

Supplementary Materials: Identifying Shared Risk Genes between Nonalcoholic Fatty Liver Disease and Metabolic Traits by Cross-Trait Association Analysis

Hongping Guo ^{1,2} and Zuguo Yu ^{1,3,*}

Table S1. Cross-trait meta-analysis result between NAFLD, obesity and T2D.

SNP	Genome Position	A1/A2	P_RE2C	Genes within Clumping Region
rs7903146	chr10:114597109-114914665	T/C	6.95×10^{-206}	TCF7L2
rs10811661	chr9:22130065-22134094	C/T	1.50×10^{-34}	-
rs1421085	chr16:53800387-53839135	C/T	4.47×10^{-34}	FTO
rs7651090	chr3:185473065-185547917	G/A	9.28×10^{-34}	IGF2BP2
rs2206734	chr6:20529542-20766697	T/C	1.61×10^{-32}	CDKAL1
rs13266634	chr8:118183551-118217307	T/C	1.79×10^{-31}	SLC30A8
rs849135	chr7:28138639-28256240	G/A	1.97×10^{-26}	JAZF1
rs7018475	chr9:22137685-22137685	G/T	3.23×10^{-26}	-
rs7923837	chr10:94232247-94499577	A/G	3.04×10^{-24}	HHEX, IDE, KIF11
rs2972144	chr2:226897985-227199263	A/G	9.76×10^{-21}	-
rs10244051	chr7:15023729-15065467	T/G	1.49×10^{-20}	-
rs11708067	chr3:123065778-123131254	G/A	3.18×10^{-20}	ADCY5
rs2796441	chr9:84304985-84380739	A/G	5.11×10^{-20}	-
rs738408	chr22:44324730-44395451	T/C	6.84×10^{-20}	PARVB, PNPLA3, SAMM50
rs1128249	chr2:165501849-165558252	T/G	2.05×10^{-19}	COBLL1
rs13411629	chr2:43450138-43848664	C/T	1.06×10^{-18}	THADA, ZFP36L2
rs10885414	chr10:114835452-114916586	G/A	1.29×10^{-18}	TCF7L2
rs1801206	chr4:6264968-6321396	C/T	2.19×10^{-18}	WFS1
rs11651755	chr17:36098040-36103565	C/T	1.43×10^{-16}	HNF1B
rs476828	chr18:57732689-57912785	C/T	2.62×10^{-15}	-
rs3217992	chr9:21997872-22072719	T/C	4.67×10^{-15}	CDKN2B
rs703979	chr10:80926036-80988837	T/C	5.39×10^{-15}	ZMIZ1
rs2237896	chr11:2831541-2858440	A/G	9.80×10^{-15}	KCNQ1
rs7129793	chr11:72432985-72727840	T/C	1.14×10^{-14}	ARAP1, ATG16L2, FCHSD2, STARD10
rs2583940	chr12:66165471-66260924	T/C	1.77×10^{-14}	HMGA2, LOC100129940
rs4731702	chr7:130433384-130453382	T/C	2.77×10^{-14}	-
rs7202877	chr16:75246419-75295639	G/T	2.88×10^{-14}	BCAR1, CTRB1
rs4273712	chr6:126717064-127251021	G/A	9.93×10^{-14}	-
rs508419	chr8:41464871-41533514	A/G	1.05×10^{-13}	AGPAT6, ANK1, NKX6-3
rs2011946	chr2:136381348-136925439	C/A	1.95×10^{-13}	CXCR4, DARS, LCT, MCM6, R3HDM1, UBXN4
rs13064760	chr3:12027240-12396955	T/C	1.08×10^{-12}	PPARG, SYN2, TIMP4
rs163184	chr11:2837625-2852529	G/T	2.06×10^{-12}	KCNQ1
rs340874	chr1:214145389-214163675	T/C	2.30×10^{-12}	PROX1
rs1260326	chr2:27730940-27742603	T/C	3.97×10^{-12}	GCKR
rs9856344	chr3:23222657-23454790	G/T	4.69×10^{-12}	UBE2E2, UBE2E2-AS1
rs11196181	chr10:114749018-114805860	A/G	5.32×10^{-12}	TCF7L2
rs6066149	chr20:45582954-45602638	A/G	6.27×10^{-12}	EYA2
rs10401969	chr19:19329924-19746151	C/T	8.06×10^{-12}	CILP2, GATAD2A, GMIP, HAPLN4, LPAR2, MAU2, NCAN, NDUFA13, PBX4, SUGP1, TM6SF2,

rs1375131	chr2:135837906–136092061	C/T	8.94×10^{-12}	TSSK6, YJEFN3
rs17746916	chr10:114704781–114704781	T/C	1.90×10^{-11}	RAB3GAP1, ZRANB3
rs2074314	chr11:17372443–17421860	C/T	2.25×10^{-11}	-
rs3217795	chr12:4386064–4386064	G/A	3.98×10^{-11}	ABCC8, KCNJ11, NCR3LG1
rs1215468	chr13:80706455–80747701	G/A	7.30×10^{-11}	CCND2
rs12221133	chr10:12253597–12307894	A/G	8.08×10^{-11}	-
rs11672660	chr19:46180184–46202172	T/C	1.59×10^{-10}	CDC123
rs2602734	chr19:4947041–4947041	A/G	2.96×10^{-10}	GIPR, QPCTL, SNRPD2
rs11182168	chr12:43817445–43973663	T/C	5.99×10^{-10}	UHRF1
rs13365225	chr8:36846109–36858483	G/A	6.89×10^{-10}	ADAMTS20
rs2820443	chr1:219734960–219762581	C/T	7.95×10^{-10}	-
rs2115107	chr19:7968168–7970635	A/G	8.41×10^{-10}	-
rs12454712	chr18:60845884–60845884	C/T	1.16×10^{-9}	MAP2K7
rs881929	chr16:31011183–31145219	T/G	1.17×10^{-9}	BCL2
rs231361	chr11:2691500–2691500	A/G	1.56×10^{-9}	BCKDK, KAT8, PRSS8, PRSS53, STX1B, STX4, VKORC1, ZNF646, ZNF668
rs1335579	chr20:62691313–62697000	A/G	1.78×10^{-9}	KCNQ1
rs719727	chr6:127412728–127414838	G/A	1.79×10^{-9}	TCEA2
rs11667352	chr19:33899065–34000725	G/A	2.01×10^{-9}	-
rs2248191	chr1:212241848–212248936	C/T	2.09×10^{-9}	PEPD
rs1562444	chr11:92673828–92724351	G/A	2.41×10^{-9}	DTL
rs6087526	chr20:32398295–32451693	C/A	2.61×10^{-9}	MTNR1B
rs998584	chr6:43757896–43757896	A/C	2.96×10^{-9}	CHMP4B
rs12907907	chr15:90425002–90441870	C/T	3.42×10^{-9}	-
rs244415	chr16:69572892–69666683	A/G	4.53×10^{-9}	AP3S2, C15orf38-AP3S2
rs279075	chr13:51094114–51100714	C/A	4.65×10^{-9}	NFAT5
rs3811976	chr5:101553800–101570236	C/T	5.93×10^{-9}	-
rs9911672	chr17:17528670–17554563	C/T	8.10×10^{-9}	SLCO4C1
rs258222	chr5:14777799–14810834	C/T	8.73×10^{-9}	-
rs12484907	chr22:50588313–50588313	A/G	9.76×10^{-9}	ANKH
rs4422297	chr3:64701146–64704860	G/A	1.05×10^{-8}	MOV10L1
rs598747	chr3:12106191–12116620	G/A	1.31×10^{-8}	-
rs10408179	chr19:46157004–46157019	C/T	1.33×10^{-8}	-
rs10758593	chr9:4292083–4292083	A/G	1.35×10^{-8}	-
rs2820000	chr6:20758347–20774410	G/A	1.51×10^{-8}	GLIS3
rs740099	chr7:70899397–70913398	C/T	1.57×10^{-8}	CDKAL1
rs9990427	chr4:10283627–10406291	A/G	2.10×10^{-8}	WBSCR17
rs1054873	chr2:111871897–111909247	A/G	2.32×10^{-8}	-
rs6968302	chr7:36116073–36116073	G/A	2.32×10^{-8}	ACOXL, BCL2L11
rs6062541	chr20:62449320–62449320	T/C	2.36×10^{-8}	-
rs16833240	chr2:136940954–136940954	A/G	2.54×10^{-8}	ZBTB46
rs8017244	chr14:49063108–49085802	C/T	2.54×10^{-8}	-
rs2842363	chr6:7267582–7267582	G/A	2.58×10^{-8}	-
rs555225	chr8:41546484–41546484	A/G	2.60×10^{-8}	-
rs1579238	chr12:97865504–97865504	G/A	2.72×10^{-8}	ANK1
rs2537833	chr17:65650626–65650626	T/C	3.32×10^{-8}	-
rs12925931	chr16:54491967–54491967	T/C	3.68×10^{-8}	PITPNC1
rs863750	chr12:124505444–124505444	C/T	4.49×10^{-8}	-
				ZNF664-FAM101A

chr: chromosome; A1/A2 refers to the effect allele and reference allele; -: no corresponding gene.

Table S2. The functional relevance of genes in Tables 3 and 4.

Gene Name	Full Form	Functional Relevance	Reference (PubMed ID)
TCF7L2	Transcription Factor 7 Like 2	Metabolites related to purine catabolism and risk of type 2 diabetes incidence; modifying effects of the TCF7L2-rs7903146 polymorphism.	30814579
FTO	FTO alpha-ketoglutarate dependent dioxygenase	FTO gene expression in white subcutaneous adipose tissue with overweight/obesity, lipid profile and glycemia.	33237144
IGF2BP2	insulin like growth factor 2 mRNA binding protein 2 CDK5 regulatory	At the IGF2BP2 locus, type 2 diabetes risk alleles reduce islet chromatin accessibility and expression of target gene IGF2BP2 and that conditional knockout of IGF2BP2 homolog	31064983
CDKAL1	subunit associated protein 1 like 1	CDKAL1 gene is associated with development of type 2 diabetes.	29372795
SLC30A8	solute carrier family 30 member 8	SLC30A8 gene polymorphism could have an increased risk of type 2 diabetes mellitus	30485937
JAZF1	JAZF zinc finger 1	JAZF1 is a relevant metabolic regulator in type 2 diabetes.	30838734
HHEX	hematopoietically expressed homeobox	Data indicate the potential importance of CDKAL1 protein and homeobox protein HHEX in glucose homeostasis in this Alaska Native population with a low prevalence of type 2 diabetes (T2D).	24112421
IDE	insulin degrading enzyme	HHEX, IDE and SLC30A8 showed strongest tissue-specific mRNA expression bias and are associated with increased risk of type 2 diabetes.	20703447
KIF11	kinesin family member 11	Genetic variants of the IDE-KIF11-HHEX region at 10q23.33 contribute to type 2 diabetes susceptibility.	22506066
ADCY5	adenylate cyclase 5	ADCY5 locus have been reported to be associated with birth weight and type 2 diabetes.	28877031
PARVB	parvin beta	Variations, including insertion/deletions, in PARVB, as well as those in PNPLA3, are important in the progression of NAFLD.	24621583
PNPLA3	patatin like phospholipase domain containing 3	The effect of PNPLA3 polymorphism as gain in function mutation in the pathogenesis of non-alcoholic fatty liver disease.	32333362
SAMM50	SAMM50 sorting and assembly machinery component	SNP in the SAMM50 gene is significantly associated with the presence and severity of NAFLD in a Korean populations.	29271184
COBLL1	cordon-bleu WH2 repeat protein like 1	An SNP in COBLL1 (rs7607980; TC or CC) is associated with lower insulin resistance and lower serum insulin levels in overweight/obese children/adolescents	23463496
THADA	THADA armadillo repeat containing	SNPs in THADA is associated with body mass index (BMI) and weight.	23349771
ZFP36L2	ZFP36 ring finger protein like 2	Insulin increases tristetraprolin (including gene ZFP36L2) and decreases VEGF gene expression in mouse 3T3-L1 adipocytes	18388887
WFS1	wolframin ER transmembrane glycoprotein	A positive association with T2D risk was found for WFS1 rs6446482 under an additive model.	31759989
HNF1B	HNF1 homeobox B	The rs4430796 SNP of the HNF1B gene associates with type 2 diabetes in older adults	30365659
SLC22A3	solute carrier family 22 member 3	The rs3088442 G>A variant of SLC22A3 acts as a protective allele and is associated with the clinical response to metformin. Overexpression of microRNA 147 is associated with a downward expression of the SLC22A3	30297296

		gene in patients who have type 2 diabetes.	
ZMIZ1	zinc finger MIZ-type containing 1 NPC intracellular	Perturbation of ZMIZ1 expression in human islets and beta-cells influences exocytosis and insulin secretion, highlighting a novel role for ZMIZ1 in the maintenance of glucose	26624892
NPC1	cholesterol transporter 1	NPC1 gene variations may predispose to common metabolic diseases by modulating steroid hormone synthesis and/or lipid homeostasis.	29325023

Table S3. Significant overlap transcriptome-wide association analysis results between NAFLD, obesity and T2D ($P < 5 \times 10^{-8}$).

Trait	Tissue	Gene	CHR	eQTL	P_TWAS
NAFLD	Cells_Transformed_fibroblasts	ATP13A1	19	rs16996148	4.93×10^{-9}
Obesity	Adipose_Visceral_Omentum	KAT8	16	rs2855475	1.65×10^{-8}
Obesity	Adrenal_Gland	KAT8	16	rs10871454	1.16×10^{-8}
Obesity	Artery_Aorta	KAT8	16	rs2855475	1.13×10^{-7}
Obesity	Artery_Coronary	KAT8	16	rs2855475	1.10×10^{-7}
Obesity	Brain_Cerebellar_Hemisphere	KAT8	16	rs2855475	1.83×10^{-7}
Obesity	Brain_Cerebellum	KAT8	16	rs4527034	3.10×10^{-7}
Obesity	Brain_Cortex	KAT8	16	rs8046707	1.39×10^{-7}
Obesity	Brain_Frontal_Cortex	KAT8	16	rs12597511	5.18×10^{-8}
Obesity	Breast_Mammary_Tissue	KAT8	16	rs4527034	2.81×10^{-7}
Obesity	Esophagus_Gastroesophageal	RP11-196G11.2	16	rs732172	4.92×10^{-7}
Obesity	Esophagus_Gastroesophageal	KAT8	16	rs11865499	3.61×10^{-7}
Obesity	Esophagus_Mucosa	BCKDK	16	rs2303222	4.72×10^{-8}
Obesity	Liver	PRSS53	16	rs11640961	5.53×10^{-9}
Obesity	Liver	VKORC1	16	rs2303222	2.87×10^{-8}
Obesity	Lung	KAT8	16	rs4527034	4.98×10^{-7}
Obesity	Ovary	KAT8	16	rs2855475	2.08×10^{-7}
Obesity	Stomach	KAT8	16	rs11865499	4.01×10^{-7}
Obesity	Testis	AKTIP	16	rs8056923	1.09×10^{-8}
Obesity	Thyroid	KAT8	16	rs12597511	5.07×10^{-7}
Obesity	Uterus	FBR5	16	rs749671	3.35×10^{-8}
Obesity	Whole_Blood	HSD3B7	16	rs4889606	3.70×10^{-8}
Obesity	Whole_Blood	ZNF668	16	rs12597511	8.03×10^{-8}
T2D	Adipose_Subcutaneous	AC074117.10	2	rs780110	2.69×10^{-7}
T2D	Artery_Aorta	JAZF1	7	rs1985152	4.67×10^{-7}
T2D	Artery_Aorta	TCF7L2	10	rs10885409	1.96×10^{-39}
T2D	Brain_Caudate_basal_ganglia	RFT1	3	rs2564921	4.06×10^{-7}
T2D	Brain_Cerebellar_Hemisphere	WFS1	4	rs4689391	4.56×10^{-15}
T2D	Brain_Cerebellum	WFS1	4	rs4689391	9.24×10^{-15}
T2D	Brain_Cortex	RFT1	3	rs2564921	2.27×10^{-7}
T2D	Cells_Transformed_fibroblasts	WFS1	4	rs13107806	6.92×10^{-14}
T2D	Esophagus_Mucosa	AC074117.10	2	rs780110	1.22×10^{-7}
T2D	Esophagus_Mucosa	APIP	11	rs7111607	5.62×10^{-7}
T2D	Esophagus_Muscularis	AC074117.10	2	rs780110	4.49×10^{-7}
T2D	Esophagus_Muscularis	NRBP1	2	rs780110	3.23×10^{-7}
T2D	Esophagus_Muscularis	EIF2S2P3	10	rs10882099	2.12×10^{-15}
T2D	Heart_Atrial_Appendage	ZCCHC24	10	rs942791	4.85×10^{-8}
T2D	Lung	CAMK1D	10	rs11257655	2.88×10^{-8}
T2D	Muscle_Skeletal	WFS1	4	rs13107806	5.34×10^{-14}
T2D	Muscle_Skeletal	ZZEF1	17	rs12947597	6.46×10^{-8}

T2D	Nerve_Tibial	NRBP1	2	rs780110	4.61×10^{-7}
T2D	Ovary	AC074117.10	2	rs1260320	5.12×10^{-7}
T2D	Pituitary	SMYD2	1	rs1431985	3.39×10^{-9}
T2D	Prostate	EIF2S2P3	10	rs10882099	3.91×10^{-13}
T2D	Skin_Not_Sun_Exposed	WFS1	4	rs13107806	1.19×10^{-13}
T2D	Skin_Not_Sun_Exposed	KCNJ11	11	rs5215	1.75×10^{-7}
T2D	Skin_Sun_Exposed	WFS1	4	rs4689391	1.94×10^{-14}
T2D	Skin_Sun_Exposed	KCNJ11	11	rs2051772	2.86×10^{-7}
T2D	Spleen	EIF2S2P3	10	rs2488071	3.89×10^{-11}
T2D	Stomach	APIP	11	rs7937316	5.56×10^{-7}
T2D	Testis	AC074117.10	2	rs715326	1.73×10^{-8}
T2D	Testis	NRBP1	2	rs780110	2.14×10^{-8}
T2D	Testis	WFS1	4	rs13107806	5.18×10^{-7}
T2D	Testis	HHEX	10	rs2497306	2.32×10^{-10}
T2D	Testis	AKTIP	16	rs8056923	3.69×10^{-7}
T2D	Testis	WWP2	16	rs17299478	3.64×10^{-7}
T2D	Thyroid	AC010883.5	2	rs13419550	1.32×10^{-12}
T2D	Thyroid	SFMBT1	3	rs9844736	5.26×10^{-7}
T2D	Thyroid	WFS1	4	rs4689391	1.94×10^{-14}
T2D	Thyroid	EIF2S2P3	10	rs1111875	2.66×10^{-14}
T2D	Thyroid	ZZEF1	17	rs10521129	2.45×10^{-8}
T2D	Whole_Blood	EIF2S2P3	10	rs7087591	2.79×10^{-10}
T2D	Whole_Blood	AP3S2	15	rs1371135	4.07×10^{-7}
T2D	Whole_Blood	PPM1N	19	rs1049698	5.50×10^{-7}

Abbreviations: CHR: chromosome; eQTL: expression quantitative trait loci; NAFLD: nonalcoholic fatty liver disease; T2D: type II diabetes.

Table S4. KEGG pathway analysis for NAFLD, obesity and T2D.

Pathway ID	Description	# Overlap Genes	Adjusted P-Value
hsa05200	Pathways in cancer	9	0.0016
hsa04950	Maturity onset diabetes of the young	2	0.0077
hsa05210	Colorectal cancer	3	0.0097
hsa04911	Insulin secretion	3	0.0097
hsa04130	SNARE interactions in vesicular transport	2	0.0130
hsa04972	Pancreatic secretion	3	0.0138
hsa05202	Transcriptional misregulation in cancer	4	0.0152
hsa05216	Thyroid cancer	2	0.0153
hsa04510	Focal adhesion	4	0.0190
hsa05169	Epstein-Barr virus infection	4	0.0196
hsa04725	Cholinergic synapse	3	0.0197
hsa04930	Type II diabetes mellitus	2	0.0230
hsa04340	Hedgehog signaling pathway	2	0.0240
hsa04110	Cell cycle	3	0.0256
hsa04068	FoxO signaling pathway	3	0.0301
hsa04261	Adrenergic signaling in cardiomyocytes	3	0.0381
hsa05226	Gastric cancer	3	0.0408
hsa04934	Cushing syndrome	3	0.0450
hsa04218	Cellular senescence	3	0.0486

Abbreviations: KEGG: Kyoto Encyclopedia of Genes and Genomes; NAFLD: nonalcoholic fatty liver disease; T2D: type II diabetes.