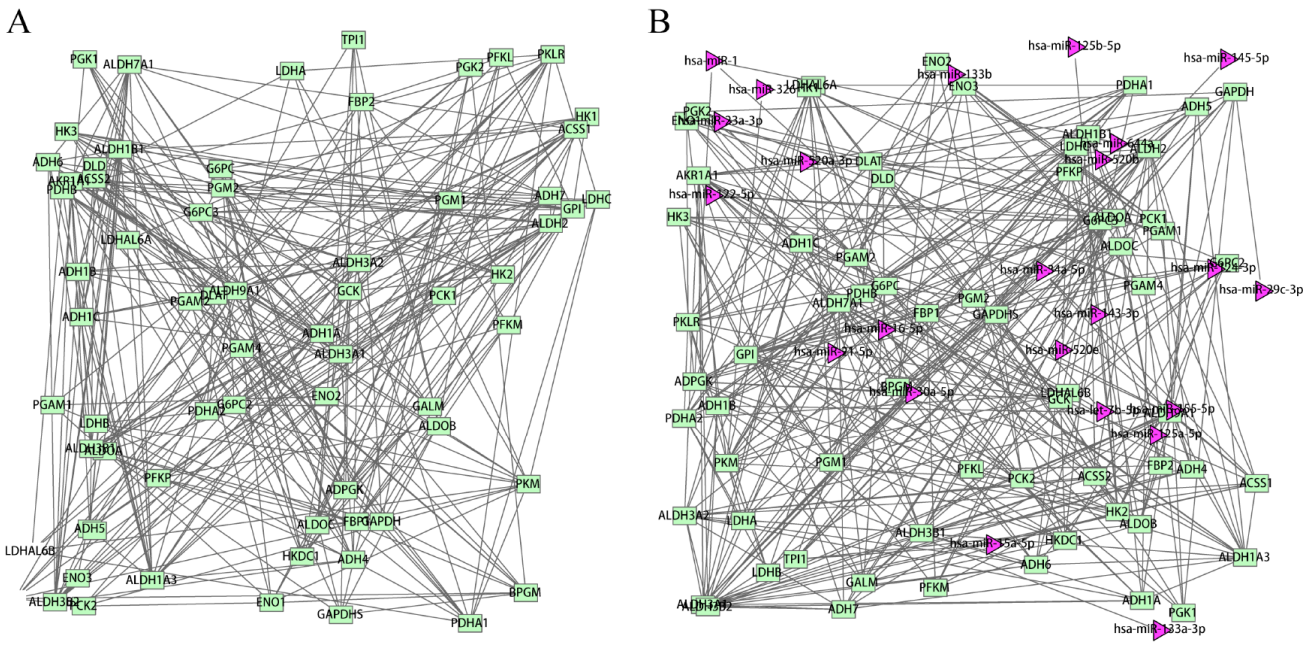
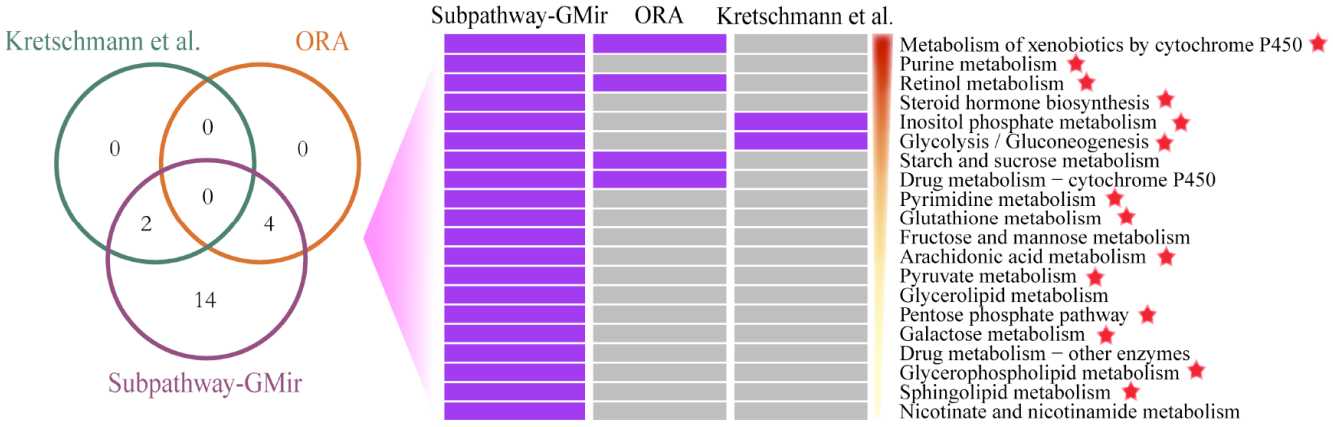
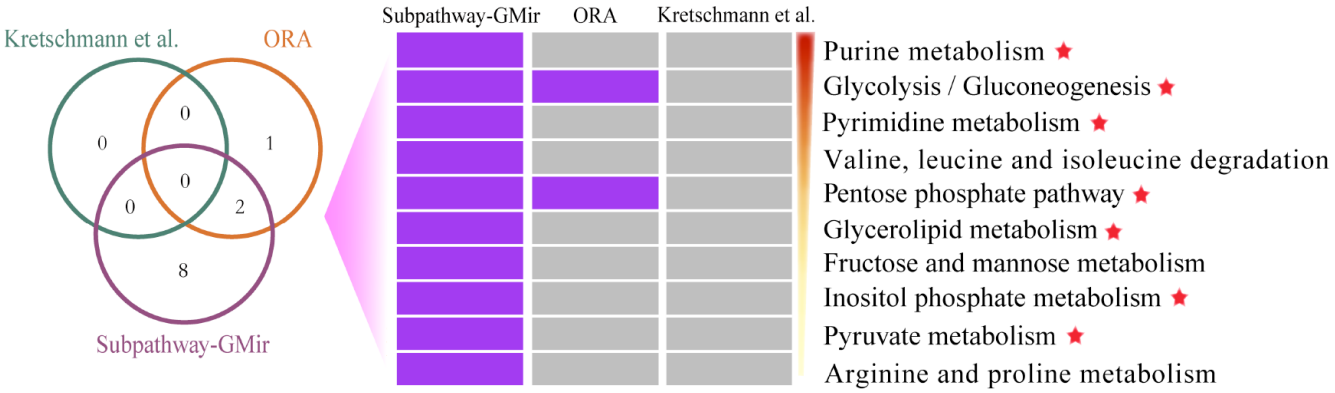
SUPPLEMENTARY FIGURES AND TABLES



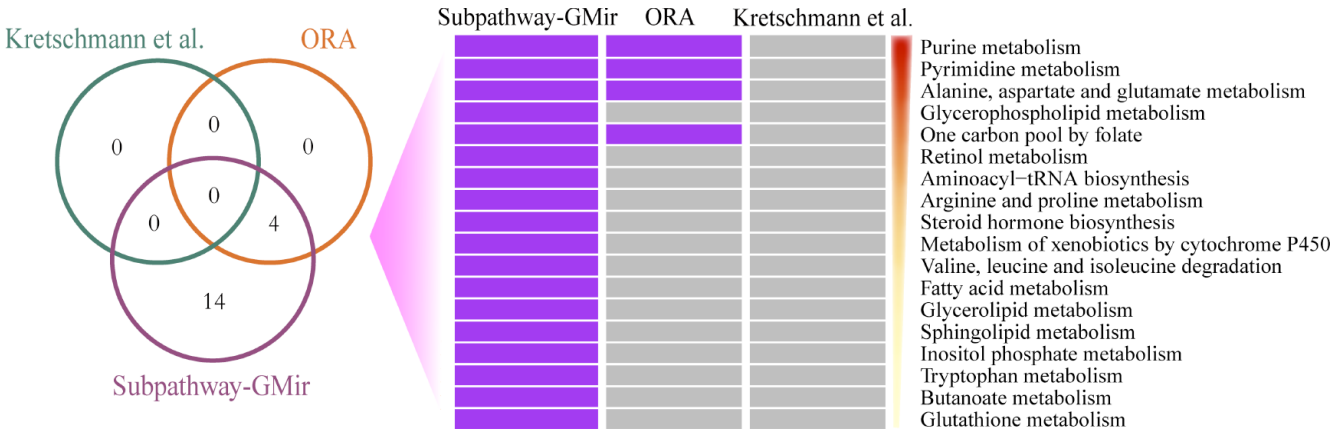
Supplementary Figure S1: The "Glycolysis/Gluconeogenesis" metabolic pathway graph before and after reconstructing. The rectangle and triangle nodes represent genes and miRNAs, respectively. **A.** The graph before reconstructing. **B.** The graph after reconstructing.



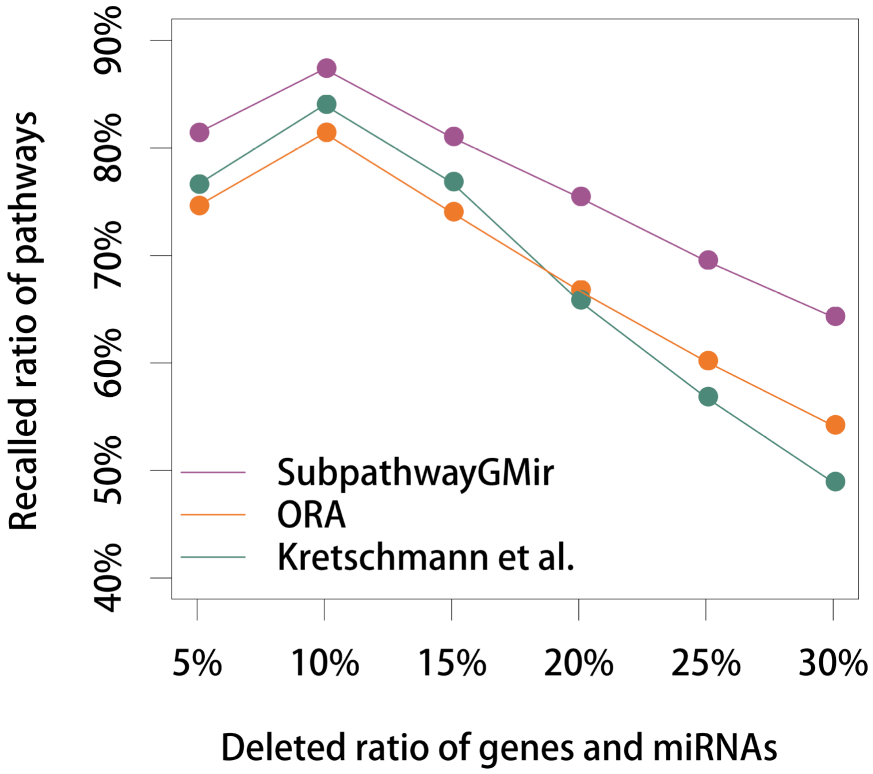
Supplementary Figure S2: Comparison of pathways identified by Subpathway-GMir, ORA and the Kretschmann *et al*. method in STAD data set (*FDR* < 0.01). Venn diagram depicting the overlap of pathways. These pathways were sorted by statistical significance (using Subpathway-GMir) in descending order. Each row represents a pathway and each column represents a method. The purple and grey grid represents that the pathway was or wasn't identified by the method, respectively. Pathways supported by scientific studies are marked with red stars.



Supplementary Figure S3: Comparison of pathways identified by Subpathway-GMir, ORA and the Kretschmann *et al.* method in T2D data set (*FDR* < 0.01). Venn diagram depicting the overlap of pathways. These pathways were sorted by statistical significance (using Subpathway-GMir) in descending order. Each row represents a pathway and each column represents a method. The purple and grey grid represents that the pathway was or wasn't identified by the method, respectively. Pathways supported by scientific studies are marked with red stars.



Supplementary Figure S4: Comparison of pathways identified by Subpathway-GMir, ORA and the Kretschmann *et al.* method in LIHC data set 2 (*FDR* < 0.01). Venn diagram depicting the overlap of pathways. These pathways were sorted by statistical significance (using Subpathway-GMir) in descending order. Each row represents a pathway and each column represents a method. The purple and grey grid represents that the pathway was or wasn't identified by the method, respectively.



Supplementary Figure S5: The mean ratio of recalled pathways using Subpathway-GMir, ORA and the Kretschmann *et al.* method (*FDR* < 0.05).

Supplementary Table S1: Subpathways identified using subpathway-GMir in LIHC data set 1

Pathway Id	Pathway Name	FDR	Possible relations to cancers	Cancer-related miRNAs	Reference
path:00010_1	Glycolysis / Gluconeogenesis	<1.00E-16	MiR-520a/b/e regulate glycolysis in HCC	miR-34a-5p;miR-21-5p; miR-133a-3p;miR-326; miR-29c-3p;miR-520b; miR-520e;miR-125b-5p	[1]
path:00230_1	Purine metabolism	<1.00E-16	Transformation and progression in hepatomas	miR-34a-5p;miR-24-3p; let-7c-5p;miR-182-5p; miR-133a-3p;miR-326	[2]
path:00240_1	Pyrimidine metabolism	<1.00E-16	Transformation and progression in hepatomas	miR-34a-5p;miR-24-3p; let-7c-5p;miR-133a-3p	[2]
path:00562_1	Inositol phosphate metabolism	<1.00E-16	MiR-21 mediate the increase of cell proliferation and invasion in HCC MiR-221&222 enhance tumorigenicity in HCC	miR-217;miR-216a-5p; miR-214-3p;miR-21-5p; miR-519a-3p;miR-519d-3p; miR-19a-3p;miR-141-3p; miR-18a-5p;miR-221-3p; miR-222-3p;miR-93-5p; miR-519c-3p;miR-34a-5p; miR-205-5p;miR-184	[3, 4]
path:00564_1	Glycerophospholipid metabolism	<1.00E-16	Drug target against cancer	miR-338-3p;miR-34a-5p	[5]
path:00980_1	Metabolism of xenobiotics by cytochrome P450	3.86E-14	Poor prognosis of HCC	miR-513a-3p;miR-133a-3p	[6]

(*Continued*)

Pathway Id	Pathway Name	FDR	Possible relations to cancers	Cancer-related miRNAs	Reference
path:00310_1	Lysine degradation	1.18E-12	—	miR-34a-5p;miR-21-5p	—
path:00590_1	Arachidonic acid metabolism	4.07E-12	MiRNA-101 promotes apoptosis and suppress in HCC Cox-2 promotes the growth of HCC cell	miR-137;miR-101-3p; miR-338-3p	[7, 8]
path:00071_1	Fatty acid metabolism	1.63E-11	Significantly altered fatty acid-related metabolic pathways in HCC	miR-34a-5p	[9]
path:00561_1	Glycerolipid metabolism	1.52E-10	MiR-125b could inhibit cell proliferation, cell cycle progression and metastasis of HCC cells	miR-125b-5p;miR-34a-5p	[10]
path:00830_1	Retinol metabolism	2.72E-10	The high prediagnostic serum level of retinol is associated with a decreased risk of HCC	miR-34a-5p;miR-125b-5p	[11, 12]
path:00051_1	Fructose and mannose metabolism	8.50E-10	—	miR-34a-5p;miR-125b-5p; miR-520b;miR-520e	—
path:00982_1	Drug metabolism - cytochrome P450	8.88E-10	—	miR-513a-3p;miR-133a-3p	—
path:00600_1	Sphingolipid metabolism	4.79E-09	Chemoprevention target of HCC; Tumor growth of hepatocellular carcinoma	miR-221-3p;miR-222-3p; miR-125b-5p	[13–15]
path:00030_1	Pentose phosphate pathway	6.28E-09	PPP activity is elevated in rapidly proliferating tumor cells	miR-34a-5p;miR-520b; miR-520e	[16, 17]
path:00140_1	Steroid hormone biosynthesis	8.86E-09	Carcinogenesis in HCC	miR-199a-5p	[18, 19]
path00380_1	Tryptophan metabolism	2.54E-08	—	miR-34a-5p	—
path:00500_1	Starch and sucrose metabolism	2.54E-08	—	miR-125b-5p;miR-34a-5p	—
path:00330_2	Arginine and proline metabolism	2.54E-08	—	miR-34a-5p;miR-24-3p	—
path:00565_1	Ether lipid metabolism	2.54E-08	—	miR-338-3p	—
path:00250_1	Alanine, aspartate and glutamate metabolism	3.63E-08	—	miR-34a-5p	—
path:00620_1	Pyruvate metabolism	1.24E-07	Metabolism and tumour growth	miR-21-5p;miR-133a-3p; miR-326;miR-34a-5p	[20, 21]
path:00410_1	beta-Alanine metabolism	1.64E-07	—	miR-34a-5p;miR-24-3p	—

(*Continued*)

Pathway Id	Pathway Name	FDR	Possible relations to cancers	Cancer-related miRNAs	Reference
path:00350_1	Tyrosine metabolism	1.14E-06	Pathogenesis of HCC	—	[22]
path:00280_2	Valine, leucine and isoleucine degradation	1.58E-06	—	miR-34a-5p	—
path:00480_1	Glutathione metabolism	3.83E-06	The growth of liver cancer cells	miR-183-5p;miR-513a-3p; miR-133a-3p	[23]
path:00260_1	Glycine, serine and threonine metabolism	2.03E-05	—	—	—
path:00052_1	Galactose metabolism	2.03E-05	The treatment of HCC	miR-34a-5p;miR-125b-5p	[24, 25]
path:00340_2	Histidine metabolism	2.03E-05	Carcinogenesis	miR-24-3p;miR-34a-5p	[26]

Supplementary Table S2: Subpathways identified using subpathway-GMir in STAD data set

Pathway Id	Pathway Name	FDR	Possible relations to cancer	Cancer-related miRNAs	Reference
path:00980_1	Metabolism of xenobiotics by cytochrome P450	2.22E-15	Development of STAD	miR-122-5p;miR-133a-3p; miR-1;miR-145-5p	[27, 28]
path:00230_1	Purine metabolism	1.89E-14	Development of STAD	miR-1;miR-182-5p;miR-122-5p; miR-133a-3p;miR-133b	[29]
path:00830_1	Retinol metabolism	3.12E-13	Prognosis of STAD	—	[30]
path:00140_1	Steroid hormone biosynthesis	9.63E-13	Apoptosis and Prognosis	miR-1;miR-19b-3p;miR-122-5p	[31, 32]
path:00562_2	Inositol phosphate metabolism	9.86E-12	Cancer aggressiveness	miR-217;miR-17-5p;miR-216a-5p; miR-21-5p;miR-519a-3p;miR-19a-3p; miR-19b-3p;miR-18a-5p;miR-20a-5p; miR-222-3p;miR-106b-5p;miR-93-5p; miR-519c-3p;miR-1	[33]
path:00010_1	Glycolysis / Gluconeogenesis	1.46E-11	Prognosis	miR-122-5p;miR-1;miR-145-5p; miR-29c-3p;miR-15a-5p; miR-520b;miR-520e	[34]
path:00500_1	Starch and sucrose metabolism	4.02E-11	—	miR-122-5p;miR-1	—
path:00982_1	Drug metabolism - cytochrome P450	1.49E-09	—	miR-145-5p;miR-122-5p; miR-133a-3p;miR-1	—
path:00240_1	Pyrimidine metabolism	1.88E-09	Differentiation of STAD	miR-1;miR-122-5p;miR-17-3p; miR-133a-3p	[35]
path:00480_1	Glutathione metabolism	1.86E-08	Development of STAD	miR-1;miR-17-3p;miR-122-5p; miR-133a-3p	[36, 37]

(*Continued*)

Pathway Id	Pathway Name	FDR	Possible relations to cancer	Cancer-related miRNAs	Reference
path:00051_1	Fructose and mannose metabolism	3.64E-08	—	miR-145-5p;miR-122-5p; miR-520b;miR-520e;miR-15a-5p	—
path:00590_1	Arachidonic acid metabolism	4.27E-08	Apoptosis of gastric cancer	miR-1;miR-17-3p	[38, 39]
path:00620_1	Pyruvate metabolism	6.46E-08	Growth of gastric cancer	miR-21-5p;miR-133b; miR-133a-3p;miR-145-5p;miR-1	[40, 41]
path:00561_1	Glycerolipid metabolism	7.24E-08	—	miR-1;miR-145-5p	—
path:00030_1	Pentose phosphate pathway	1.49E-07	Apoptosis of gastric cancer	miR-1;miR-122-5p; miR-520b;miR-520e	[42]
path:00052_1	Galactose metabolism	3.02E-07	Metastases	miR-145-5p;miR-1;miR-122-5p	[43]
path:00983_4	Drug metabolism - other enzymes	5.07E-07	—	—	—
path:00564_1	Glycerophospholipid metabolism	7.71E-06	The treatment of cancer	miR-1;miR-210-3p	[5]
path:00600_1	Sphingolipid metabolism	4.08E-05	Apoptosis, Progression and survival of gastric cancer	miR-1;miR-222-3p	[44, 45]
path:00760_1	Nicotinate and nicotinamide metabolism	4.76E-04	—	miR-1;miR-122-5p;miR-133a-3p	—

Supplementary Table S3: Subpathways identified using subpathway-GMir in T2D data set

Pathway Id	Pathway Name	FDR	Possible relations to T2D	T2D-related miRNAs	Reference
path:00230_1	Purine metabolism	<1.00E-16	Progression and treatment	miR-320a;miR-133b	[46, 47]
path:00010_1	Glycolysis / Gluconeogenesis	1.04E-12	Gluconeogenesis is enhanced in T2D The sustained gluconeogenesis produced the hallmark of T2D	miR-133b;miR-143-3p	[48, 49]
path:00240_1	Pyrimidine metabolism	2.12E-09	Progression and treatment	—	[50]
path:00280_1	Valine, leucine and isoleucine degradation	1.39E-08	—	—	—
path:00030_1	Pentose phosphate pathway	1.39E-08	Progression and treatment	—	[51]
path:00561_1	Glycerolipid metabolism	2.25E-08	Treatment of T2D	—	[52, 53]
path:00051_1	Fructose and mannose metabolism	9.07E-08	—	miR-143-3p	—
path:00562_1	Inositol phosphate metabolism	2.16E-07	Downregulated in T2D	miR-17-5p;miR-107;hsa-miR-184	[54]
path:00620_1	Pyruvate metabolism	6.75E-07	Development of T2D	miR-133b	[55, 56]
path:00330_1	Arginine and proline metabolism	3.21E-06	—	—	—

Supplementary Table S4: Subpathways identified using subpathway-GMir in LIHC data set 2

Pathway Id	Pathway Name	FDR
path:00230_1	Purine metabolism	<1.00E-16
path:00240_1	Pyrimidine metabolism	<1.00E-16
path:00250_1	Alanine, aspartate and glutamate metabolism	1.56E-11
path:00564_1	Glycerophospholipid metabolism	1.11E-08
path:00670_1	One carbon pool by folate	1.11E-08
path:00830_1	Retinol metabolism	1.11E-08
path:00970_1	Aminoacyl-tRNA biosynthesis	3.56E-08
path:00330_1	Arginine and proline metabolism	4.22E-08
path:00140_1	Steroid hormone biosynthesis	7.29E-08
path:00980_1	Metabolism of xenobiotics by cytochrome P450	7.29E-08
path:00280_1	Valine, leucine and isoleucine degradation	1.13E-07
path:00071_1	Fatty acid metabolism	1.52E-07
path:00561_1	Glycerolipid metabolism	1.52E-07
path:00600_1	Sphingolipid metabolism	1.78E-07
path:00562_1	Inositol phosphate metabolism	4.66E-07
path:00380_1	Tryptophan metabolism	1.42E-06
path:00650_1	Butanoate metabolism	1.42E-06
path:00480_1	Glutathione metabolism	3.46E-06

Supplementary Table S5: The T2D-related risk miRNAs

miRNA	PMID
hsa-miR-196a2	25557604
hsa-miR-107	25522185
hsa-miR-17-5p	25409512
hsa-miR-221	25409512
hsa-miR-124a	25408296
hsa-miR-375	25408296
hsa-let-7	25399420
hsa-miR-18a	25371752
hsa-miR-199a-3p	25180600
hsa-miR-342	25180600
hsa-miR-195	25138607
hsa-miR-29a	25138607
hsa-miR-103	25010252
hsa-miR-143	25010252
hsa-miR-483-3p	25010252
hsa-miR-23a	24981880

(*Continued*)

miRNA	PMID
hsa-miR-196a2	24972764
hsa-miR-143-3p	24970281
hsa-miR-126	24927146
hsa-miR-191	24795757
hsa-miR-378	24771406
hsa-miR-149	24757201
hsa-miR-130a	24750349
hsa-miR-375	24741571
hsa-miR-146a	24682535
hsa-miR-128a	24682535
hsa-miR-27a	24682535
hsa-miR-15a	24497980
hsa-miR-20	24497980
hsa-miR-21	24497980
hsa-miR-24	24497980
hsa-miR-29b	24497980
hsa-miR-126	24497980
hsa-miR-144	24497980
hsa-miR-150	24497980
hsa-miR-197	24497980
hsa-miR-223	24497980
hsa-miR-191	24497980
hsa-miR-320a	24497980
hsa-miR-486-5p	24497980
hsa-miR-28-3p	24497980
hsa-miR-140-5p	24478399
hsa-miR-142-3p	24478399
hsa-miR-222	24478399
hsa-miR-423-5p	24478399
hsa-miR-125b	24478399
hsa-miR-192	24478399
hsa-miR-195	24478399
hsa-miR-130b	24478399
hsa-miR-532-5p	24478399
hsa-miR-126	24478399
hsa-miR-126	24455723
hsa-miR-92a	24379347
hsa-miR-193b	24379347

(*Continued*)

miRNA	PMID
hsa-miR-126	24379347
hsa-miR-375	24366165
hsa-miR-377-5p	24352417
hsa-miR-628-3p	24352417
hsa-miR-3137	24352417
hsa-miR-143	24333576
hsa-miR-145	24333576
hsa-miR-138	24204780
hsa-miR-15b	24204780
hsa-miR-376a	24204780
hsa-miR-503	24204780
hsa-miR-187	24149837
hsa-miR-184	24109547
hsa-let-7a	24105413
hsa-let-7d	24105413
hsa-miR-146a	24023848
hsa-miR-106b	23954742
hsa-miR-34a	23828613
hsa-miR-96	23828613
hsa-miR-143	23812417
hsa-miR-21	23771797
hsa-miR-155	23616185
hsa-miR-150	23391324
hsa-miR-342	23391324
hsa-miR-126	23386708
hsa-miR-375	23372846
hsa-miR-223	23305783
hsa-miR-30c	21878751
hsa-miR-146a	21249428
hsa-miR-34a	20857148
hsa-miR-181d	20639500
hsa-miR-375	20467341
hsa-miR-375	20224724
hsa-miR375	20221699
hsa-miR-223	20080987
hsa-miR-375	25120598
hsa-miR-143-3p	24970281
hsa-miR-326	24937531

(*Continued*)

miRNA	PMID
hsa-miR-let-7a	24937531
hsa-miR-let-7f	24937531
hsa-miR-92a	24379347
hsa-miR-181a	22476949
hsa-miR-483-3p	22223106
hsa-miR-27a	23032062
hsa-miR-320a	23032062
hsa-miR-192	21829658
hsa-miR-29a	21829658
hsa-miR-30d	21829658
hsa-miR-320a	21829658
hsa-miR-20b	20651284
hsa-miR-21	20651284
hsa-miR-24	20651284
hsa-miR-15a	20651284
hsa-miR-126	20651284
hsa-miR-191	20651284
hsa-miR-197	20651284
hsa-miR-223	20651284
hsa-miR-320	20651284
hsa-miR-486	20651284
hsa-miR-28-3p	20651284
hsa-miR-133a	20353613
hsa-miR-133b	20353613
hsa-miR-206	20353613
hsa-miR-107	25522185
hsa-miR-195	25138607
hsa-miR-7	24944010
hsa-miR-124a	24944010
hsa-miR-9	24944010
hsa-miR-96	24944010
hsa-miR-15a	24944010
hsa-miR-15b	24944010
hsa-miR-34a	24944010
hsa-miR-195a	24944010
hsa-miR-376	24944010
hsa-miR-107	24944010
hsa-miR-146	24944010

(*Continued*)

miRNA	PMID
hsa-miR-320	24944010
hsa-miR-383	24944010
hsa-miR-181b	24944010
hsa-miR-128a	24944010
hsa-miR-29	24944010
hsa-miR-384-5p	24944010
hsa-miR-126	24944010
hsa-miR-143	24944010
hsa-miR-145	24944010
hsa-miR-33a	24944010
hsa-miR-33b	24944010
hsa-miR-21	24944010
hsa-miR-133a	24944010
hsa-miR-133b	24944010
hsa-miR-223	24944010
hsa-miR-103	24944010
hsa-miR-29a	24944010
hsa-miR-27b	24944010
hsa-miR-15b	25403480
hsa-miR-16	25403480
hsa-miR-17	25403480
hsa-miR-451	25403480
hsa-miR-106b	25403480
hsa-miR-103	25403480
hsa-miR-425	25403480
hsa-miR-106a	25403480
hsa-miR-10b	25403480
hsa-miR-25	25403480
hsa-miR-93	25403480
hsa-miR-363	25403480
hsa-miR-107	25403480
hsa-miR-191	25403480
hsa-miR-30e*	25403480
hsa-let-7i	25403480
hsa-miR-20a	25403480
hsa-miR-223	25403480
hsa-miR-92a	25403480
hsa-miR-20b	25403480

(*Continued*)

miRNA	PMID
hsa-miR-18a	25677225
hsa-miR-221	25677225
hsa-miR-144	25677225
hsa-miR-320a	25677225
hsa-miR-375	25677225
hsa-miR-589	25677225
hsa-miR-665	25677225
hsa-miR-376a	25677225
hsa-miR-140-5p	25677225
hsa-miR-374b	25677225
hsa-miR-155	25677225
hsa-miR-20b	25677225
hsa-miR-126a	25677225
hsa-miR-342-3p	25677225
hsa-miR-107	25677225
hsa-miR-29a	25677225
hsa-miR-34a	25677225
hsa-miR-142-3p	25677225
hsa-miR-106b	25677225
hsa-miR-146a	18633110
hsa-miR-107	19689793
hsa-miR-24-1	20651284
hsa-miR-24-2	20651284
hsa-miR-320a	20651284
hsa-miR-146a	21249428
hsa-miR-143	21441927
hsa-miR-103a-1	21654750
hsa-miR-103a-2	21654750
hsa-miR-144	21829658
hsa-miR-483	22223106
hsa-miR-107	22645244
hsa-miR-126	23144172
hsa-miR-99a	23762265
has-miR-26a	25961460

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