SUPPLEMENTARY DATA

Extracellular RNAs are associated with insulin resistance and metabolic phenotypes

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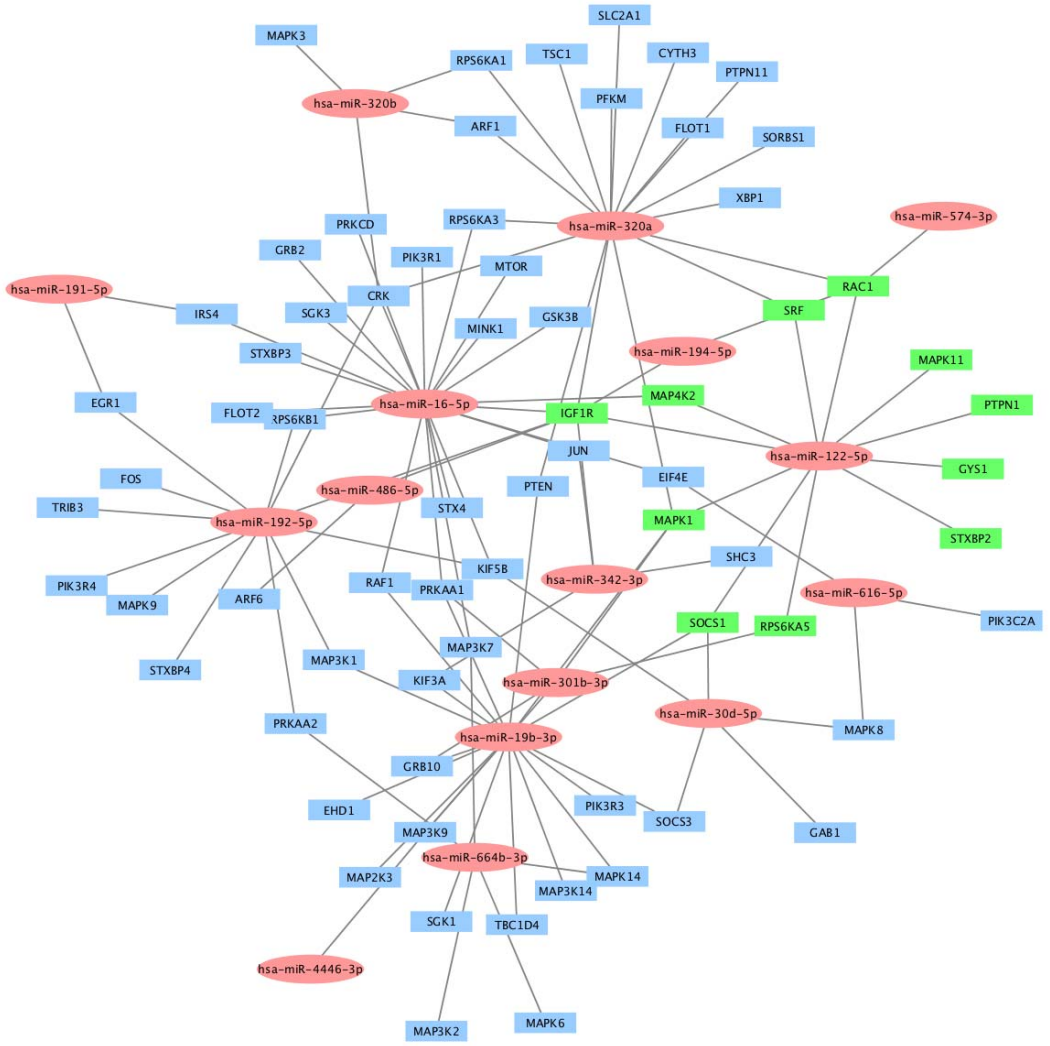
Supplementary Figure 1. Network visualization of 16 miRNAs (red) targeting 69 Insulin Signaling pathway genes (blue). The miR-122 targets are highlighted in green. The interactions are from miRTarBase and the pathway gene set was extracted from WikiPathways.



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Supplementary Figure 2. Visualization of selected miRNA targeting events on three selected pathways from WikiPathways. The genes targeted by miRNA per pathway, as counted in **Supplemental Table 3**, are visualized here for selected pathways. Pathway was imported into Cytoscape from WikiPathways and ID mapping was performed to obtain Entrez Gene identifiers for each gene. An intermediate file from the Pathway Finder tool was parsed and imported into Cytoscape to supply the mappings between Entrez Gene and the selected set of miRNAs. A visual style was defined in Cytoscape to highlight any gene targeted by these miRNA in preferential order: miR-122 (blue), miR-192 (red), and any of the other 14 possible miRNAs (gray).

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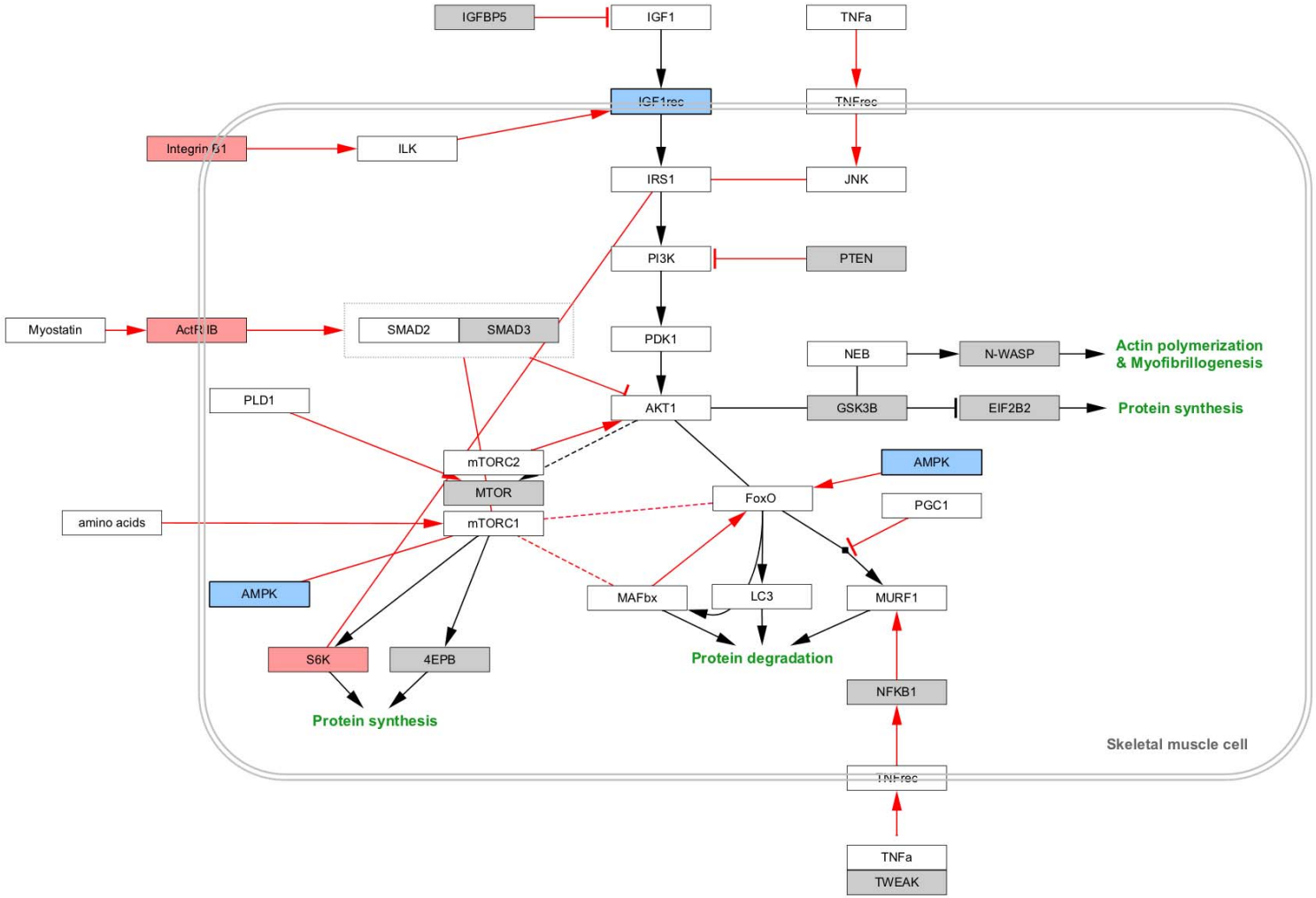
(A) Factors and pathways affecting insulin-like growth factor signaling



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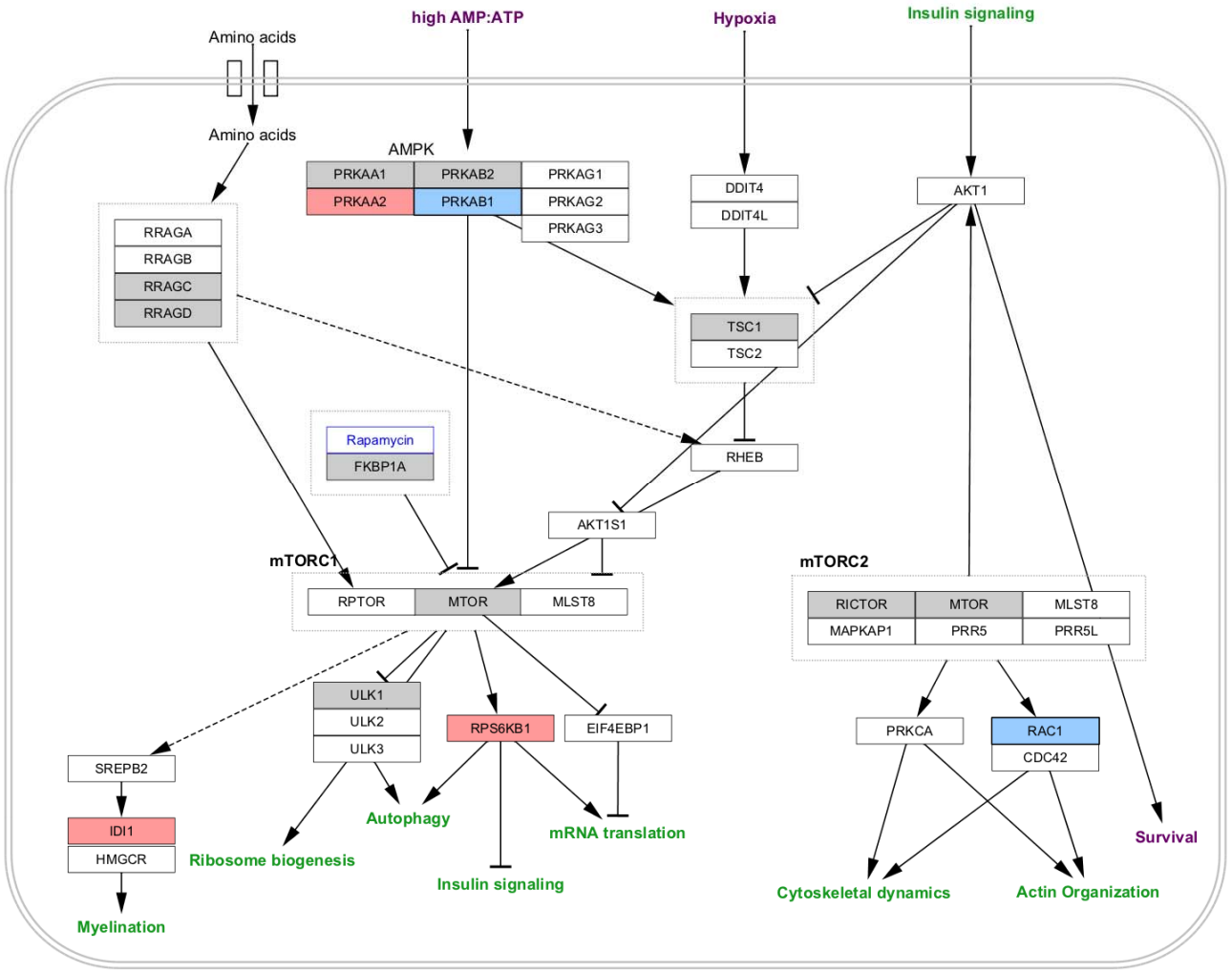
(B) TOR signaling



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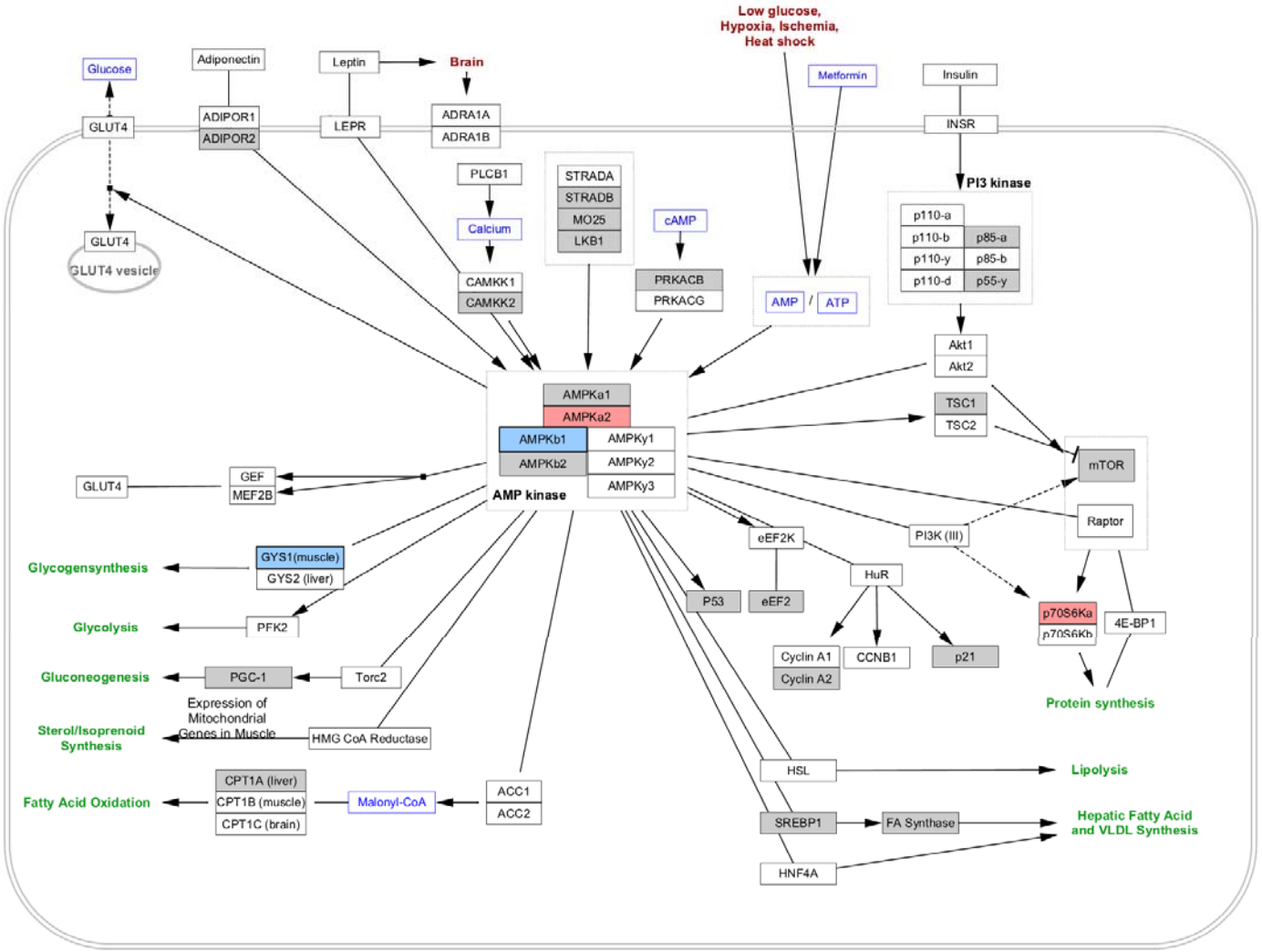
(C) AMP-activated protein kinase signaling



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Supplementary Table 1. Ex-RNAs detectable in at least 100 FHS participants included in study cohort. Detectable expression is any C_q value that was detected by the Fludigm platform ($6 < C_q < 23$ cycles).

Variable	N	% Expressed
let-7a-3p	695	30.0
let-7a-5p	1950	84.2
let-7b-3p	760	32.8
let-7b-5p	1930	83.3
let-7c-5p	1685	72.7
let-7d-3p	1798	77.6
let-7d-5p	1885	81.4
let-7e-5p	1108	47.8
let-7f-1-3p	371	16.0
let-7f-2-3p	463	20.0
let-7f-5p	1545	66.7
let-7g-5p	1851	79.9
let-7i-5p	1797	77.6
miR-1-3p	275	11.9
miR-100-5p	1137	49.1
miR-101-3p	2126	91.8
miR-103a-3p	1893	81.7
miR-106b-3p	1603	69.2
miR-106b-5p	2192	94.6
miR-107	237	10.2
miR-10a-5p	669	28.9
miR-10b-5p	1102	47.6
miR-1180-3p	1018	43.9
miR-122-3p	888	38.3
miR-122-5p	2201	95.0
miR-1226-3p	771	33.3
miR-1229-3p	375	16.2
miR-124-3p	237	10.2
miR-1246	1410	60.9
miR-1247-5p	877	37.9
miR-125a-5p	1978	85.4
miR-125b-5p	1965	84.8
miR-126-3p	2243	96.8
miR-126-5p	2266	97.8
miR-1260a	2163	93.4
miR-1260b	1622	70.0
miR-1271-5p	1229	53.0
miR-128-3p	2018	87.1
miR-129-2-3p	236	10.2
miR-129-5p	152	6.6

miR-1301-3p	816	35.2
miR-1304-3p	172	7.4
miR-1306-5p	645	27.8
miR-1307-3p	312	13.5
miR-1307-5p	150	6.5
miR-130a-3p	1989	85.8
miR-130b-3p	955	41.2
miR-130b-5p	438	18.9
miR-132-3p	695	30.0
miR-133a-3p	484	20.9
miR-134-5p	122	5.3
miR-136-3p	138	6.0
miR-136-5p	472	20.4
miR-139-5p	1521	65.6
miR-140-3p	2109	91.0
miR-141-3p	136	5.9
miR-142-3p	863	37.2
miR-142-5p	2120	91.5
miR-143-3p	819	35.3
miR-144-3p	1751	75.6
miR-144-5p	768	33.1
miR-145-3p	217	9.4
miR-145-5p	2074	89.5
miR-146a-5p	2192	94.6
miR-146b-5p	1275	55.0
miR-148a-3p	2152	92.9
miR-148b-3p	2135	92.1
miR-150-5p	2213	95.5
miR-151a-3p	985	42.5
miR-151a-5p	2060	88.9
miR-151b-	2188	94.4
miR-152-3p	747	32.2
miR-154-3p	862	37.2
miR-155-5p	424	18.3
miR-15a-5p	1556	67.2
miR-15b-3p	763	32.9
miR-15b-5p	2219	95.8
miR-16-2-3p	841	36.3
miR-16-5p	2282	98.5
miR-17-3p	287	12.4
miR-17-5p	2192	94.6
miR-181a-2-3p	1489	64.3
miR-181a-3p	875	37.8
miR-181a-5p	675	29.1

miR-181b-5p	916	39.5
miR-181c-3p	788	34.0
miR-181c-5p	528	22.8
miR-181d-5p	871	37.6
miR-182-5p	256	11.0
miR-183-5p	143	6.2
miR-185-3p	125	5.4
miR-185-5p	2068	89.3
miR-186-5p	2035	87.8
miR-18a-5p	1822	78.6
miR-190a-3p	661	28.5
miR-191-5p	2229	96.2
miR-192-5p	1727	74.5
miR-193a-5p	575	24.8
miR-193b-3p	622	26.8
miR-194-5p	2026	87.4
miR-195-5p	2167	93.5
miR-197-3p	2017	87.1
miR-199a-3p	2154	93.0
miR-199a-5p	822	35.5
miR-199b-5p	1231	53.1
miR-19a-3p	2216	95.6
miR-19b-3p	2234	96.4
miR-200a-3p	130	5.6
miR-200b-3p	773	33.4
miR-200c-3p	340	14.7
miR-203a-3p	110	4.7
miR-204-5p	1405	60.6
miR-205-5p	976	42.1
miR-206	336	14.5
miR-20a-5p	2213	95.5
miR-20b-5p	1014	43.8
miR-21-3p	157	6.8
miR-21-5p	2235	96.5
miR-2110	979	42.3
miR-212-3p	926	40.0
miR-214-3p	559	24.1
miR-215-5p	431	18.6
miR-22-3p	2210	95.4
miR-22-5p	847	36.6
miR-221-3p	2223	95.9
miR-221-5p	650	28.1
miR-222-3p	2125	91.7
miR-223-3p	2238	96.6

miR-223-5p	628	27.1
miR-224-5p	624	26.9
miR-2355-5p	737	31.8
miR-23a-3p	2226	96.1
miR-23b-3p	2068	89.3
miR-24-2-5p	243	10.5
miR-24-3p	2224	96.0
miR-25-3p	2235	96.5
miR-26a-5p	2227	96.1
miR-26b-5p	2223	95.9
miR-27a-3p	2188	94.4
miR-27b-3p	1960	84.6
miR-28-3p	2071	89.4
miR-28-5p	1699	73.3
miR-296-5p	584	25.2
miR-29a-3p	2207	95.3
miR-29b-3p	1886	81.4
miR-29c-3p	2206	95.2
miR-29c-5p	964	41.6
miR-301a-3p	754	32.5
miR-301b-3p	1421	61.3
miR-30a-3p	1283	55.4
miR-30a-5p	2238	96.6
miR-30b-5p	1962	84.7
miR-30c-5p	1901	82.0
miR-30d-5p	2225	96.0
miR-30e-3p	188	8.1
miR-30e-5p	2229	96.2
miR-31-3p	101	4.4
miR-32-5p	1294	55.8
miR-320a	2212	95.5
miR-320b	1667	71.9
miR-320c	522	22.5
miR-320d	197	8.5
miR-323a-3p	727	31.4
miR-324-3p	1126	48.6
miR-324-5p	1259	54.3
miR-326	476	20.5
miR-329-3p	1089	47.0
miR-330-3p	152	6.6
miR-331-3p	866	37.4
miR-335-3p	135	5.8
miR-335-5p	1158	50.0
miR-337-3p	342	14.8

miR-337-5p	148	6.4
miR-338-3p	724	31.2
miR-338-5p	123	5.3
miR-339-3p	128	5.5
miR-339-5p	943	40.7
miR-33a-3p	746	32.2
miR-340-5p	1267	54.7
miR-342-3p	2250	97.1
miR-342-5p	373	16.1
miR-345-5p	507	21.9
miR-34a-3p	669	28.9
miR-34a-5p	322	13.9
miR-34c-5p	1171	50.5
miR-361-5p	716	30.9
miR-3613-3p	1190	51.4
miR-3615	1042	45.0
miR-362-3p	1360	58.7
miR-363-3p	1711	73.8
miR-365a-3p	1232	53.2
miR-374a-5p	736	31.8
miR-374b-5p	1246	53.8
miR-375	794	34.3
miR-376a-3p	548	23.7
miR-376b-3p	1027	44.3
miR-376c-3p	1219	52.6
miR-377-3p	869	37.5
miR-378a-3p	652	28.1
miR-378a-5p	422	18.2
miR-381-3p	774	33.4
miR-382-3p	886	38.2
miR-409-3p	433	18.7
miR-409-5p	709	30.6
miR-411-3p	122	5.3
miR-423-3p	1792	77.3
miR-423-5p	2053	88.6
miR-424-3p	111	4.8
miR-424-5p	1821	78.6
miR-425-3p	970	41.9
miR-425-5p	1707	73.7
miR-432-5p	1242	53.6
miR-433-3p	1515	65.4
miR-4429	877	37.9
miR-4433a-5p	503	21.7
miR-4433b-3p	280	12.1

miR-4433b-5p	2054	88.6
miR-4446-3p	2107	90.9
miR-451a	2240	96.7
miR-452-5p	130	5.6
miR-454-3p	113	4.9
miR-4732-5p	469	20.2
miR-4770	1181	51.0
miR-483-3p	685	29.6
miR-483-5p	843	36.4
miR-484	2214	95.6
miR-485-3p	428	18.5
miR-486-3p	667	28.8
miR-486-5p	2272	98.1
miR-487b-3p	536	23.1
miR-494-3p	1592	68.7
miR-495-3p	568	24.5
miR-496	102	4.4
miR-497-5p	620	26.8
miR-500a-3p	316	13.6
miR-503-5p	212	9.1
miR-505-3p	680	29.3
miR-519b-5p	925	39.9
miR-532-3p	1643	70.9
miR-532-5p	1262	54.5
miR-542-3p	965	41.6
miR-543	319	13.8
miR-545-5p	225	9.7
miR-548e-3p	1147	49.5
miR-550a-3p	372	16.1
miR-564	1007	43.5
miR-574-3p	1919	82.8
miR-576-5p	166	7.2
miR-582-3p	816	35.2
miR-582-5p	903	39.0
miR-584-5p	404	17.4
miR-589-5p	705	30.4
miR-590-3p	226	9.8
miR-590-5p	591	25.5
miR-596	202	8.7
miR-598-3p	135	5.8
miR-613	424	18.3
miR-616-5p	1091	47.1
miR-624-5p	111	4.8
miR-625-3p	481	20.8

miR-627-5p	569	24.6
miR-628-3p	1012	43.7
miR-642a-5p	887	38.3
miR-6511b-3p	1819	78.5
miR-652-3p	1755	75.7
miR-652-5p	263	11.4
miR-654-3p	167	7.2
miR-654-5p	176	7.6
miR-656-3p	1158	50.0
miR-659-3p	270	11.7
miR-660-5p	954	41.2
miR-664a-3p	984	42.5
miR-664a-5p	154	6.6
miR-664b-3p	1680	72.5
miR-6803-3p	145	6.3
miR-7-1-3p	189	8.2
miR-7-5p	169	7.3
miR-744-5p	1559	67.3
miR-766-3p	1674	72.2
miR-769-5p	1006	43.4
miR-7977	1489	64.3
miR-877-3p	130	5.6
miR-877-5p	227	9.8
miR-885-5p	1593	68.8
miR-9-3p	237	10.2
miR-92a-3p	2238	96.6
miR-92b-3p	1001	43.2
miR-93-3p	361	15.6
miR-93-5p	2197	94.8
miR-941	1119	48.3
miR-942-5p	333	14.4
miR-95-3p	110	4.7
miR-96-5p	324	14.0
miR-98-3p	152	6.6
miR-98-5p	580	25.0
miR-99a-5p	1650	71.2
miR-99b-5p	1847	79.7
piRNA-12151	2308	99.6
piRNA-1340	1377	59.4
piRNA-20101	1724	74.4
piRNA-2096	233	10.1
piRNA-212993	248	10.7
piRNA-218424	110	4.7
piRNA-2229	682	29.4

piRNA-22527	694	30.0
piRNA-227919	323	13.9
piRNA-23216	282	12.2
piRNA-232882	1316	56.8
piRNA-243353	1211	52.3
piRNA-248758	658	28.4
piRNA-251099	224	9.7
piRNA-265711	964	41.6
piRNA-2888	2275	98.2
piRNA-2962	1314	56.7
piRNA-31112	1265	54.6
piRNA-32212	186	8.0
piRNA-32519	1074	46.4
piRNA-32636	289	12.5
piRNA-32637	256	11.0
piRNA-33384	1395	60.2
piRNA-33872	1455	62.8
piRNA-36598	122	5.3
piRNA-36667	440	19.0
piRNA-36772	1110	47.9
piRNA-37355	257	11.1
piRNA-38142	137	5.9
piRNA-40039	112	4.8
piRNA-40304	1801	77.7
piRNA-40506	228	9.8
piRNA-40766	134	5.8
piRNA-41574	140	6.0
piRNA-41647	1180	50.9
piRNA-43147	275	11.9
piRNA-43376	1788	77.2
piRNA-44080	100	4.3
piRNA-45809	398	17.2
piRNA-46358	101	4.4
piRNA-48383	1802	77.8
piRNA-49867	189	8.2
piRNA-49916	1562	67.4
piRNA-51124	1477	63.7
piRNA-51374	510	22.0
piRNA-52468	2111	91.1
piRNA-54042	2286	98.7
piRNA-54043	2285	98.6
piRNA-54782	177	7.6
piRNA-55662	255	11.0
piRNA-56396	164	7.1

piRNA-57322	1652	71.3
piRNA-57387	244	10.5
piRNA-57403	1436	62.0
piRNA-57576	1061	45.8
piRNA-57581	1025	44.2
piRNA-58593	181	7.8
piRNA-58596	1435	61.9
snoRNA-1209	454	19.6
snoRNA-1210	1533	66.2
snoRNA-1257	176	7.6
snoRNA-1277	2101	90.7
snoRNA-1289	198	8.5
snoRNA-1290	196	8.5
snoRNA-1291	321	13.9
snoRNA-1374	1020	44.0
snoRNA-1382	225	9.7
snoRNA-1384	553	23.9
snoRNA-1387	1214	52.4
snoRNA-1394	404	17.4
snoRNA-1399	174	7.5
snoRNA-1401	1694	73.1
snoRNA-1403	216	9.3
snoRNA-1405	439	18.9
snoRNA-1407	257	11.1
snoRNA-1408	2191	94.6
snoRNA-1409	2206	95.2
snoRNA-1413	578	24.9
snoRNA-1414	1107	47.8
snoRNA-1417	457	19.7
snoRNA-1426	1119	48.3
snoRNA-1441	2138	92.3
snoRNA-1457	727	31.4
snoRNA-1458	1204	52.0
snoRNA-1460	1767	76.3
snoRNA-1465	111	4.8
snoRNA-1466	114	4.9
snoRNA-1472	1172	50.6
snoRNA-1502	816	35.2
snoRNA-1507	428	18.5
snoRNA-1549	147	6.3
snoRNA-1550	577	24.9
snoRNA-1563	452	19.5
snoRNA-1568	331	14.3

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Supplementary Table 2. Association between ex-RNAs and anthropometric, imaging, and biochemical measures of adiposity. In age/sex-adjusted linear models, we estimated the association between insulin-associated ex-RNAs and different metrics of adiposity. Panel (A) represents regressions including individuals without diabetes (N≤2317; as defined in the manuscript); panel (B) represents regressions over the entire cohort (N≤2763). We performed regressions across the entire population to maximize power to detect association with imaging indices, and to include individuals with greatest metabolic dysfunction (e.g., individuals with diabetes). Given that several measures (e.g., imaging) were only performed on a subset of FHS participants, *N* specifies the number of observations as each regression was performed only among those participants with detectable ex-RNAs. We estimated regression coefficients as an increase in the dependent variable (e.g., BMI or visceral fat) per a 2-fold increase in plasma ex-RNA concentration. Significant associations are shown here only for those ex-RNAs that passed an FDR threshold of 0.05. P values are raw.

(A)

Phenotype	**N**	**Estimated β**	**P-value**
Body mass index			
miR-122-5p	2198	0.38	1.32×10^{-7}
Waist circumference			
miR-122-5p	2187	0.84	8.41×10^{-6}
miR-616-5p	1083	0.91	3.75×10^{-3}
miR-301b-3p	1413	0.46	7.97×10^{-3}
Visceral fat quantity (log)			
miR-122-5p	1002	0.053	5.72×10^{-7}
Visceral fat quality (HU)			
miR-122-5p	1002	-0.43	3.92×10^{-6}
VAT/SAT ratio (log)			
miR-122-5p	1002	0.026	1.49×10^{-3}
Liver attenuation (HU)			
miR-122-5p	1030	-0.79	2.15×10^{-5}
Interleukin-6 (log)			
miR-342-3p	2180	-0.060	1.76×10^{-5}
miR-486-5p	2202	-0.039	5.23×10^{-4}
miR-19b-3p	2165	-0.039	9.42×10^{-4}
miR-191-5p	2161	-0.026	1.63×10^{-3}
miR-16-5p	2211	-0.029	5.32×10^{-3}
miR-30d-5p	2156	-0.028	1.23×10^{-2}
Tumor necrosis factor receptor-II (log)			
miR-191-5p	2226	-0.040	6.64×10^{-16}
miR-664b-3p	1678	-0.019	4.92×10^{-13}
miR-320b	1664	0.026	4.06×10^{-12}
miR-194-5p	2024	-0.035	1.72×10^{-10}
miR-30d-5p	2222	-0.040	2.69×10^{-9}
miR-4446-3p	2104	0.031	5.86×10^{-7}
miR-574-3p	1918	-0.031	2.89×10^{-6}
miR-486-5p	2269	-0.029	9.46×10^{-6}
miR-19b-3p	2231	-0.031	1.11×10^{-5}
snoRNA-1210	1531	-0.020	1.28×10^{-5}
miR-342-3p	2247	-0.032	9.68×10^{-5}

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miR-301b-3p	1419	-0.019	$2.73x10^{-4}$
miR-16-5p	2279	-0.022	$2.91x10^{-4}$
miR-320a	2209	-0.020	$9.53x10^{-3}$
miR-122-5p	2198	0.014	$2.92x10^{-2}$
Triglyceride-HDL ratio (log) miR-122-5p	2200	0.070	$7.08x10^{-14}$
miR-192-5p	1726	0.067	$6.66x10^{-6}$
miR-342-3p	2249	0.041	$1.18x10^{-3}$

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Supplementary Table 3. Full pathway analysis of 16 miRNAs associated with insulin in FHS. Table of pathway titles from WikiPathways ranked by number of input miRNAs targeting genes on each pathway and, secondarily, by number of genes targeted by those miRNA. The last column lists the total number of genes on each pathway, defining an upper limit. The table was generated by the Pathway Finder tool (see Methods).

Pathway Title	miRNAs Targeting Genes	Genes Targeted by miRNA	Total Genes on Pathway
Insulin Signaling	16	69	160
EGF/EGFR Signaling Pathway	16	65	163
Focal Adhesion	16	64	191
Circadian rhythm related genes	16	62	201
Ectoderm Differentiation	16	44	139
Signaling Pathways in Glioblastoma	16	39	83
Integrated Pancreatic Cancer Pathway	15	83	192
Integrated Breast Cancer Pathway	15	72	155
MAPK Signaling Pathway	15	64	168
Cell Cycle	15	59	103
DNA Damage Response (only ATM dependent)	15	58	111
BDNF signaling pathway	15	57	144
Senescence and Autophagy in Cancer	15	54	105
Wnt Signaling Pathway and Pluripotency	15	49	103
Regulation of Actin Cytoskeleton	15	47	150
Adipogenesis	15	44	130
Oncostatin M Signaling Pathway	15	37	65
Integrin-mediated Cell Adhesion	15	32	101
MicroRNAs in cardiomyocyte hypertrophy	15	32	101
Wnt Signaling Pathway Netpath	15	26	52
TGF-beta Signaling Pathway	14	67	132
SIDS Susceptibility Pathways	14	59	160
Mesodermal Commitment Pathway	14	57	153
Retinoblastoma (RB) in Cancer	14	48	90
Regulation of toll-like receptor signaling pathway	14	40	141
TSH signaling pathway	14	38	66
G1 to S cell cycle control	14	38	68
miRNA Regulation of DNA Damage Response	14	37	87
DNA Damage Response	14	35	68
B Cell Receptor Signaling Pathway	14	35	97
Apoptosis	14	34	86
Hepatitis C and Hepatocellular Carcinoma	14	30	51
AGE/RAGE pathway	14	27	66
Toll-like Receptor Signaling Pathway	14	26	102
mRNA Processing	13	48	127

Spinal Cord Injury	13	44	119
Androgen receptor signaling pathway	13	43	89
TNF alpha Signaling Pathway	13	38	92
Leptin signaling pathway	13	37	75
NRF2 pathway	13	37	146
Corticotropin-releasing hormone	13	36	93
Wnt Signaling Pathway	13	34	68
TCR Signaling Pathway	13	34	90
Neural Crest Differentiation	13	30	101
TGF-beta Receptor Signaling	13	28	56
Notch Signaling Pathway	13	25	46
IL-4 Signaling Pathway	13	25	54
ErbB Signaling Pathway	13	25	55
ATM Signaling Pathway	13	24	40
Interferon type I signaling pathways	13	24	54
PDGF Pathway	13	22	39
Cardiac Hypertrophic Response	13	22	55
Endochondral Ossification	13	22	64
RANKL/RANK Signaling Pathway	13	20	55
Bladder Cancer	13	18	31
TWEAK Signaling Pathway	13	17	42
Physiological and Pathological Hypertrophy of the Heart	13	16	25
G13 Signaling Pathway	13	16	40
miRNAs involved in DNA damage response	13	16	52
p38 MAPK Signaling Pathway	13	15	34
Rac1/Pak1/p38/MMP-2 pathway	12	31	67
Integrated Cancer Pathway	12	28	48
IL-1 signaling pathway	12	28	55
Mecp2 and Associated Rett Syndrome	12	28	62
Apoptosis-related network due to altered Notch3 in ovarian cancer	12	26	53
Kit receptor signaling pathway	12	25	59
Aryl Hydrocarbon Receptor	12	24	46
Histone Modifications	12	24	66
IL-6 signaling pathway	12	21	43
Diurnally Regulated Genes with Circadian Orthologs	12	20	48
Alpha 6 Beta 4 signaling pathway	12	16	33
TOR Signaling	12	14	36
Cytoplasmic Ribosomal Proteins	11	47	89
Myometrial Relaxation and Contraction Pathways	11	42	157
Calcium Regulation in the Cardiac Cell	11	35	149
Apoptosis Modulation and Signaling	11	32	93
SREBP signalling	11	30	71
G Protein Signaling Pathways	11	30	95
Endoderm Differentiation	11	29	71

Structural Pathway of Interleukin 1 (IL-1)	11	25	47
AMPK Signaling	11	25	69
Primary Focal Segmental Glomerulosclerosis FSGS	11	25	72
Alzheimers Disease	11	24	120
FAS pathway and Stress induction of HSP regulation	11	21	42
Folate Metabolism	11	20	67
Pathogenic Escherichia coli infection	11	19	55
Selenium Micronutrient Network	11	18	89
TP53 Network	11	12	19
IL17 signaling pathway	11	12	31
Ovarian Infertility Genes	11	10	32
Parkin-Ubiquitin Proteasomal System pathway	10	30	70
Copper homeostasis	10	29	54
Interleukin-11 Signaling Pathway	10	23	44
IL-2 Signaling Pathway	10	20	42
IL-5 Signaling Pathway	10	19	40
IL-3 Signaling Pathway	10	19	49
Allograft Rejection	10	19	79
Signaling of Hepatocyte Growth Factor Receptor	10	18	34
DNA Replication	10	18	42
Trans-sulfuration and one carbon metabolism	10	17	31
Glycogen Metabolism	10	16	36
TSLP Signaling Pathway	10	16	47
Estrogen signaling pathway	10	14	23
Nanoparticle-mediated activation of receptor signaling	10	12	28
Gastric Cancer Network 2	10	12	31
Vitamin B12 Metabolism	10	12	52
Hypothetical Network for Drug Addiction	10	11	32
Amyotrophic lateral sclerosis (ALS)	10	11	38
Hair Follicle Development: Induction (Part 1 of 3)	10	11	42
MAPK Cascade	10	10	29
Signal Transduction of S1P Receptor	10	9	25
Translation Factors	9	29	51
Metapathway biotransformation	9	29	179
Electron Transport Chain	9	26	103
Proteasome Degradation	9	21	62
Arrhythmogenic Right Ventricular Cardiomyopathy	9	21	75
Cardiac Progenitor Differentiation	9	16	53
Parkinsons Disease Pathway	9	16	55
Extracellular vesicle-mediated signaling in recipient cells	9	15	30
One Carbon Metabolism	9	14	29
Serotonin Receptor 4/6/7 and NR3C Signaling	9	13	19
Hematopoietic Stem Cell Differentiation	9	13	47
IL-7 Signaling Pathway	9	12	25

Preimplantation Embryo	9	12	59
Oxidative Stress	9	10	31
NOD pathway	9	10	41
Aryl Hydrocarbon Receptor Pathway	9	10	46
EBV LMP1 signaling	9	9	23
Transcription factor regulation in adipogenesis	9	7	22
miRNA Biogenesis	9	5	6
Eukaryotic Transcription Initiation	8	16	44
Glycolysis and Gluconeogenesis	8	14	49
FSH signaling pathway	8	13	27
Gastric Cancer Network 1	8	13	29
Type II interferon signaling (IFNG)	8	12	37
Heart Development	8	11	47
Interactome of polycomb repressive complex 2 (PRC2)	8	10	16
Hypertrophy Model	8	10	20
Mitochondrial Gene Expression	8	9	20
PPAR Alpha Pathway	8	9	26
Endothelin Pathways	8	9	34
Angiogenesis	8	7	24
BMP Signalling and Regulation	8	6	12
Transcriptional activation by NRF2	8	6	15
mir-124 predicted interactions with cell cycle and differentiation	8	5	6
RalA downstream regulated genes	8	5	12
Metastatic brain tumor	8	5	14
TCA Cycle Nutrient Utilization and Invasiveness of Ovarian Cancer	8	4	5
GPCRs, Class A Rhodopsin-like	7	17	260
Factors and pathways affecting insulin-like growth factor (IGF1)-Akt signaling	7	16	35
Fluoropyrimidine Activity	7	14	33
Zinc homeostasis	7	13	37
Selenium Metabolism and Selenoproteins	7	13	47
Complement and Coagulation Cascades	7	13	59
Initiation of transcription and translation elongation at the HIV-1 LTR	7	11	32
miRs in Muscle Cell Differentiation	7	11	38
Oxidation by Cytochrome P450	7	11	62
Nucleotide Metabolism	7	10	19
Osteopontin Signaling	7	9	13
Fatty Acid Biosynthesis	7	9	22
EPO Receptor Signaling	7	8	26
Fatty Acid Beta Oxidation	7	8	34
IL-9 Signaling Pathway	7	7	17
Differentiation of white and brown adipocyte	7	7	25
NLR Proteins	7	6	9
Cytokines and Inflammatory Response	7	6	27
Vitamin A and Carotenoid Metabolism	7	6	43

Trans-sulfuration pathway	7	5	10
Osteoclast Signaling	7	5	16
Type II diabetes mellitus	7	5	22
RNA interference	7	4	5
MFAP5-mediated ovarian cancer cell motility and invasiveness	7	4	12
SRF and miRs in Smooth Muscle Differentiation and Proliferation	7	4	17
Blood Clotting Cascade	7	4	22
Oxidative phosphorylation	6	14	60
Nuclear Receptors	6	13	38
Differentiation Pathway	6	12	48
Synaptic Vesicle Pathway	6	11	51
SREBF and miR33 in cholesterol and lipid homeostasis	6	10	18
Tryptophan metabolism	6	10	46
Serotonin Receptor 2 and ELK-SRF/GATA4 signaling	6	8	20
IL1 and megakaryotyces in obesity	6	8	24
T-Cell Receptor and Co-stimulatory Signaling	6	8	29
Inflammatory Response Pathway	6	8	30
Apoptosis Modulation by HSP70	6	7	19
GPCRs, Other	6	7	93
Dopaminergic Neurogenesis	6	6	30
Cytosine methylation	6	5	9
Liver X Receptor Pathway	6	5	10
Folate-Alcohol and Cancer Pathway	6	4	8
Triacylglyceride Synthesis	6	4	24
Statin Pathway	6	4	31
ID signaling pathway	5	9	16
Nuclear Receptors in Lipid Metabolism and Toxicity	5	9	36
Melatonin metabolism and effects	5	8	29
Quercetin and Nf-kB/ AP-1 Induced Cell Apoptosis	5	7	16
TarBasePathway	5	6	17
Prostaglandin Synthesis and Regulation	5	6	30
Constitutive Androstane Receptor Pathway	5	6	32
Monoamine Transport	5	6	32
Cell Differentiation - Index	5	6	49
Iron metabolism in placenta	5	5	12
Homologous recombination	5	5	13
Peptide GPCRs	5	5	75
Mitochondrial LC-Fatty Acid Beta-Oxidation	5	4	17
NOTCH1 regulation of human endothelial cell calcification	5	4	17
Evolocumab Mechanism	5	2	2
PCSK9-mediated LDLR degradation	5	2	2
TCA Cycle	4	8	17
Overview of nanoparticle effects	4	8	19
Estrogen Receptor Pathway	4	7	13

Sphingolipid Metabolism	4	7	20
Urea cycle and metabolism of amino groups	4	7	20
Striated Muscle Contraction	4	7	38
TCA Cycle and PDHc	4	6	16
miRNA targets in ECM and membrane receptors	4	5	41
Cori Cycle	4	4	16
Farnesoid X Receptor Pathway	4	4	19
Nicotine Activity on Dopaminergic Neurons	4	4	22
Glucuronidation	4	4	26
eIF5A regulation in response to inhibition of the nuclear export system	4	3	4
DDX1 as a regulatory component of the Drosha microprocessor	4	3	7
Dual hijack model of Vif in HIV infection	4	3	9
Type III interferon signaling	4	3	10
Hypoxia-mediated EMT and Stemness	4	1	2
miR-517 relationship with ARCN1 and USP1	3	5	5
Irinotecan Pathway	3	4	14
Drug Induction of Bile Acid Pathway	3	4	17
Globo Sphingolipid Metabolism	3	4	22
Pilocytic astrocytoma	3	3	4
Pentose Phosphate Pathway	3	3	7
Vitamin D Metabolism	3	3	10
Serotonin Transporter Activity	3	3	11
Gene regulatory network modelling somitogenesis	3	3	11
Cholesterol Biosynthesis	3	3	15
Deregulation of Rab and Rab Effector Genes in Bladder Cancer	3	3	16
Glycerophospholipid Biosynthetic Pathway	3	3	21
Glutathione metabolism	3	3	23
Eicosanoid Synthesis	3	3	24
Monoamine GPCRs	3	3	33
miR-148a/miR-31/FIH1/HIF1Î±-Notch signaling in glioblastoma	3	2	8
Phase I biotransformations, non P450	3	2	8
EV release from cardiac cells and their functional effects	3	2	9
TFs Regulate miRNAs related to cardiac hypertrophy	3	2	13
FTO Obesity Variant Mechanism	3	1	8
Composition of Lipid Particles	3	1	9
Small Ligand GPCRs	3	1	19
GPCRs, Class B Secretin-like	2	4	24
Matrix Metalloproteinases	2	4	30
Osteoblast Signaling	2	3	14
Glial Cell Differentiation	2	2	7
Mismatch repair	2	2	9
Alanine and aspartate metabolism	2	2	12
Dopamine metabolism	2	2	13
Ganglio Sphingolipid Metabolism	2	2	13

SUPPLEMENTARY DATA

ACE Inhibitor Pathway	2	2	17
Tamoxifen metabolism	2	2	21
Complement Activation	2	2	22
Influenza A virus infection	2	1	1
Peroxisomal beta-oxidation of tetracosanoyl-CoA	2	1	4
Effects of Nitric Oxide	2	1	8
GPCRs, Class C Metabotropic glutamate, pheromone	2	1	15
Butyrate-induced histone acetylation	1	1	2
Catalytic cycle of mammalian Flavin-containing MonoOxygenases (FMOs)	1	1	5
Sulindac Metabolic Pathway	1	1	5
Acetylcholine Synthesis	1	1	7
Non-homologous end joining	1	1	7
NAD Biosynthesis II (from tryptophan)	1	1	8
Codeine and Morphine Metabolism	1	1	8
Methylation Pathways	1	1	9
Biogenic Amine Synthesis	1	1	15
Sulfation Biotransformation Reaction	1	1	19