.641
24	*NEDD4L*	2.593
25	*ALDH18A1*	2.555
26	*SULF1*	2.407
27	*IGFBP4*	2.362
28	*IGFBP2*	2.281

29	*RET*	2.277
30	*TIMP4*	2.123

Supplementary Table 7 mRNA–miRNA pairs

Gene	miRNA
TDO2	hsa-miR-6754-5p
TDO2	hsa-let-7a-2-3p
TDO2	hsa-let-7g-3p
TDO2	hsa-miR-6878-5p
TDO2	hsa-miR-4270
TDO2	hsa-miR-4441
TDO2	hsa-miR-7974
COL3A1	hsa-miR-4458
COL3A1	hsa-miR-6759-3p
COL3A1	hsa-miR-3145-3p
COL3A1	hsa-miR-3928-3p
COL3A1	hsa-miR-3681-3p
COL3A1	hsa-miR-29b-3p
COL3A1	hsa-miR-205-3p
COL3A1	hsa-miR-196b-5p
COL3A1	hsa-miR-520d-5p
COL3A1	hsa-miR-6871-3p
COL3A1	hsa-miR-767-5p
COL3A1	hsa-let-7c-5p
COL3A1	hsa-let-7d-5p
COL3A1	hsa-miR-563
COL3A1	hsa-miR-29a-3p
COL3A1	hsa-miR-6805-3p
COL3A1	hsa-miR-196a-5p
COL3A1	hsa-miR-548e-5p
COL3A1	hsa-miR-3663-3p
COL3A1	hsa-let-7b-5p
COL3A1	hsa-miR-186-5p

COL3A1	hsa-miR-5682
COL3A1	hsa-miR-634
COL3A1	hsa-miR-3115
COL3A1	hsa-miR-548az-5p
COL3A1	hsa-miR-216a-3p
COL3A1	hsa-miR-380-5p
COL3A1	hsa-miR-665
COL3A1	hsa-miR-5691
COL3A1	hsa-miR-29c-3p
COL3A1	hsa-miR-219a-2-3p
HSD17B6	hsa-miR-661
HSD17B6	hsa-miR-26a-5p
HSD17B6	hsa-miR-3671
HSD17B6	hsa-miR-664a-3p
KCNMA1	hsa-miR-4736
KCNMA1	hsa-miR-5706
KCNMA1	hsa-miR-6730-5p
KCNMA1	hsa-miR-4755-5p
KCNMA1	hsa-miR-4778-5p
KCNMA1	hsa-miR-6776-5p
KCNMA1	hsa-miR-4646-5p
KCNMA1	hsa-miR-4294
KCNMA1	hsa-miR-6506-5p
KCNMA1	hsa-miR-6780a-5p
KCNMA1	hsa-miR-9500
KCNMA1	hsa-miR-876-3p
KCNMA1	hsa-miR-3689c
KCNMA1	hsa-miR-520d-5p
KCNMA1	hsa-miR-934
KCNMA1	hsa-miR-3190-3p

KCNMA1	hsa-miR-33b-5p
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KCNMA1	hsa-miR-670-3p
KCNMA1	hsa-miR-5010-3p
KCNMA1	hsa-miR-509-3p
KCNMA1	hsa-miR-3658
KCNMA1	hsa-miR-487a-3p
KCNMA1	hsa-miR-876-5p
KCNMA1	hsa-miR-6770-5p
KCNMA1	hsa-miR-4726-5p
KCNMA1	hsa-miR-6748-3p
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KCNMA1	hsa-miR-204-5p
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KCNMA1	hsa-miR-6874-3p
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KCNMA1	hsa-miR-212-3p
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KCNMA1	hsa-miR-4517
KCNMA1	hsa-miR-101-5p
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KCNMA1	hsa-miR-5003-3p
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KCNMA1	hsa-miR-141-5p
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KCNMA1	hsa-miR-1207-5p
KCNMA1	hsa-miR-33a-5p
KCNMA1	hsa-miR-3663-5p
KCNMA1	hsa-miR-5189-3p
KCNMA1	hsa-miR-3145-3p
KCNMA1	hsa-miR-6514-3p
KCNMA1	hsa-miR-4666a-5p
KCNMA1	hsa-miR-519e-5p
KCNMA1	hsa-miR-4727-5p
KCNMA1	hsa-miR-4763-3p
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SDR16C5	hsa-miR-4685-5p
SDR16C5	hsa-miR-3148
SDR16C5	hsa-miR-525-5p
SDR16C5	hsa-miR-5003-3p
SDR16C5	hsa-miR-3909
SDR16C5	hsa-miR-3688-3p

SDR16C5	hsa-miR-554
SDR16C5	hsa-miR-488-5p
SDR16C5	hsa-miR-6837-5p
SDR16C5	hsa-miR-1205
SDR16C5	hsa-miR-7113-5p
SDR16C5	hsa-miR-6890-3p
SDR16C5	hsa-miR-4675
SDR16C5	hsa-miR-6875-3p
SDR16C5	hsa-miR-6760-3p
SDR16C5	hsa-miR-3978
SDR16C5	hsa-miR-5585-5p
SDR16C5	hsa-miR-6798-3p
SDR16C5	hsa-miR-5093
SDR16C5	hsa-miR-7850-5p
SDR16C5	hsa-miR-520a-5p
SDR16C5	hsa-miR-4741
SULF1	hsa-miR-3128
SULF1	hsa-miR-7156-5p
SULF1	hsa-miR-500a-5p
SULF1	hsa-miR-1915-5p
SULF1	hsa-miR-7162-5p
SULF1	hsa-miR-3925-3p
SULF1	hsa-miR-892a
SULF1	hsa-miR-6847-5p
SULF1	hsa-miR-2681-3p
SULF1	hsa-miR-26a-5p
SULF1	hsa-miR-148b-3p
SULF1	hsa-miR-6722-3p
SULF1	hsa-miR-6515-3p
SULF1	hsa-miR-376a-3p

SULF1	hsa-miR-378a-3p
SULF1	hsa-miR-4693-5p
SULF1	hsa-miR-200b-3p
SULF1	hsa-miR-924
SULF1	hsa-miR-6128
SULF1	hsa-miR-922
SULF1	hsa-miR-3666
SULF1	hsa-miR-4519
SULF1	hsa-miR-103a-2-5p
SULF1	hsa-miR-422a
SULF1	hsa-miR-4781-3p
SULF1	hsa-miR-7853-5p
SULF1	hsa-miR-515-5p
SULF1	hsa-miR-518c-5p
SULF1	hsa-miR-199a-5p
SULF1	hsa-miR-215-3p
SULF1	hsa-miR-378b
SULF1	hsa-miR-378c
SULF1	hsa-miR-378d
SULF1	hsa-miR-378e
SULF1	hsa-miR-429
SULF1	hsa-miR-4786-3p
SULF1	hsa-miR-519e-5p
SULF1	hsa-miR-4742-5p
SULF1	hsa-miR-378h
SULF1	hsa-miR-1825
SULF1	hsa-miR-4252
SULF1	hsa-miR-3156-5p
SULF1	hsa-miR-613
SULF1	hsa-miR-200c-3p

SULF1	hsa-miR-19b-3p
SULF1	hsa-miR-676-5p
SULF1	hsa-miR-8063
SULF1	hsa-miR-26b-5p
SULF1	hsa-miR-206
SULF1	hsa-miR-3191-5p
SULF1	hsa-miR-3972
SULF1	hsa-miR-199b-5p
SULF1	hsa-miR-4318
SULF1	hsa-miR-193a-5p
SULF1	hsa-miR-106a-5p
SULF1	hsa-miR-548o-3p
SULF1	hsa-miR-4677-5p
SULF1	hsa-miR-4273
SULF1	hsa-miR-1323
SULF1	hsa-miR-1299
SULF1	hsa-miR-454-3p
SULF1	hsa-miR-205-5p
SULF1	hsa-miR-6739-3p
SULF1	hsa-miR-5006-5p
SULF1	hsa-miR-7161-3p
SULF1	hsa-miR-409-3p
SULF1	hsa-miR-330-3p
SULF1	hsa-miR-4288
ALDH1A3	hsa-miR-301a-5p
ALDH1A3	hsa-miR-4786-3p
ALDH1A3	hsa-miR-3925-3p
ALDH1A3	hsa-miR-1304-3p
ALDH1A3	hsa-miR-153-5p
ALDH1A3	hsa-miR-6504-3p

ALDH1A3	hsa-miR-5692a
ALDH1A3	hsa-miR-4524a-5p
ALDH1A3	hsa-miR-127-5p
ALDH1A3	hsa-miR-7843-3p
ALDH1A3	hsa-miR-15b-5p
ALDH1A3	hsa-miR-301b-5p
ALDH1A3	hsa-miR-215-3p
ALDH1A3	hsa-miR-3916
ALDH1A3	hsa-miR-5196-5p
ALDH1A3	hsa-miR-4747-5p
ALDH1A3	hsa-miR-587
ALDH1A3	hsa-miR-766-3p
ALDH1A3	hsa-miR-6859-5p

Supplementary Table 8 List of 254 common overlapped differentially expressed genes

CDH3	FNDC1	COL5A2	MMP10	AOX1
DIO2	SULF1	RAPGEF5	PNMT	HMCN1
COMP	DZIP1	DOK5	CCL13	DPYS
IL13RA2	PRX	SH3BP5	MOXD1	PHACTR3
SCG5	SDR16C5	RNF144B	SLC39A8	ITM2C
HS6ST2	OSBPL3	FHL2	CCDC80	SCARA3
FAM167A	F5	HIF3A	CDCA7	DEFA4
ADRB2	S1PR1	KCND3	ALDH1A3	AFF2
DCLK1	STX11	PPIC	ARHGAP6	RCAN2
CFI	DLC1	EYA2	KDELR3	PNMAL1
COL14A1	HSPA4L	NHS	RS1	SLCO4A1
CTSE	NPR1	GPIHBP1	REPS2	IL17RD
CRTAC1	CTSK	LRRN1	SCG2	SEC14L4
FAM107A	ECHDC3	CRYM	ASPN	CLU
ABCC5	CCBE1	HSD17B6	KCNMA1	EPHA3
CTHRC1	CCDC85A	SLC1A1	BTNL8	FAP
TTC39C	GPX3	BCL11A	VGLL3	ID1
TSHZ2	COL15A1	NEDD4L	TRPS1	OGN
COL7A1	STARD13	AFF3	HHIP	TIMP4
SEL1L3	FUT1	COL18A1	MT1M	HOPX
KLHL13	CPXM1	EFNB3	TGFB3	C15ORF48
CRABP2	LIN7A	MATN3	ENC1	MT1E
SFRP2	CHRM3	PDK1	TRAF5	CEP41
MMP7	FBLN2	SLC4A11	BMP4	PCSK9
IGDCC4	PAPSS2	ALDH18A1	FMO5	IGFBP4
C12ORF49	FAM105A	EPB41L5	AQP5	PLN
LTBP1	TDO2	IGFBP2	ROR1	VSIG1
KCNN4	NEDD9	CCK	C8ORF34	KLF9

GPX8	GPR4	PREX1	EFNA4	KCNN3
DENND3	FAM46B	EDNRB	DEPDC7	DIRAS3
FAT1	IGF1	CPXM2	TNFRSF21	HLA-DOB
PLLP	BACE2	SEC24D	FDXR	VWA1
TRIM2	BTNL9	SYTL2	TRIM36	MMP25
KCNMB4	RET	LIFR	SPOCK1	CCDC146
PTPRB	CHPT1	LDLR	DZIP3	CD69
ABCC3	NEBL	PHACTR1	BHLHE22	S100A12
CNTN3	CFB	IRS2	MXRA5	CD300LG
CDH13	PROM2	COL1A2	IL1RL1	FPR2
CXCL13	GLT8D2	PRSS2	ZNF385B	CD177
ADIPOR2	ADRA2A	P2RY1	STEAP3	SLCO4C1
COL10A1	RAB7B	F2RL2	TGFBI	COLEC11
COL3A1	FMO1	SLAMF7	IP6K3	BCHE
GOLM1	SHANK3	PAMR1	SPATA18	MFAP2
LRRC17	CA4	PARD6B	SLC45A3	MUC5B
LNX2	CLIC6	BNC2	SLC28A3	MGAM
TIMP3	ST6GALNAC1	SASH1	CBS	VEPH1
NECAB1	SDPR	TMEM2	STYK1	PTGER1
EPAS1	ZMAT3	SULF2	ZNF521	TPPP3
FZD5	VSIG10	ITGB8	ODAM	BHLHE40
LMCD1	LRRC32	KCTD1	SLC35F2	NTS
ABCC13	GPM6B	IL18RAP	PLA2G1B	