

# Exome Analysis Summary Report

Andrew Ruttenberg

Ryan Koesterer

Peter Dornbos

Jason Flannick

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## 1 Introduction

This report summarizes the results of our exome analysis of type 2 diabetes (T2D) and 24 related quantitative traits (QTs), conducted as part of FNIH RFP 11. The primary exomes in the analysis are from the AMP-T2D-GENES study ( $N = 45,231$ ) and the UK Biobank ( $N = 45,650$ ). For T2D, we additionally analyzed exomes from the TOPMed ( $N = 44,127$ ), MIGen ( $N = 19,550$ ), and CHARGE ( $N = 9,480$ ) studies. Final sample sizes are shown in Tables 1 and 2.

Dataset	Cases	Controls	Total	Effective N
AMP-T2D-GENES	19,931	22,196	42,127	42,005
TOPMed	9,503	34,624	44,127	29,826
MIGen	1,888	17,662	19,550	6,823
CHARGE	2,373	7,107	9,480	7,116
UKBB	2,425	27,711	30,136	8,919
Total	36,120	109,300	145,420	94,689

Table 1: Datasets in T2D analysis

Trait	52k	UKBB	Total
2hrCpep	529	0	529
2hrGlu	3,580	0	3,580
2hrIns	2,219	0	2,219
Adiponectin	5,739	0	5,739
BMI	42,085	45,650	87,735
Chol	33,831	43,168	76,999
DBP	31,554	45,635	77,189
FastCpep	1,445	0	1,445
FastGlu	17,763	0	17,763
FastIns	12,960	0	12,960
HbA1C	8,435	40,242	48,677
HDL	32,684	40,868	73,552
Height	41,731	0	41,731
HipC	22,136	0	22,136
HOMA-B	12,392	0	12,392
HOMA-IR	12,876	0	12,876
LDL	31,836	43,126	74,962
Leptin	2,313	0	2,313
RedBloodCell	0	41,818	41,818
SBP	31,549	45,640	77,189
TG	33,299	43,135	76,434
TG:HDL	32,204	0	32,204
WaistC	32,869	0	32,869
WHR	27,380	45,647	73,027

Table 2: Datasets in QT analysis

## 2 Methods

We conducted two analyses: one for T2D, and one for the 24 quantitative traits.

For T2D, we conducted single-variant and gene-level meta-analyses. For each of the four contributing studies in Table 1, we first calculated single-variant score statistics (e.g. p-values and effect sizes) and covariance matrices using `rvtests`. Each study was responsible for performing its own quality control prior to calculating these summary statistics. We then transferred these summary statistics to a central analysis site and combined them using `RAREMETALS`. This analysis produced single-variant associations and gene-level associations for seven variant masks described in Flannick et al 2019. We further combined the associations across the seven masks into a single gene-level score using the minimum p-value method also described in Flannick et al 2019.

For the QTs, we conducted QC, single-variant, and gene-level analysis for both the AMP-T2D-GENES

and UKBB studies following the procedure outlined in Flannick et al 2019. After analyzing these two studies independently, we then combined them via an inverse-variance weighted meta-analysis.

### 3 Meta-analysis with TOPMed, MIGen, and CHARGE

The coding variants with single-variant associations achieving  $p < 4.3 \times 10^{-7}$  are shown in Table 3. We observe three associations outside of known T2D GWAS loci. The most notable novel association is a missense variant in *CHGA* (MAF=0.015), a marker for the pre-beta cell neuroendocrine lineage. *CHGA* was previously identified as a downstream effector of *PAM* activity by Thomsen et al 2018 and shown to reduce insulin content and secretion when inactivated in a cell model.

Variant	P	Odds Ratio	Gene	GWAS locus	MAF	Consequence	Protein change
8:117172544:C:T	2.366e-19	0.92	SLC30A8	SLC30A8	0.3933	missense	p.R325W
7:127613496:C:T	8.364e-17	1.44	PAX4	GRM8	0.1725	missense	p.R192H
2:27508073:T:C	7.437e-13	1.07	GCKR	GCKR	0.4257	missense,splice_region	p.L446P
11:17388025:T:C	9.556e-11	0.94	ABCC8	KCNJ11	0.2724	downstream_gene	-
4:6300792:G:A	1.292e-10	1.07	WFS1	WFS1	0.1332	missense	p.V333I
11:17387083:C:T	6.855e-10	0.95	KCNJ11	KCNJ11	0.2729	missense	p.V250I
3:12351626:C:G	1.973e-09	0.92	PPARG	PPARG	0.1699	missense	p.P12A
2:164694691:T:C	4.4e-09	0.93	COBLL1	GRB14	0.1877	missense	p.N939D
11:131661029:G:A	1.33e-08	8.3	NTM	-	0.0003	intron	-
22:21957327:G:A	1.403e-08	23.93	TOP3B	-	0.0001	synonymous	p.G792G
15:75372229:A:T	1.672e-08	1.06	SIN3A	SIN3A	0.4221	intron	-
2:164695843:GA:G	1.695e-08	0.93	COBLL1	GRB14	0.2359	intron	-
4:6291969:C:G	2.86e-08	1.05	WFS1	WFS1	0.2080	synonymous	p.R228R
11:17396930:C:A	2.874e-08	0.95	ABCC8	KCNJ11	0.2781	missense	p.A1369S
6:7231610:G:A	3.904e-08	0.93	RREB1	SSR1	0.1762	missense	p.D1171N
17:7042968:T:C	4.53e-08	1.07	SLC16A13	SLC16A11	0.3281	downstream:gene	-
2:65071705:A:G	5.778e-08	0.95	CEP68	CEP68	0.1509	synonymous	p.T203T
19:45688570:C:T	8.318e-08	0.96	SNRPD2	EML2	0.3714	splice:region,intron	-
8:144440024:C:T	9.741e-08	1.04	TONSL	HSF1	0.4182	missense	p.G493S
19:44892887:C:T	1.19e-07	0.94	TOMM40	APOE	0.2845	synonymous	p.F131F
4:6302360:A:G	1.235e-07	1.05	WFS1	WFS1	0.2181	synonymous	p.S855S
5:103201584:A:G	2.442e-07	1.13	PPIP5K2	PAM	0.0661	missense	p.S1207G
7:44220107:G:A	2.74e-07	0.95	CAMK2B	MYL7	0.2738	synonymous	p.N528N
4:6301295:C:T	3.587e-07	1.05	WFS1	WFS1	0.2457	synonymous	p.N500N
14:92929753:G:A	3.89e-07	1.3	CHGA	-	0.0150	missense	p.S98N

Table 3: Single-variant T2D associations from the meta-analysis

The 10 strongest gene-level associations from the meta-analysis are shown in Table 4. The three exome-wide significant associations from the original AMP-T2D-GENES study (Flannick et al 2019) constitute three of

the top four associations in the meta-analysis, with *GCK* newly achieving exome-wide significance. *HNF1A* and *PAX4* also increase in significance compared to the original AMP-T2D-GENES analysis. The *GCK* signal, however, is due almost entirely to variants in TOPMed previously reported to cause MODY, suggesting that it (and perhaps *HNF1A* and *PAX4* as well) may be due to undiagnosed MODY cases in the TOPMed study.

Gene	P	Odds Ratio
SLC30A8	5.03e-09	0.489682
GCK	2.05e-08	6.29654
MC4R	1.69e-07	1.84596
PAM	8.18e-06	1.16883
HNF1A	4.7e-05	2.11488
PAX4	6.79e-05	1.24359
HLA-F	0.000106	1.30866
C2orf50	0.000116	5.00281
SOX11	0.000148	1.57145
UNC80	0.000164	1.36889

Table 4: Gene-level T2D associations from the meta-analysis

We examined the gene-level signals in the meta-analysis in greater detail to see whether “positive controls” suggested that the meta-analysis had significantly greater power than the previous AMP-T2D-GENES analysis. We curated 25 gene sets from the Mouse Genome Informatics (MGI) database that had the keywords “glucose” or “insulin” in them. We then tested whether they were enriched for rare variant gene-level associations by comparing the association rank of genes in the gene set to randomly chosen genes in the genome. The rationale for this analysis was that, in the original AMP-T2D-GENES study, we observed strong enrichment of these gene sets for T2D associations (Table 5): 13 of the 25 gene sets achieved  $p < 0.05$ , and fifteen achieved  $p < 0.1$ .

By contrast, only six of the gene sets achieved  $p < 0.05$  in the meta-analysis (Table 5), despite its larger sample size and its inclusion of the AMP-T2D-GENES study. The decrease in signal seems mostly attributable to the TOPMed study, for which only one gene set achieves  $p < 0.05$  and only four gene sets achieve  $p < 0.1$ . We did not find any obvious quality control issues with TOPMed to explain these results.

Our current working hypothesis is that TOPMed, which was ascertained as a population-based study with a focus on broad cardiometabolic phenotypes, may contain T2D cases phenotypically different than those in AMP-T2D-GENES, which was ascertained directly on T2D and (in some cases) extreme forms of T2D (e.g. young and lean). If true, this hypothesis would suggest that the T2D associations observed in TOPMed may be (a) overall much weaker than they would be for a T2D-ascertained study of the same size and/or (b) mediated by different pathways, for example insulin resistance as opposed to insulin secretion. We are conducting further analysis to test this hypothesis by comparing effect sizes in TOPMed across both common and rare variants, but these analyses are still in progress.

Therefore, for the time being, we did not pursue the T2D meta-analysis results any further.

Gene Set	AMP-T2D-GENES P-value	Meta-analysis P-value	TOPMed P-value	Log Ratio
mp_improved_glucose_tolerance	2.958e-05	0.05901	0.06908	7.59836
mp_decreased_insulin_secretion	0.0001504	0.07143	0.679	6.16317
mp_decreased_circulating_insulin_level	7.648e-05	0.01661	0.08243	5.38073
mp_impaired_glucose_tolerance	2.174e-06	0.0002499	0.1736	4.74449
mp_increased_insulin_sensitivity	0.004329	0.4502	0.1206	4.64436
mp_increased_urine_glucose_level	0.007167	0.1523	0.4247	3.05637
mp_abnormal_glucose_homeostasis	0.007679	0.1487	0.1457	2.96344
mp_decreased_muscle_cell_glucose_uptake	0.09644	0.8305	0.4586	2.15311
mp_increased_circulating_glucose_level	0.001659	0.01255	0.8812	2.02351
mp_abnormal_insulin_secretion	0.01514	0.1034	0.4875	1.92126
mp_decreased_fasting_circulating_glucose_level	0.16	0.7334	0.3429	1.52252
mp_increased_muscle_cell_glucose_uptake	0.2275	0.8952	0.7554	1.3699
mp_abnormal_glucose_tolerance	0.04482	0.1742	0.1597	1.35755
mp_abnormal_circulating_insulin_level	0.1354	0.3352	0.6798	0.906494
mp_abnormal_circulating_glucose_level	0.1373	0.2353	0.4517	0.538693
mp_increased_cardiac_cell_glucose_uptake	0.5125	0.6826	0.8334	0.286608
mp_increased_insulin_secretion	0.04452	0.0531	0.02647	0.176238
mp_increased_adipocyte_glucose_uptake	0.4845	0.5128	0.161	0.0567685
mp_decreased_adipocyte_glucose_uptake	0.7554	0.63	0.6382	-0.181528
mp_decreased_circulating_glucose_level	0.07064	0.05673	0.2775	-0.219293
mp_insulin_resistance	0.01149	0.006727	0.1953	-0.535348
mp_decreased_circulating_insulin-like_growth_factor_I_level	0.9706	0.4643	0.4873	-0.737384
mp_increased_circulating_insulin_level	0.03218	0.008789	0.05495	-1.29784
mp_increased_fasting_circulating_glucose_level	0.6286	0.07725	0.2939	-2.09645
mp_increased_circulating_insulin-like_growth_factor_I_level	0.4117	0.04069	0.2506	-2.31431

Table 5: Gene-level T2D associations from the meta-analysis

## 4 Quantitative trait analysis

We summarized results from the quantitative trait analysis in five ways: (a) exome-wide significant associations; (b) loss-of-function associations; (c) genes achieving nominal associations with with multiple traits; (d) genes with a pattern of associations reflective of different T2D subtypes; and (e) genes in the grey zone list associated with one or more traits of interest. In all analyses, we focused on gene-level associations.

### 4.1 Exome-wide significant genes

Table 6 shows all genes achieving  $p < 2.5 \times 10^{-6}$  for at least one QT. P-values are based on the combined analysis of the AMP-T2D-GENES and UKBB studies.

Of the 78 exome-wide significant associations, 66 are with lipid traits. The only other QTs with more than one exome-wide significant association are HbA1C levels (*GCK*, *PIEZO1*, *ANK1*, *G6PD*, and *RNF123*) and red blood cell levels (*HBB*, *PCOLCE*, and *HBA2*). The genes for BMI (*MC4R*), Adiponectin (*ADIPOQ*), and fasting glucose (*G6PC2*) are well-known. *GCK* was the sole gene to achieve exome-wide significance for T2D in the combined analysis; we report its association in Table 6, but for the remainder of this section we use the AMP-T2D-GENES results in all analyses involving T2D.

Phenotype	Gene	P	Effect	Phenotype	Gene	P	Effect
TG:HDL	APOC3	<1e-300	-0.752	Chol	CBLC	9.66e-11	-3.23
TG	APOC3	4.05e-114	-0.682	FastGlu	G6PC2	1.03e-10	-0.164
LDL	APOE	4.72e-90	-22.5	HDL	APOE	1.04e-10	2.17
LDL	LDLR	1.18e-83	46.3	HDL	SCARB1	1.59e-10	6.22
HDL	APOC3	2.01e-65	14.6	TG:HDL	CD36	3.18e-10	-0.0807
Chol	LDLR	7.02e-63	42.3	Chol	ANGPTL3	3.91e-10	-19.2
LDL	PCSK9	9.47e-56	-40.6	HbA1c	G6PD	4.64e-10	-0.0282
HDL	LIPG	4.48e-51	5.83	LDL	APOH	8.11e-10	4.97
HDL	LPL	3.03e-50	-4.75	LDL	ABCG5	1.12e-09	5.88
Chol	PCSK9	2.11e-48	-40.1	Chol	ABCG5	1.27e-09	6.28
TG	LPL	1.26e-38	0.161	HDL	PLA2G12A	2.03e-09	-2.79
Chol	APOE	4.49e-38	-15.5	Chol	TM6SF2	3.28e-09	-8.06
LDL	APOB	4.05e-31	-38.3	RBC	PCOLCE	3.4e-09	-0.0421
Chol	APOB	2.17e-29	-39.5	TG	TM6SF2	3.81e-09	-0.0863
HDL	CETP	2.01e-28	-2.67	HDL	APOA1	9.65e-09	-4.06
HDL	LIPC	1.01e-26	3.59	HDL	NR1H3	1.62e-08	7.23
HbA1c	GCK	7.84e-26	0.231	TG:HDL	LPL	1.72e-08	0.404
LDL	BCAM	3.35e-25	-7.69	BMI	MC4R	1.84e-08	0.0502
Chol	LIPG	8.29e-25	15	T2D	GCK	3.77e-08	2.41
HDL	ABCA1	8.34e-24	-2.19	LDL	SLC22A1	6.17e-08	1.96
TG	ANGPTL4	1.01e-22	-0.116	LDL	LIPG	6.42e-08	7.63
TG	APOB	1.19e-22	-0.0642	TG:HDL	APOB	9.05e-08	-0.681
HDL	CD300LG	1.22e-22	-3.25	Chol	ALB	9.96e-08	65
HDL	ANGPTL4	1.51e-22	3.05	HDL	APOB	1.07e-07	0.939
HDL	CD36	5.93e-22	2.25	LDL	ALB	1.48e-07	60.2
LDL	ABCA6	1.5e-20	7.84	LDL	TM6SF2	1.72e-07	-6.48
HbA1c	PIEZO1	5.99e-20	-0.0208	Chol	APOH	1.96e-07	4.6
TG	APOA5	1.14e-19	0.696	LDL	ZNF229	2.36e-07	-9.21
Chol	BCAM	2.76e-17	-6.96	HbA1c	RNF123	2.66e-07	0.0134
LDL	CBLC	9.53e-17	-3.95	HDL	SLC39A8	3.7e-07	-2.4
RBC	HBB	2.22e-15	1.02	LDL	APOC3	6.27e-07	-15.5
Chol	ABCA6	2.97e-15	7.1	HDL	APOA5	7.04e-07	-10.1
TG	CD300LG	9.48e-15	0.0988	Chol	ABCA1	9.53e-07	-3.97
HDL	LCAT	1.87e-14	-2.74	HDL	CCL22	1.19e-06	-1.21
HbA1c	ANK1	3.42e-14	-0.0132	HDL	ANGPTL8	1.44e-06	14.1
LDL	PVR	7.89e-13	-5.52	Chol	PVR	1.54e-06	-4.09
HDL	HNF4A	2.21e-12	-2.34	LDL	TIRAP	1.55e-06	6.04
TG	ANGPTL3	2.96e-12	-0.349	RBC	HBA2	1.77e-06	0.479
Adiponectin	ADIPOQ	3.34e-12	-0.512	HDL	PLIN1	2.41e-06	7.65

Table 6: Genes with exome-wide significant rare variant associations from the AMP-T2D-GENES and UKBB meta-analysis.

## 4.2 Loss-of-function signals

Table 7 shows all genes achieving  $p < 2.5 \times 10^{-6}$  for the LofTee mask, which consists of high-confidence predicted protein truncating variants.

Phenotype	Gene	P	Effect
TG	APOC3	5.23e-107	<b>-0.7534</b>
HDL	APOC3	6.306e-66	<b>15.9624</b>
LDL	PCSK9	4.832e-43	<b>-59.1703</b>
Chol	PCSK9	1.352e-37	<b>-58.5272</b>
TG:HDL	APOC3	3.9856e-36	<b>-0.9362</b>
LDL	APOB	9.953e-32	<b>-37.8380</b>
Chol	APOB	5.275e-30	<b>-39.2664</b>
HDL	CETP	5.385e-22	<b>15.5487</b>
TG	APOA5	3.141e-20	0.6940
LDL	LDLR	1.977e-18	71.6452
HDL	CD36	3.214e-17	<b>2.4459</b>
RBC	HBB	1.1082e-15	1.0227
TG	APOB	7.5e-14	<b>-0.2886</b>
TG	ANGPTL3	4.712e-12	<b>-0.3665</b>
Chol	LDLR	1.16e-11	60.0928
HbA1c	TMEM201	1.402e-11	0.4037
Chol	ANGPTL3	6.258e-09	<b>-26.7450</b>
HbA1c	GCK	8.201e-09	0.4870
TG:HDL	APOB	2.4542e-08	<b>-0.68127</b>
LDL	ZNF229	6.193e-08	<b>-9.9231</b>
HbA1c	SLC4A1	1.251e-07	<b>-0.3003</b>
LDL	APOC3	1.946e-07	<b>-15.4743</b>
HDL	APOA5	2.658e-07	-10.5699
HDL	ANGPTL8	5.299e-07	<b>14.0850</b>
HDL	PLIN1	6.559e-07	<b>7.6422</b>
FastGlu	DUSP27	7.7217e-07	0.53396
Adiponectin	ADIPOQ	8.809e-07	<b>-1.6768</b>
HbA1c	PPP5D1	1.008e-06	0.5843
Chol	ZNF229	1.156e-06	<b>-9.6098</b>
HDL	LIPC	1.483e-06	<b>7.2184</b>
Chol	ALB	1.572e-06	59.7550
TG	ANGPTL4	1.926e-06	<b>-0.3100</b>
HDL	ARF4	2.073e-06	<b>40.6029</b>
LDL	RSPH14	2.167e-06	100.1000

Table 7: Genes with significant LofTee signals.

Phenotype	Gene	P	Effect
RBC	HBB	1.1082e-15	1.0227
HbA1c	TMEM201	1.402e-11	0.4037
HbA1c	GCK	8.201e-09	0.4870
HbA1c	SLC4A1	1.251e-07	<b>-0.3003</b>
FastGlu	DUSP27	7.7217e-07	0.53396
Adiponectin	ADIPOQ	8.809e-07	<b>-1.6768</b>
HbA1c	PPP5D1	1.008e-06	0.5843
DBP	TRIM9	3.012e-06	26.8751
RBC	HBA2	3.0151e-06	0.47542
HbA1c	SOX3	3.146e-06	<b>-0.5570</b>
HbA1c	CLNS1A	3.465e-06	0.1933
DBP	GPR34	6.736e-06	14.8486
FastCpep	KHDC1	7.4226e-06	<b>-0.35069</b>
HOMA-IR	THAP2	8.6557e-06	1.782
BMI	WIPF2	8.867e-06	0.5393
RBC	TOB2	9.0934e-06	<b>-1.4984</b>
WHR	NT5C3B	1.009e-05	<b>-0.0758</b>
DBP	KCNK12	1.014e-05	40.1671
HipC	OXNAD1	1.0989e-05	10.841
Height	PEX11A	1.253e-05	10.147
WHR	SPATA2	1.282e-05	0.2194
BMI	OR11A1	1.342e-05	0.2715
RBC	ALB	1.787e-05	0.36221
Height	HECTD1	1.9441e-05	<b>-12.284</b>
RBC	EMD	2.0763e-05	1.4373
DBP	CCDC9	2.284e-05	3.6992
BMI	SEMA6B	2.422e-05	0.3074
WaistC	GIPC2	2.6361e-05	16.32
DBP	ZBTB2	2.721e-05	53.9883
FastGlu	MPO	2.755e-05	0.2367

Table 8: The genes with the 30 strongest LofTee associations with non-lipid traits.

Because lipid associations dominate the results, Table 8 shows the 25 genes with the strongest LofTee associations across non-lipid traits, including some that do not achieve exome-wide significance.

In each table, **bold** font indicates a signal with a putatively protective effect.

### 4.3 Genes associated with independent traits

We next filtered our results to genes associated with multiple traits. Many of the QTs we analyzed are not independent of one another, showing correlations of both individual measurements (Figure 1) and gene-level associations (Figure 2). To develop a more accurate measure of the number of “independent” traits associated with a gene, we therefore conducted a principal component analysis (PCA) of the QTs, using their p-values of association across each gene as input vectors to the calculations.

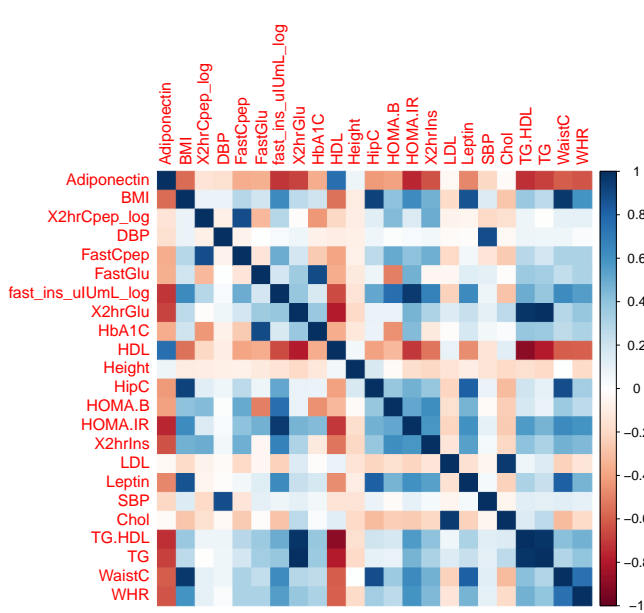


Figure 1: Correlations of individual trait measurements

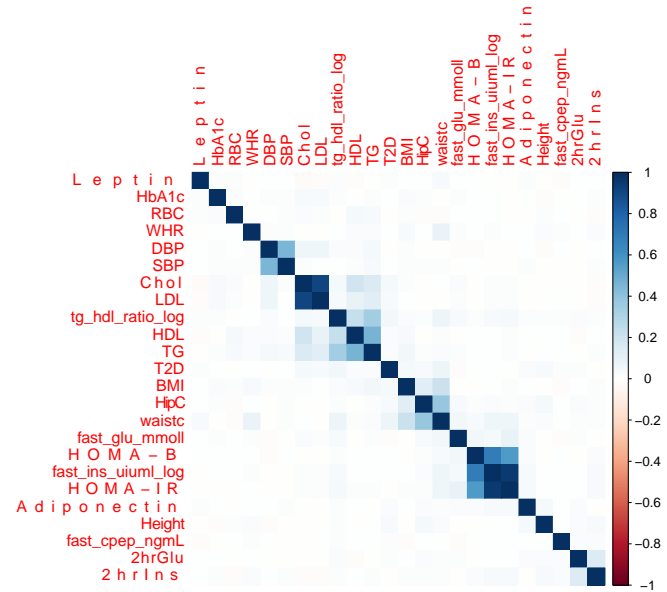


Figure 2: Correlations of gene-level association p-values

Figure 3 shows the loadings of each QT on each PC, and Figure 4 confirms that the PCs are uncorrelated. We identified QTs highly loaded on a PC as those whose loadings were more than two standard deviations above the mean loading across all QTs. The QTs highly loaded on each PC were (PC1) FastIns, HOMA-B, HOMA-IR; (PC2) Chol, LDL; (PC3) Chol, LDL; (PC4) HDL, TG; (PC5) DBP, SBP; (PC6) 2hrGlu, 2hrIns; (PC7) Adiponectin, Leptin; (PC8) HbA1c, Height; (PC9) T2D, FastGlu; and (PC10) WHR, RBC

We then counted the number of PCs that each gene was associated with, defining a PC association as a significant ( $p < 0.05$ ) association for any of the QTs highly loaded on the PC. Table 9 shows the genes associated with at least four PCs, together with their original association p-values across all QTs. The table is sorted first by the number of associated PCs, and then by the strength of T2D association. QTs with  $p < 0.05$  associations are shown in bold font and yellow-colored cells.



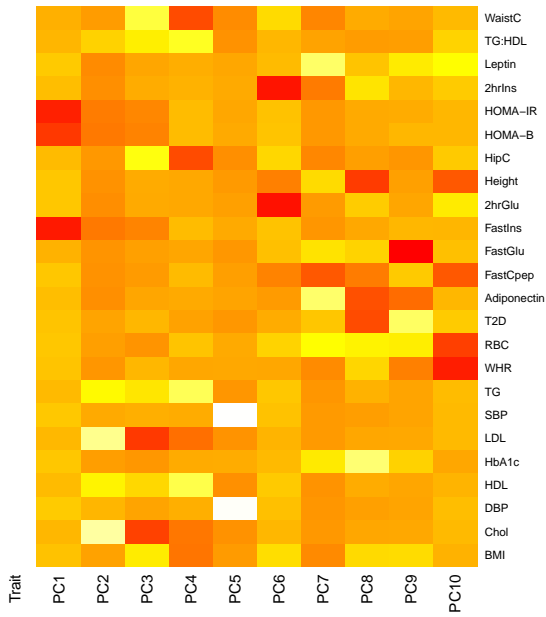


Figure 3: PC loadings across QTs. Red color indicates a higher loading.

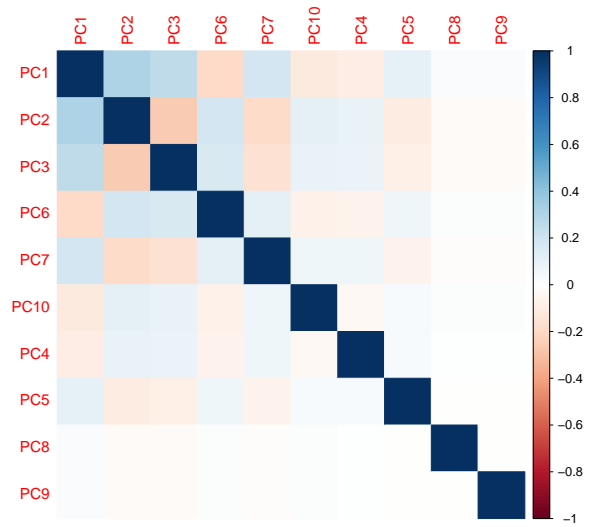


Figure 4: Correlations of PCs



## 4.4 Genes with a pre-defined pattern of associations

We next searched for genes with a pattern of gene-level associations that matched one of the clusters in Udler et al 2018. For each of the five clusters identified in the Udler et al analysis, we identified the pattern of traits associated with the cluster (i.e. traits and direction of effect for each trait association). We then identified genes that had  $p < 0.05$  and the correct direction of effect for at least  $n$  traits, where  $n$  was chosen to be the largest number that produced a list of at least ten genes.

### 4.4.1 Beta-cell cluster

The beta-cell cluster is characterized by associations with BMI, FastIns, HipC, and HOMA-B. Table 10 shows the genes that matched our beta-cell cluster filter; genes are sorted by T2D association strength, and associations with  $p < 0.05$  are colored yellow and bolded. The presence of *HNF1A* serves as a positive control.

Gene	T2D P-value	T2D Effect	BMI P-value	BMI Effect	FastIns P-value	FastIns Effect	HipC P-value	HipC Effect	HOMA-B P-value	HOMA-B Effect
DNAJB7	<b>0.00297</b>	<b>0.11</b>	0.321	-0.0046	<b>0.0132</b>	<b>-0.0528</b>	0.277	-0.297	<b>0.0118</b>	<b>-0.0541</b>
SYT3	<b>0.00917</b>	<b>0.274</b>	0.0988	-0.014	<b>0.0464</b>	<b>-0.174</b>	0.361	-1.02	<b>0.0181</b>	<b>-0.206</b>
LRRC72	<b>0.0179</b>	<b>0.862</b>	0.72	-0.014	<b>0.00225</b>	<b>-0.414</b>	0.109	-2.46	<b>0.0227</b>	<b>-0.311</b>
HNF1A	<b>0.0219</b>	<b>0.206</b>	0.217	-0.0083	<b>0.0359</b>	<b>-0.355</b>	<b>0.00193</b>	<b>-4.78</b>	<b>0.0332</b>	<b>-0.368</b>
KIAA2022	<b>0.0227</b>	<b>0.231</b>	0.644	-0.0062	<b>0.0416</b>	<b>-0.0783</b>	<b>0.00489</b>	<b>-1.28</b>	<b>0.0138</b>	<b>-0.093</b>
ARL5B	0.0632	-0.608	0.552	-0.0278	<b>0.0239</b>	<b>-0.341</b>	<b>0.0478</b>	<b>-4.37</b>	<b>0.0038</b>	<b>-0.428</b>
FAM134A	0.136	-0.197	<b>0.0277</b>	<b>-0.014</b>	<b>0.0208</b>	<b>-0.155</b>	0.299	-3.52	<b>0.0201</b>	<b>-0.143</b>
MMADHC	0.2	-0.366	<b>0.00477</b>	<b>-0.0412</b>	0.171	-0.0958	<b>0.0323</b>	<b>-1.79</b>	<b>0.0474</b>	<b>-0.123</b>
EIF2S2	0.276	0.167	0.463	-0.0161	<b>0.000882</b>	<b>-0.283</b>	<b>0.0259</b>	<b>-1.68</b>	<b>0.000221</b>	<b>-0.319</b>
RASGRF2	0.308	-0.118	<b>0.0449</b>	<b>-0.0105</b>	<b>0.0342</b>	<b>-0.0952</b>	<b>0.0187</b>	<b>-1.48</b>	0.241	-0.0672
DPCD	0.319	-0.305	<b>0.0483</b>	<b>-0.0776</b>	<b>0.00728</b>	<b>-0.343</b>	0.514	-1.39	<b>0.000788</b>	<b>-0.402</b>
HCAR1	0.445	0.192	<b>0.0281</b>	<b>-0.0147</b>	<b>0.037</b>	<b>-0.264</b>	0.429	-1.92	<b>0.026</b>	<b>-0.281</b>
WDR92	0.449	0.398	<b>0.00367</b>	<b>-0.0638</b>	0.141	-0.0953	<b>0.0435</b>	<b>-1.67</b>	<b>0.0367</b>	<b>-0.137</b>
UPK1B	0.511	0.186	<b>0.0128</b>	<b>-0.0309</b>	<b>0.0264</b>	<b>-0.201</b>	0.136	1.65	<b>0.00999</b>	<b>-0.158</b>
MRGPRF	0.695	-0.312	0.56	-0.0134	<b>0.000905</b>	<b>-0.221</b>	<b>0.0433</b>	<b>-1.9</b>	<b>0.000504</b>	<b>-0.236</b>
UQCC3	0.733	-0.156	<b>0.00252</b>	<b>-0.189</b>	<b>0.00051</b>	<b>-0.367</b>	0.105	-4.87	<b>0.0107</b>	<b>-0.288</b>
SNAPC4	0.767	-0.0254	<b>0.0425</b>	<b>-0.0048</b>	<b>0.0183</b>	<b>-0.0555</b>	<b>0.00968</b>	<b>-0.737</b>	<b>0.024</b>	<b>-0.055</b>
AC011530	0.848	0.0503	<b>0.00527</b>	<b>-0.0469</b>	<b>0.00239</b>	<b>-0.373</b>	<b>0.00219</b>	<b>-5.89</b>	<b>0.0283</b>	<b>-0.286</b>
TMEM98	0.858	-0.0506	<b>0.0298</b>	<b>-0.0189</b>	<b>0.0209</b>	<b>-0.144</b>	0.724	-0.96	<b>0.00878</b>	<b>-0.161</b>
SLC2A5	0.938	0.2	<b>0.0433</b>	<b>-0.0256</b>	<b>0.000469</b>	<b>-0.197</b>	0.928	0.457	<b>0.017</b>	<b>-0.149</b>
MTX1	0.948	-0.0958	<b>0.0474</b>	<b>-0.0387</b>	<b>0.0355</b>	<b>-0.129</b>	0.209	1.31	<b>0.037</b>	<b>-0.143</b>

Table 10: Genes with a pattern of associations characteristic of the beta-cell cluster

### 4.4.2 Lipodystrophy

The lipodystrophy cluster is characterized by associations with aiponectin, BMI, FastIns, HDL, HipC, Height, HOMA-IR, Leptin, WaistC, and WHR. Tables 11 and 12 show the genes that matched our lipodystrophy cluster filter; genes are sorted by T2D association strength, and associations with  $p < 0.05$  are colored yellow and bolded. The presence of *PPARG* serves as a positive control.

Gene	T2D	Adiponectin	BMI	FastIns	HDL	HipC	Height	HOMA-IR	Leptin	WaistC	WHR
CGRRF1	0.559	<b>0.0428</b>	0.72	<b>0.00142</b>	0.53	0.524	<b>0.0375</b>	<b>0.0016</b>	0.475	0.381	<b>0.0363</b>
FGF9	<b>0.00378</b>	0.662	0.0774	<b>0.0174</b>	0.145	0.0803	0.437	<b>0.00616</b>	0.678	<b>0.0447</b>	<b>0.0488</b>
GALE	0.795	0.172	<b>0.00166</b>	0.719	0.729	<b>0.0137</b>	0.116	0.736	0.614	<b>0.00942</b>	<b>0.0425</b>
GIPR	0.786	0.969	<b>0.000163</b>	0.722	<b>0.0125</b>	<b>0.013</b>	0.362	0.788	0.711	<b>0.0154</b>	0.366
METAP1D	<b>0.049</b>	0.569	0.816	<b>0.00481</b>	0.187	0.976	0.734	<b>0.00429</b>	<b>0.0219</b>	0.963	0.638
OR52N2	<b>0.0059</b>	<b>0.0181</b>	<b>0.0235</b>	0.108	0.608	0.235	0.737	0.21	<b>0.015</b>	<b>0.0129</b>	0.0806
PPARG	0.0755	0.98	<b>0.00125</b>	<b>0.04</b>	<b>0.000192</b>	<b>0.0106</b>	0.673	0.0912	0.371	0.0847	<b>0.00333</b>
QRFPR	<b>0.0226</b>	0.711	0.952	<b>0.0308</b>	0.804	0.878	0.109	<b>0.0429</b>	<b>0.0153</b>	0.408	0.288
TSPEAR	0.19	0.901	<b>0.0261</b>	0.0983	<b>0.0283</b>	<b>0.00146</b>	0.881	0.0975	<b>0.0164</b>	<b>0.0091</b>	0.818

Table 11: Genes with a pattern of associations characteristic of the lipodystrophy cluster (p-values)

Gene	T2D	Adiponectin	BMI	FastIns	HDL	HipC	Height	HOMA-IR	Leptin	WaistC	WHR
CGRRF1	-0.265	<b>0.137</b>	0.0036	<b>0.152</b>	-2.79	-0.613	<b>1.87</b>	<b>0.159</b>	-0.0941	2.8	<b>0.0058</b>
FGF9	<b>0.317</b>	-0.0573	0.0203	<b>0.188</b>	-13.6	1.56	0.366	<b>0.229</b>	0.0555	<b>1.79</b>	<b>0.0113</b>
GALE	0.299	0.152	<b>-0.0281</b>	-0.114	-3.19	<b>-2.41</b>	-1.7	-0.117	-0.081	<b>-2.53</b>	<b>0.0443</b>
GIPR	-0.202	-0.0546	<b>-0.018</b>	-0.0586	<b>-0.936</b>	<b>-1.47</b>	-1.34	-0.0572	0.083	<b>-1.35</b>	-0.003
METAP1D	<b>0.192</b>	0.066	-0.0063	<b>0.358</b>	1.8	-0.865	-0.812	<b>0.382</b>	<b>-0.332</b>	0.328	0.0027
OR52N2	<b>1.46</b>	<b>-0.203</b>	<b>0.108</b>	-0.0998	-1.44	2.65	0.325	-0.0888	<b>-0.292</b>	<b>-1.92</b>	-0.0085
PPARG	0.341	-0.0162	<b>-0.148</b>	<b>0.22</b>	<b>-7.81</b>	<b>-5.96</b>	-0.642	0.198	0.215	-5.01	<b>0.0174</b>
QRFPR	<b>0.0437</b>	-0.0236	0.0018	<b>0.27</b>	0.792	0.0616	0.138	<b>0.27</b>	<b>-0.186</b>	0.528	0.0026
TSPEAR	-0.118	0.0278	<b>-0.0096</b>	-0.0823	<b>3.07</b>	<b>-6.67</b>	-1.21	-0.0868	<b>-0.162</b>	<b>-5.44</b>	0.0063

Table 12: Genes with a pattern of associations characteristic of the lipodystrophy cluster (effect sizes)

#### 4.4.3 Liver/Lipid

The liver/lipid cluster is characterized by associations with FastIns, HOMA-IR, Leptin, and Chol. Table 13 shows the genes that matched our liver/lipid cluster filter; genes are sorted by T2D association strength, and associations with  $p < 0.05$  are colored yellow and bolded. The presence of *PCSK9* serves as a positive control.

Gene	T2D P-value	T2D Effect	Chol P-value	Chol Effect	FastIns P-value	FastIns Effect	HOMA-IR P-value	HOMA-IR Effect	Leptin P-value	Leptin Effect
ING3	<b>0.000112</b>	<b>0.829</b>	0.627	17.1	<b>0.0447</b>	<b>0.302</b>	<b>0.0368</b>	<b>0.326</b>	NA	NA
FGF9	<b>0.00378</b>	<b>0.317</b>	0.162	-45.7	<b>0.0174</b>	<b>0.188</b>	<b>0.00616</b>	<b>0.229</b>	0.678	0.0555
ARGLU1	<b>0.00786</b>	<b>0.612</b>	0.609	4.58	<b>0.0212</b>	<b>0.304</b>	<b>0.0264</b>	<b>0.311</b>	NA	NA
TERF2IP	<b>0.0165</b>	<b>1.34</b>	0.646	2.2	<b>0.0266</b>	<b>0.226</b>	<b>0.0344</b>	<b>0.23</b>	0.411	0.144
QRFPR	<b>0.0226</b>	<b>0.0437</b>	0.427	-3.5	<b>0.0308</b>	<b>0.27</b>	<b>0.0429</b>	<b>0.27</b>	<b>0.0153</b>	<b>-0.186</b>
ZNF812	<b>0.0258</b>	<b>0.0543</b>	0.846	-0.388	<b>0.0402</b>	<b>0.0308</b>	0.0813	0.0282	<b>0.0312</b>	<b>0.0734</b>
ATXN2L	<b>0.0262</b>	<b>0.0442</b>	<b>0.0106</b>	<b>-3.4</b>	<b>0.015</b>	<b>0.0276</b>	<b>0.019</b>	<b>0.0284</b>	0.75	0.0248
DNLZ	<b>0.0373</b>	<b>0.279</b>	0.342	2.22	<b>0.02</b>	<b>0.185</b>	<b>0.00836</b>	<b>0.215</b>	0.99	-0.028
ATXN7	<b>0.0428</b>	<b>0.0739</b>	0.602	0.852	<b>0.0108</b>	<b>0.0562</b>	<b>0.00868</b>	<b>0.0604</b>	0.957	0.0285
MS4A2	<b>0.0457</b>	<b>0.204</b>	0.771	2.47	<b>0.00753</b>	<b>0.138</b>	<b>0.00342</b>	<b>0.155</b>	0.866	-0.0558
FANCG	<b>0.0485</b>	<b>1.03</b>	0.65	-2.39	<b>0.0126</b>	<b>0.133</b>	<b>0.0115</b>	<b>0.142</b>	0.373	0.175
METAP1D	<b>0.049</b>	<b>0.192</b>	0.353	5.73	<b>0.00481</b>	<b>0.358</b>	<b>0.00429</b>	<b>0.382</b>	<b>0.0219</b>	<b>-0.332</b>
NPIP15	0.105	-0.397	<b>0.0278</b>	<b>-3.2</b>	<b>0.0153</b>	<b>0.217</b>	<b>0.0102</b>	<b>0.241</b>	0.205	0.224
PCSK9	0.426	0.319	<b>2.11e-48</b>	<b>-40.1</b>	<b>0.038</b>	<b>0.105</b>	<b>0.0166</b>	<b>0.121</b>	0.81	0.0615
RNF39	0.451	0.467	0.709	-1.92	<b>0.00516</b>	<b>0.148</b>	<b>0.00558</b>	<b>0.154</b>	<b>0.0183</b>	<b>0.173</b>
TSNARE1	0.504	-0.489	0.921	3.42	<b>0.00794</b>	<b>0.0863</b>	<b>0.00507</b>	<b>0.0953</b>	<b>0.0109</b>	<b>0.201</b>
SRMS	0.517	-0.492	<b>0.0423</b>	<b>-2.04</b>	<b>0.0349</b>	<b>0.0724</b>	<b>0.05</b>	<b>0.0726</b>	1	0.00795
CEP97	0.567	0.671	<b>0.0286</b>	<b>-4.78</b>	<b>0.00361</b>	<b>0.135</b>	<b>0.00696</b>	<b>0.133</b>	0.996	-0.0373
IL17C	0.664	-0.363	0.566	3.89	<b>0.0063</b>	<b>0.152</b>	<b>0.00651</b>	<b>0.16</b>	<b>0.0162</b>	<b>0.29</b>
EBF1	0.768	-0.199	<b>0.0478</b>	<b>-63.7</b>	<b>0.0126</b>	<b>0.287</b>	<b>0.0125</b>	<b>0.302</b>	NA	NA
DDX19A	0.851	-0.102	<b>0.00369</b>	<b>-59.3</b>	<b>0.00636</b>	<b>0.207</b>	<b>0.00791</b>	<b>0.213</b>	NA	NA
GPN3	0.944	-0.108	0.457	-10.4	<b>0.0397</b>	<b>0.168</b>	<b>0.0462</b>	<b>0.174</b>	<b>0.0247</b>	<b>0.392</b>
VIT	0.998	-0.0639	<b>0.0484</b>	<b>-1.91</b>	<b>0.0307</b>	<b>0.154</b>	<b>0.0318</b>	<b>0.161</b>	0.999	0.0772

Table 13: Genes with a pattern of associations characteristic of the liver/lipid cluster

#### 4.4.4 Obesity

The obesity cluster is characterized by associations with BMI, FastIns, Height, HipC, HOMA-B, HOMA-IR, Leptin, WaistC, and WHR. Tables 14 and 15 show the genes that matched our obesity cluster filter; genes are sorted by T2D association strength, and associations with  $p < 0.05$  are colored yellow and bolded.

Gene	T2D	BMI	FastIns	HipC	Height	HOMA-B	HOMA-IR	Leptin	Height	HOMA-B	HOMA-IR	Leptin
ATXN2L	<b>0.0262</b>	0.381	<b>0.015</b>	0.0698	0.694	<b>0.0269</b>	<b>0.019</b>	0.75	0.694	<b>0.0269</b>	<b>0.019</b>	0.75
ATXN7	<b>0.0428</b>	<b>0.00306</b>	<b>0.0108</b>	0.768	0.826	<b>0.0316</b>	<b>0.00868</b>	0.957	0.826	<b>0.0316</b>	<b>0.00868</b>	0.957
ELAC2	0.229	0.303	<b>0.00173</b>	<b>0.0203</b>	0.369	<b>0.00488</b>	<b>0.00496</b>	0.973	0.369	<b>0.00488</b>	<b>0.00496</b>	0.973
FAM69A	<b>0.00103</b>	<b>0.019</b>	<b>0.0186</b>	<b>0.0225</b>	0.553	<b>0.0249</b>	<b>0.0212</b>	NA	0.553	<b>0.0249</b>	<b>0.0212</b>	NA
FGF9	<b>0.00378</b>	0.0774	<b>0.0174</b>	0.0803	0.437	0.477	<b>0.00616</b>	0.678	0.437	0.477	<b>0.00616</b>	0.678
GALNT6	0.359	0.168	<b>9.23e-05</b>	0.384	0.836	<b>0.00564</b>	<b>3.14e-05</b>	0.334	0.836	<b>0.00564</b>	<b>3.14e-05</b>	0.334
GDPD1	0.85	0.277	<b>0.00789</b>	<b>0.000209</b>	0.974	<b>0.044</b>	<b>0.0111</b>	NA	0.974	<b>0.044</b>	<b>0.0111</b>	NA
GNB1	0.231	<b>0.00826</b>	<b>0.031</b>	<b>0.00557</b>	0.296	0.0854	<b>0.021</b>	NA	0.296	0.0854	<b>0.021</b>	NA
KHDRBS2	0.533	0.134	<b>0.00769</b>	<b>0.00635</b>	0.849	<b>0.00704</b>	<b>0.0138</b>	0.0643	0.849	<b>0.00704</b>	<b>0.0138</b>	0.0643
KIAA0196	0.206	<b>0.0098</b>	<b>0.00945</b>	0.409	0.438	<b>0.039</b>	<b>0.0183</b>	0.237	0.438	<b>0.039</b>	<b>0.0183</b>	0.237
MED9	0.585	<b>0.037</b>	<b>0.0053</b>	<b>0.000584</b>	0.051	0.176	<b>0.00213</b>	NA	0.051	0.176	<b>0.00213</b>	NA
OR10P1	0.21	<b>0.00938</b>	<b>0.0147</b>	0.879	0.664	<b>0.0117</b>	<b>0.0255</b>	0.112	0.664	<b>0.0117</b>	<b>0.0255</b>	0.112
RPP30	<b>0.0483</b>	<b>0.0369</b>	0.288	<b>0.0442</b>	0.998	0.271	<b>0.0103</b>	NA	0.998	0.271	<b>0.0103</b>	NA
RSRC2	0.989	<b>0.0166</b>	<b>0.0196</b>	<b>0.00248</b>	0.831	<b>0.00499</b>	<b>0.0486</b>	NA	0.831	<b>0.00499</b>	<b>0.0486</b>	NA
TFCP2	0.828	0.315	<b>0.0108</b>	<b>0.0232</b>	0.357	<b>0.0182</b>	<b>0.0156</b>	NA	0.357	<b>0.0182</b>	<b>0.0156</b>	NA
TMEM154	0.798	0.261	<b>0.0119</b>	0.425	<b>0.0446</b>	<b>0.0136</b>	<b>0.015</b>	0.796	<b>0.0446</b>	<b>0.0136</b>	<b>0.015</b>	0.796
YBX2	0.373	0.799	<b>0.0175</b>	<b>0.00879</b>	0.546	<b>0.000755</b>	<b>0.0441</b>	NA	0.546	<b>0.000755</b>	<b>0.0441</b>	NA

Table 14: Genes with a pattern of associations characteristic of the obesity cluster (p-values)

Gene	T2D	BMI	FastIns	HipC	Height	HOMA-B	HOMA-IR	Leptin	Height	HOMA-B	HOMA-IR	Leptin
ATXN2L	<b>0.0442</b>	0.0259	<b>0.0276</b>	0.28	0.0826	<b>0.0263</b>	<b>0.0284</b>	0.0248	0.0826	<b>0.0263</b>	<b>0.0284</b>	0.0248
ATXN7	<b>0.0739</b>	<b>0.0098</b>	<b>0.0562</b>	0.174	0.0936	<b>0.0496</b>	<b>0.0604</b>	0.0285	0.0936	<b>0.0496</b>	<b>0.0604</b>	0.0285
ELAC2	-0.273	0.0128	<b>0.132</b>	<b>3.82</b>	-0.554	<b>0.125</b>	<b>0.129</b>	-0.115	-0.554	<b>0.125</b>	<b>0.129</b>	-0.115
FAM69A	<b>-0.671</b>	<b>0.0354</b>	<b>0.276</b>	<b>4.24</b>	2.74	<b>0.276</b>	<b>0.286</b>	NA	2.74	<b>0.276</b>	<b>0.286</b>	NA
FGF9	<b>0.317</b>	0.0203	<b>0.188</b>	1.56	0.366	0.0562	<b>0.229</b>	0.0555	0.366	0.0562	<b>0.229</b>	0.0555
GALNT6	0.363	0.0107	<b>0.203</b>	1.55	-0.257	<b>0.155</b>	<b>0.226</b>	0.163	-0.257	<b>0.155</b>	<b>0.226</b>	0.163
GDPD1	-0.432	0.0182	<b>0.244</b>	<b>4.66</b>	0.818	<b>0.204</b>	<b>0.247</b>	NA	0.818	<b>0.204</b>	<b>0.247</b>	NA
GNB1	0.666	<b>0.0715</b>	<b>0.303</b>	<b>8.09</b>	-1.5	0.248	<b>0.341</b>	NA	-1.5	0.248	<b>0.341</b>	NA
KHDRBS2	0.209	0.0126	<b>0.173</b>	<b>2.52</b>	0.323	<b>0.178</b>	<b>0.172</b>	-0.291	0.323	<b>0.178</b>	<b>0.172</b>	-0.291
KIAA0196	0.247	<b>0.0124</b>	<b>0.196</b>	0.671	0.392	<b>0.167</b>	<b>0.193</b>	0.141	0.392	<b>0.167</b>	<b>0.193</b>	0.141
MED9	0.235	<b>0.0745</b>	<b>0.394</b>	<b>5.8</b>	3.07	0.191	<b>0.457</b>	NA	3.07	0.191	<b>0.457</b>	NA
OR10P1	0.106	<b>0.0206</b>	<b>0.137</b>	-0.341	-0.234	<b>0.143</b>	<b>0.102</b>	0.138	-0.234	<b>0.143</b>	<b>0.102</b>	0.138
RPP30	<b>0.378</b>	<b>0.0242</b>	0.119	<b>2.47</b>	-0.474	0.129	<b>0.52</b>	NA	-0.474	0.129	<b>0.52</b>	NA
RSRC2	0.0768	<b>0.0267</b>	<b>0.238</b>	<b>3.12</b>	-2.23	<b>0.284</b>	<b>0.22</b>	NA	-2.23	<b>0.284</b>	<b>0.22</b>	NA
TFCP2	-0.161	0.0241	<b>0.264</b>	<b>2.87</b>	1.13	<b>0.246</b>	<b>0.265</b>	NA	1.13	<b>0.246</b>	<b>0.265</b>	NA
TMEM154	-0.109	0.0532	<b>0.209</b>	3.31	<b>-1.25</b>	<b>0.213</b>	<b>0.216</b>	-0.0871	<b>-1.25</b>	<b>0.213</b>	<b>0.216</b>	-0.0871
YBX2	0.54	0.0053	<b>0.208</b>	<b>3.07</b>	0.769	<b>0.297</b>	<b>0.191</b>	NA	0.769	<b>0.297</b>	<b>0.191</b>	NA

Table 15: Genes with a pattern of associations characteristic of the obesity cluster (effect sizes)

#### 4.4.5 Proinsulin

The proinsulin cluster is characterized by associations with BMI, Height, HOMA-B, HipC, and WaistC. Table 16 shows the genes that matched our proinsulin cluster filter; genes are sorted by T2D association strength, and associations with  $p < 0.05$  are colored yellow and bolded.

Gene	T2D P-value	T2D Effect	BMI P-value	BMI Effect	HipC P-value	HipC Effect	Height P-value	Height Effect	HOMA-B P-value	HOMA-B Effect	WaistC P-value	WaistC Effect
HNF1A	<b>0.0219</b>	<b>0.206</b>	0.217	-0.0083	<b>0.00193</b>	<b>-4.78</b>	0.649	-0.858	<b>0.0332</b>	<b>-0.368</b>	<b>0.00792</b>	<b>-4.37</b>
KIAA2022	<b>0.0227</b>	<b>0.231</b>	0.644	-0.0062	<b>0.00489</b>	<b>-1.28</b>	<b>0.0333</b>	<b>-0.907</b>	<b>0.0138</b>	<b>-0.093</b>	<b>0.0025</b>	<b>-1.44</b>
MMADHC	0.2	-0.366	<b>0.00477</b>	<b>-0.0412</b>	<b>0.0323</b>	<b>-1.79</b>	0.75	-0.344	<b>0.0474</b>	<b>-0.123</b>	<b>0.00866</b>	<b>-2.05</b>
SNAPC4	0.767	-0.0254	<b>0.0425</b>	<b>-0.0048</b>	<b>0.00968</b>	<b>-0.737</b>	<b>0.00209</b>	<b>-0.485</b>	<b>0.024</b>	<b>-0.055</b>	<b>0.0235</b>	<b>-0.701</b>
AC011530	0.848	0.0503	<b>0.00527</b>	<b>-0.0469</b>	<b>0.00219</b>	<b>-5.89</b>	0.916	-0.132	<b>0.0283</b>	<b>-0.286</b>	<b>0.0302</b>	<b>-3.59</b>

Table 16: Genes with a pattern of associations characteristic of the proinsulin cluster

## 5 Grey Zone genes

We repeated the above analyses with a focus on the “grey zone”, genes of interest to AMP-T2D partners grouped into three “tiers” of descending priority order.

### 5.1 Significant grey-zone associations

Table 17 shows the genes in the grey zone with exome-wide significant associations. Table 18 show the genes in the grey zone with the 30 strongest associations with non-lipid traits.

Table 19 shows the genes in tier 1 of the grey zone with the strongest gene-level associations. Table 20 shows the strongest gene-level LoF associations across all tiers of the grey zone; associations with a protective direction of effect have their effect sizes highlighted in **bold**.

Phenotype	Gene	P	Effect
HDL	LIPC	1.01e-26	3.59
HbA1c	GCK	7.84e-26	0.231
TG	ANGPTL4	1.01e-22	-0.116
HDL	ANGPTL4	1.51e-22	3.05
HDL	CD36	5.93e-22	2.25
HDL	HNF4A	2.21e-12	-2.34
TG	ANGPTL3	2.96e-12	-0.349
Adiponectin	ADIPOQ	3.34e-12	-0.512
FastGlu	G6PC2	1.03e-10	-0.164
T2D	MC4R	2.74e-10	0.726
TG:HDL	CD36	3.18e-10	-0.0807
Chol	ANGPTL3	3.91e-10	-19.2
HDL	PLA2G12A	2.03e-09	-2.79
Chol	TM6SF2	3.28e-09	-8.06
TG	TM6SF2	3.81e-09	-0.0863
BMI	MC4R	1.84e-08	0.0502
LDL	SLC22A1	6.17e-08	1.96
LDL	TM6SF2	1.72e-07	-6.48
T2D	SLC30A8	1.85e-07	-0.514
HDL	ANGPTL8	1.44e-06	14.1
HDL	PLIN1	2.41e-06	7.65

Table 17: Genes in the grey zone achieving exome-wide significance.

Phenotype	Gene	P	Effect
HbA1c	GCK	7.84e-26	0.231
Adiponectin	ADIPOQ	3.34e-12	-0.512
FastGlu	G6PC2	1.03e-10	-0.164
T2D	MC4R	2.74e-10	0.726
BMI	MC4R	1.84e-08	0.0502
T2D	SLC30A8	1.85e-07	-0.514
RBC	KLK7	2.77e-06	1.15
HbA1c	PFKL	4.6e-06	0.0128
RBC	RAB2A	3.75e-05	-1.03
Height	FDFT1	4.36e-05	2.31
FastGlu	UCN3	6.04e-05	-0.201
2hrGlu	HTR6	7.36e-05	1.15
WaistC	GDA	8.24e-05	1.91
FastCpep	MAPK8IP1	0.000108	-0.43
BMI	GIPR	0.000163	-0.018
HipC	GDA	0.000166	2.06
HOMA-B	ADAMTS9	0.00019	0.181
WaistC	MC4R	0.000203	2.19
WHR	SLC5A10	0.000227	0.019
WaistC	LAMA1	0.000324	-1.58
Height	ALDH2	0.000325	-1.4
FastIns	ADAMTS9	0.000417	0.163
WHR	RASGRP1	0.000419	0.0411

Table 18: The genes in the grey zone with the 30 strongest associations with non-lipid traits.



Phenotype	Gene	P	Effect
HDL	CD36	5.93e-22	2.25
TG:HDL	CD36	3.18e-10	-0.0807
TG	CD36	0.000516	-0.0349
SBP	SPTLC1	0.00121	0.0404
HbA1c	FFAR4	0.00342	0.0327
BMI	CRY2	0.00455	0.162
Height	PPP1R3B	0.00505	-3.74
SBP	NPR1	0.00578	0.0293
RBC	CD36	0.00614	0.081
Adiponectin	CRHR2	0.00738	0.157
HDL	DYRK1B	0.00748	19.7
FastCpep	CD36	0.00782	-0.269
RBC	IGF2BP2	0.00888	0.502
BMI	DEGS1	0.0089	0.0247
RBC	MGLL	0.0101	0.509
TG	CRY2	0.0111	0.198
T2D	GPRC6A	0.0113	0.0686
HDL	CYP27A1	0.0128	0.895
RBC	CYP8B1	0.0128	-0.0533
DBP	CD36	0.0139	0.633
T2D	SPTLC1	0.0164	0.915
HipC	CERS6	0.0174	2.49
Leptin	LGR5	0.0175	-0.217
RBC	CERS2	0.0207	-0.0149
FastCpep	SPTLC2	0.0209	-0.219
RBC	MTNR1B	0.021	0.0564
TG	ASGR2	0.0212	0.176
Chol	DEGS1	0.0222	-6.51
Chol	FFAR4	0.0222	-5.77
T2D	IGF2	0.0235	-0.415
HOMA-B	SPTLC1	0.0235	0.422
DBP	SPTLC1	0.0252	2.26
FastGlu	GPRC6A	0.0256	0.0328
FastGlu	CERS6	0.0278	0.159
HbA1c	GLRB	0.0286	-0.0857
DBP	NPR3	0.0286	-2.71
HOMA-IR	CD36	0.0291	-0.063
2hrIns	ACSL1	0.0293	-0.385
BMI	FFAR2	0.0295	-0.0402
FastIns	CD36	0.03	-0.0594
FastCpep	CRHR2	0.0305	-0.205
SBP	ACSL1	0.0326	0.0332
Height	CYP8B1	0.0349	-4.81
HOMA-B	LGR5	0.0358	0.0737
HOMA-IR	GPRC6A	0.0375	0.0382
HDL	NPR3	0.039	-1.21
FastIns	LGR5	0.0407	0.0516
RBC	IGF2	0.0408	0.08
HOMA-B	CD36	0.0416	-0.0483
DBP	P2RY2	0.0416	2.74
LDL	LYPLAL1	0.0427	-22.4
RBC	PPP1R3B	0.0429	0.0233
BMI	FFAR1	0.0448	-0.061
Height	TRPM8	0.045	-0.523
Chol	FFAR2	0.0453	-11.3
HDL	NPR1	0.0456	0.82
WaistC	MGLL	0.0466	1.44
Adiponectin	TRPM8	0.0477	-0.0943
HOMA-IR	LGR5	0.0486	0.0529
LDL	FFAR4	0.0489	-4.86
TG:HDL	CRY2	0.0494	0.272

Table 19: Genes in tier 1 of the grey zone achieving  $p < 0.05$  for at least one trait

Phenotype	Gene	P	Effect
HDL	CD36	3.214e-17	<b>2.4459</b>
TG	ANGPTL3	4.712e-12	<b>-0.3665</b>
Chol	ANGPTL3	6.258e-09	<b>-26.7450</b>
HbA1c	GCK	8.201e-09	0.4870
HDL	ANGPTL8	5.299e-07	<b>14.0850</b>
HDL	PLIN1	6.559e-07	<b>7.6422</b>
Adiponectin	ADIPOQ	8.809e-07	<b>-1.6768</b>
HDL	LIPC	1.483e-06	<b>7.2184</b>
TG	ANGPTL4	1.926e-06	<b>-0.3100</b>
TG:HDL	CD36	2.6992e-06	<b>-0.072059</b>
LDL	AVPR2	0.0001039	<b>-121.0448</b>
WHR	SLC5A10	0.0001592	0.0188
Height	CYP4F2	0.00015932	<b>-2.6994</b>
HipC	P2RY2	0.00016463	<b>-42.027</b>
FastIns	HCRTR2	0.00024893	1.5231
HipC	PPARG	0.0003116	<b>-29.22</b>
TG	SDHB	0.0003138	<b>-0.7947</b>
2hrCpep	ACP2	0.00031466	<b>-6.0663</b>
WaistC	HEXB	0.00031622	9.4316
2hrCpep	CYP3A4	0.0003283	12.951
RBC	CCR10	0.00034257	0.69811
HbA1c	EPT1	0.000375	<b>-0.2454</b>
DBP	COX5A	0.0003794	45.7405
TG	SLC19A2	0.0003816	0.5933
LDL	ANGPTL3	0.0003817	<b>-14.9661</b>
HbA1c	IL17RA	0.0003824	0.1005
HOMA-B	HCRTR2	0.00041164	1.4767
DBP	CNKSR3	0.0004174	10.7236
BMI	ARL15	0.0004272	0.2025
HOMA-IR	HCRTR2	0.00043167	1.562
BMI	UGT2B15	0.0004698	<b>-0.0893</b>
HipC	UPP1	0.00047245	<b>-7.5821</b>
Adiponectin	CHL1	0.00048455	2.2476
FastIns	XDH	0.00050991	<b>-0.40421</b>
FastCpep	PCK2	0.00056094	0.50192
Adiponectin	ACSL1	0.0005619	1.6992
RBC	NMUR2	0.00057365	<b>-0.21239</b>
Adiponectin	SPTLC3	0.00058331	<b>-1.6915</b>
HDL	ANGPTL3	0.0006595	-4.5146
WaistC	HCRTR2	0.00070336	23.314
HbA1c	SLC19A2	0.0007084	0.0961
HipC	UGT2B15	0.0007248	<b>-7.224</b>
TG	RFK	0.0008132	0.9395
BMI	ZDHHC17	0.0008912	0.2140
FastGlu	IL17A	0.00090389	1.9263

Table 20: Genes in the grey zone with LofTee signals  $p < 1 \times 10^{-3}$ .

## 5.2 Grey zone genes associated with independent traits

Table 21 shows the genes in the grey zone associated with the most number of PCs (as defined in section 4.3). Table 22 shows the tier 1 grey zone genes associated with the most number of PCs.

Because of the small number of genes in tier 1, we relaxed our definition of PC association for this table; rather than defining a PC association as  $p < 0.05$  for at least one QT highly loaded on the PC, we defined a PC association as  $p < 0.1$  for at least one QT highly loaded on the PC.

Phenotype	SH2B1	ARG1	HNF1A	PPARG	GPR39	PGM2	G6PC2	GRM3	NPFFR2	PKLR	CD36
PCs	5	4	4	4	4	4	4	4	4	4	4
BMI	0.349	0.875	0.217	<b>0.00125</b>	0.959	0.529	0.651	0.733	<b>0.013</b>	0.0637	0.869
Chol	<b>0.0118</b>	0.573	0.525	<b>0.0409</b>	<b>0.0274</b>	0.13	0.877	<b>0.0025</b>	0.181	<b>0.0399</b>	0.167
DBP	0.117	0.505	0.274	0.804	0.176	0.586	0.491	<b>0.0303</b>	0.299	0.504	<b>0.0139</b>
HDL	0.589	0.27	0.35	<b>0.000192</b>	<b>0.0286</b>	0.617	0.934	<b>0.0046</b>	0.793	0.156	<b>5.93e-22</b>
HbA1c	0.0558	<b>0.035</b>	<b>0.0231</b>	0.258	0.55	<b>0.0324</b>	<b>0.000438</b>	0.885	0.782	<b>0.0264</b>	0.184
LDL	<b>0.00816</b>	0.156	0.396	0.396	<b>0.00508</b>	0.427	0.275	0.0565	<b>0.0243</b>	0.544	0.718
SBP	<b>0.0213</b>	0.99	0.331	0.506	<b>0.0414</b>	0.887	0.74	<b>0.0365</b>	0.607	0.913	0.195
TG	<b>0.0229</b>	0.52	0.643	<b>0.0265</b>	0.961	<b>0.0328</b>	0.715	0.698	0.558	<b>0.00306</b>	<b>0.000516</b>
WHR	<b>0.00593</b>	0.659	0.577	<b>0.00333</b>	0.673	0.707	<b>0.0467</b>	0.875	0.512	<b>0.0445</b>	0.116
RBC	0.359	<b>0.000938</b>	<b>0.0248</b>	0.135	0.303	<b>0.00731</b>		0.735	<b>0.0478</b>		<b>0.00614</b>
Adiponectin	0.871	0.557	0.538	0.98	0.516	0.26	0.431	0.135	0.486	0.645	0.435
2hrCpep					0.323		0.959				0.579
FastCpep	0.065		<b>0.0323</b>		0.809	0.946	0.933		0.857	0.824	<b>0.00782</b>
FastGlu	0.415	<b>0.0485</b>	0.199	0.141	0.0564	0.859	<b>1.03e-10</b>	0.56	<b>0.00372</b>	0.834	0.459
FastIns	<b>0.045</b>	<b>0.0019</b>	<b>0.0359</b>	<b>0.04</b>	<b>0.0382</b>	0.184	0.805	0.357	<b>0.0476</b>	0.519	<b>0.03</b>
2hrGlu	0.963	0.527	0.0936		0.0997	0.213	0.372	<b>0.0499</b>	0.99	0.879	0.96
Height	0.744	0.544	0.649	0.673	0.28	0.957	0.881	0.978	0.692	0.248	0.864
HipC	0.461	0.572	<b>0.00193</b>	<b>0.0106</b>	0.876	0.625	0.803	0.861	0.906	0.638	0.941
HOMA-B	<b>0.00105</b>	<b>0.0304</b>	<b>0.0332</b>	<b>0.00134</b>	0.254	<b>0.0496</b>	<b>0.0423</b>	0.201	0.0957	0.273	<b>0.0416</b>
HOMA-IR	0.204	<b>0.00176</b>	0.0795	0.0912	<b>0.0229</b>	0.336	0.0834	0.498	0.0512	0.539	<b>0.0291</b>
2hrIns	0.738		0.645		0.753	0.222	0.0815	0.484	0.995	0.385	0.733
Leptin	0.295	0.6	0.371	0.371	0.358	0.567	0.32	0.856	0.6	0.214	0.999
TG:HDL	0.342	0.789	0.81	<b>0.0465</b>	0.468	0.612	0.888	0.891	0.837	0.336	<b>3.18e-10</b>
WaistC	0.226	0.904	<b>0.00792</b>	0.0847	0.841	0.518	0.208	0.341	0.583	0.0525	0.334
T2D	0.619	<b>0.019</b>	<b>0.0219</b>	0.0755	0.142	0.142	0.731	0.792	0.919	0.951	0.981

Table 21: Grey zone genes with the most number of associated PCs

Phenotype	CRY2	IGF2	CYP8B1	NPR3	PPP1R3B	CD36
PCs	5	4	4	4	4	4
BMI	<b>0.00455</b>	0.703	0.946	0.152	0.299	0.869
Chol	<b>0.0919</b>	0.139	0.967	0.31	0.309	0.167
DBP	<b>0.0891</b>	0.286	0.77	<b>0.0286</b>	0.702	<b>0.0139</b>
HDL	0.47	0.504	0.941	<b>0.039</b>	0.312	<b>5.93e-22</b>
HbA1c	<b>0.0826</b>	0.577	<b>0.0577</b>	0.757	0.381	0.184
LDL	0.163	<b>0.0613</b>	0.953	0.14	0.497	0.718
SBP	0.264	0.493	0.976	0.143	0.903	0.195
TG	<b>0.0111</b>	0.988	0.675	0.169	<b>0.0518</b>	<b>0.000516</b>
WHR	0.939	0.283	0.329	0.914	0.63	0.116
RBC	0.833	<b>0.0408</b>	<b>0.0128</b>	0.723	<b>0.0429</b>	<b>0.00614</b>
Adiponectin	0.548	<b>0.0542</b>	0.436	0.56	0.485	0.435
2hrCpep	0.795					0.579
FastCpep	0.585		0.27	0.313		<b>0.00782</b>
FastGlu	0.842	0.202	0.485	0.966	<b>0.0738</b>	0.459
FastIns	0.485	0.964	0.644	0.945	0.596	<b>0.03</b>
2hrGlu	0.46		0.82	0.667	0.969	0.96
Height	0.355	0.954	<b>0.0349</b>	<b>0.0715</b>	<b>0.00505</b>	0.864
HipC	0.133	0.448	0.756	0.97	0.466	0.941
HOMA-B	0.292	0.948	0.495	0.541	0.857	<b>0.0416</b>
HOMA-IR	0.567	0.887	0.748	0.943	0.545	<b>0.0291</b>
2hrIns	0.46		0.895	0.408	0.896	0.733
Leptin	0.718		<b>0.0586</b>	<b>0.0596</b>		0.999
TG:HDL	<b>0.0494</b>	<b>0.08</b>	0.132	0.499	0.722	<b>3.18e-10</b>
WaistC	0.207	0.907	0.435	<b>0.0947</b>	0.815	0.334
T2D	<b>0.0585</b>	<b>0.0235</b>	<b>0.0662</b>	0.366	0.51	0.981

Table 22: Tier 1 grey zone genes with the most number of associated PCs

### 5.3 Grey zone genes with a pre-defined pattern of associations

Tables 23-29 show genes in the grey zone that matched our six cluster filters, defined in section 4.4.

Gene	T2D P-value	T2D Effect	BMI P-value	BMI Effect	FastIns P-value	FastIns Effect	HipC P-value	HipC Effect	HOMA-B P-value	HOMA-B Effect
HNF1A	<b>0.0219</b>	<b>0.206</b>	0.217	-0.0083	<b>0.0359</b>	<b>-0.355</b>	<b>0.00193</b>	<b>-4.78</b>	<b>0.0332</b>	<b>-0.368</b>
ACKR3	<b>0.0345</b>	<b>0.388</b>	0.0963	-0.369	<b>0.00754</b>	<b>-0.287</b>	0.82	-0.403	0.0729	-0.22
PPARG	0.0755	0.341	<b>0.00125</b>	<b>-0.148</b>	<b>0.04</b>	<b>0.22</b>	<b>0.0106</b>	<b>-5.96</b>	<b>0.00134</b>	<b>0.327</b>
RFK	0.321	-0.514	0.0667	-0.0232	<b>0.0226</b>	<b>-0.178</b>	0.397	-1.2	0.0694	-0.15
HCAR1	0.445	0.192	<b>0.0281</b>	<b>-0.0147</b>	<b>0.037</b>	<b>-0.264</b>	0.429	-1.92	<b>0.026</b>	<b>-0.281</b>
NPFFR2	0.919	-0.174	<b>0.013</b>	<b>-0.0125</b>	<b>0.0476</b>	<b>-0.282</b>	0.906	-0.452	0.0957	-0.186
SLC2A5	0.938	0.2	<b>0.0433</b>	<b>-0.0256</b>	<b>0.000469</b>	<b>-0.197</b>	0.928	0.457	<b>0.017</b>	<b>-0.149</b>

Table 23: Grey zone genes with a pattern of associations characteristic of the beta-cell cluster

Gene	T2D	Adiponectin	BMI	FastIns	HDL	HipC	Height	HOMA-IR	Leptin	WaistC	WHR
GALE	0.795	0.172	<b>0.00166</b>	0.719	0.729	<b>0.0137</b>	0.116	0.736	0.614	<b>0.00942</b>	<b>0.0425</b>
GIPR	0.786	0.969	<b>0.000163</b>	0.722	<b>0.0125</b>	<b>0.013</b>	0.362	0.788	0.711	<b>0.0154</b>	0.366
HNF1A	<b>0.0219</b>	0.538	0.217	<b>0.0359</b>	0.35	<b>0.00193</b>	0.649	0.0795	0.371	<b>0.00792</b>	0.577
LAMA1	0.72	0.465	<b>0.024</b>	0.326	0.446	<b>0.0166</b>	0.69	0.387	0.915	<b>0.000324</b>	0.177
LGR5	0.263	0.174	0.647	<b>0.0407</b>	0.727	0.224	0.945	<b>0.0486</b>	<b>0.0175</b>	0.172	0.462
PLEKHH2	<b>0.031</b>	<b>0.0421</b>	0.144	0.777	0.351	<b>0.0394</b>	0.576	0.858	0.369	0.87	0.371
PPARG	0.0755	0.98	<b>0.00125</b>	<b>0.04</b>	<b>0.000192</b>	<b>0.0106</b>	0.673	0.0912	0.371	0.0847	<b>0.00333</b>
UGT2B15	0.159	0.708	<b>0.00127</b>	0.448	0.13	<b>0.00162</b>	0.986	0.25	0.898	<b>0.00877</b>	0.358

Table 24: Grey zone genes with a pattern of associations characteristic of the lipodystrophy cluster (p-values)

Gene	T2D	Adiponectin	BMI	FastIns	HDL	HipC	Height	HOMA-IR	Leptin	WaistC	WHR
GALE	0.299	0.152	<b>-0.0281</b>	-0.114	-3.19	<b>-2.41</b>	-1.7	-0.117	-0.081	<b>-2.53</b>	<b>0.0443</b>
GIPR	-0.202	-0.0546	<b>-0.018</b>	-0.0586	<b>-0.936</b>	<b>-1.47</b>	-1.34	-0.0572	0.083	<b>-1.35</b>	-0.003
HNF1A	<b>0.206</b>	-0.0631	-0.0083	<b>-0.355</b>	0.755	<b>-4.78</b>	-0.858	-0.335	0.124	<b>-4.37</b>	-0.0023
LAMA1	-0.0702	-0.0359	<b>-0.0043</b>	-0.0255	1.54	<b>-1.27</b>	-0.295	-0.0254	-0.0486	<b>-1.58</b>	-0.013
LGR5	-0.966	-0.0494	0.0036	<b>0.0516</b>	-0.372	-3.86	1.62	<b>0.0529</b>	<b>-0.217</b>	0.575	0.021
PLEKHH2	<b>0.194</b>	<b>-0.0882</b>	-0.0265	0.0247	-0.303	<b>-0.829</b>	-0.229	-0.107	-0.193	1.46	-0.0103
PPARG	0.341	-0.0162	<b>-0.148</b>	<b>0.22</b>	<b>-7.81</b>	<b>-5.96</b>	-0.642	0.198	0.215	-5.01	<b>0.0174</b>
UGT2B15	-0.595	0.0348	<b>-0.0891</b>	-0.0387	4.05	<b>-7.15</b>	0.491	-0.0524	-0.0395	<b>-6.56</b>	-0.0035

Table 25: Grey zone genes with a pattern of associations characteristic of the lipodystrophy cluster (effect sizes)

Gene	T2D P-value	T2D Effect	Chol P-value	Chol Effect	FastIns P-value	FastIns Effect	HOMA-IR P-value	HOMA-IR Effect	Leptin P-value	Leptin Effect
GPRC6A	<b>0.0113</b>	<b>0.0686</b>	0.205	-0.905	0.0961	0.0311	<b>0.0375</b>	<b>0.0382</b>	0.222	0.0546
ACOX2	<b>0.0295</b>	<b>0.442</b>	0.929	-1.58	0.0595	0.145	<b>0.0415</b>	<b>0.161</b>	0.789	0.0841
MGLL	0.0541	0.203	0.196	13.1	0.0662	0.0976	0.0654	0.103	0.897	0.043
PPARG	0.0755	0.341	<b>0.0409</b>	<b>-53.9</b>	<b>0.04</b>	<b>0.22</b>	0.0912	0.198	0.371	0.215
CHRM1	0.0786	0.482	<b>0.0387</b>	<b>12.1</b>	<b>0.0084</b>	<b>0.305</b>	<b>0.00784</b>	<b>0.327</b>	NA	NA
IMPA1	0.0795	0.206	0.692	-1.33	<b>0.0496</b>	<b>0.267</b>	0.0652	0.267	0.478	-0.159
LIPE	0.0882	0.0726	0.418	1.39	0.0673	0.0545	0.0913	0.0548	0.193	0.127
CDKAL1	0.386	0.108	0.425	23.9	0.0933	0.0942	0.0961	0.0986	0.0663	0.325
CYP4F11	0.893	0.13	0.208	7.15	<b>0.0229</b>	<b>0.0832</b>	0.0522	0.078	<b>0.0416</b>	<b>0.254</b>

Table 26: Grey zone genes with a pattern of associations characteristic of the liver/lipid cluster

Gene	T2D	BMI	FastIns	HipC	Height	HOMA-B	HOMA-IR	Leptin	Height	HOMA-B	HOMA-IR	Leptin
ACOX2	<b>0.0295</b>	0.374	0.0595	<b>0.0364</b>	0.332	0.0895	<b>0.0415</b>	0.789	0.332	0.0895	<b>0.0415</b>	0.789
ADAMTS9	0.78	0.834	<b>0.000417</b>	0.24	0.541	<b>0.00019</b>	<b>0.000983</b>	0.852	0.541	<b>0.00019</b>	<b>0.000983</b>	0.852
AK2	<b>0.0127</b>	<b>0.0279</b>	0.964	<b>0.0318</b>	0.525	0.92	0.992	0.647	0.525	0.92	0.992	0.647
CCR3	0.802	0.798	<b>0.0408</b>	0.8	0.616	<b>0.0419</b>	<b>0.0314</b>	0.794	0.616	<b>0.0419</b>	<b>0.0314</b>	0.794
CDC123	0.884	<b>0.0166</b>	<b>0.00716</b>	0.903	0.244	0.172	<b>0.00665</b>	NA	0.244	0.172	<b>0.00665</b>	NA
COX17	0.382	<b>0.0324</b>	NA	<b>0.0156</b>	0.561	NA	NA	NA	0.561	NA	NA	NA
CYP4F11	0.893	0.371	<b>0.0229</b>	0.835	0.92	<b>0.00757</b>	0.0522	<b>0.0416</b>	0.92	<b>0.00757</b>	0.0522	<b>0.0416</b>
GART	0.88	0.939	<b>0.0293</b>	0.991	0.999	<b>0.00897</b>	<b>0.0415</b>	0.798	0.999	<b>0.00897</b>	<b>0.0415</b>	0.798
HADH	0.81	<b>0.00387</b>	<b>0.00994</b>	0.633	0.371	0.0508	<b>0.00976</b>	0.801	0.371	0.0508	<b>0.00976</b>	0.801
HAS2	0.645	0.547	<b>0.00893</b>	0.704	0.625	<b>0.013</b>	<b>0.016</b>	NA	0.625	<b>0.013</b>	<b>0.016</b>	NA
HSD11B1	0.713	0.744	<b>0.0485</b>	0.871	0.709	<b>0.0173</b>	<b>0.0421</b>	NA	0.709	<b>0.0173</b>	<b>0.0421</b>	NA
LGR5	0.263	0.647	<b>0.0407</b>	0.224	0.945	<b>0.0358</b>	<b>0.0486</b>	<b>0.0175</b>	0.945	<b>0.0358</b>	<b>0.0486</b>	<b>0.0175</b>
MC4R	<b>2.74e-10</b>	<b>1.84e-08</b>	0.0789	<b>0.00652</b>	0.729	0.236	0.0838	0.813	0.729	0.236	0.0838	0.813
PER2	0.62	0.636	<b>0.00215</b>	0.714	0.869	<b>0.00209</b>	<b>0.0121</b>	0.625	0.869	<b>0.00209</b>	<b>0.0121</b>	0.625
PPARG	0.0755	<b>0.00125</b>	<b>0.04</b>	<b>0.0106</b>	0.673	<b>0.00134</b>	0.0912	0.371	0.673	<b>0.00134</b>	0.0912	0.371
PRKAB1	0.336	0.0785	<b>0.0498</b>	<b>0.012</b>	0.258	<b>0.0201</b>	0.0816	NA	0.258	<b>0.0201</b>	0.0816	NA
RPN2	0.773	0.349	<b>0.0155</b>	0.586	0.0923	<b>0.00227</b>	<b>0.0342</b>	0.691	0.0923	<b>0.00227</b>	<b>0.0342</b>	0.691
TMEM154	0.798	0.261	<b>0.0119</b>	0.425	<b>0.0446</b>	<b>0.0136</b>	<b>0.015</b>	0.796	<b>0.0446</b>	<b>0.0136</b>	<b>0.015</b>	0.796

Table 27: Grey zone genes with a pattern of associations characteristic of the obesity cluster (p-values)

Gene	T2D	BMI	FastIns	HipC	Height	HOMA-B	HOMA-IR	Leptin	Height	HOMA-B	HOMA-IR	Leptin
ACOX2	<b>0.442</b>	0.0149	0.145	<b>2.14</b>	0.478	0.0871	<b>0.161</b>	0.0841	0.478	0.0871	<b>0.161</b>	0.0841
ADAMTS9	0.045	0.0055	<b>0.163</b>	-4.27	-0.28	<b>0.181</b>	<b>0.162</b>	-0.0468	-0.28	<b>0.181</b>	<b>0.162</b>	-0.0468
AK2	<b>0.292</b>	<b>0.0151</b>	-0.00798	<b>-1.89</b>	-0.303	0.0131	0.0052	0.0617	-0.303	0.0131	0.0052	0.0617
CCR3	0.12	0.005	<b>0.0879</b>	1.72	-1.96	<b>0.089</b>	<b>0.0967</b>	0.0312	-1.96	<b>0.089</b>	<b>0.0967</b>	0.0312
CDC123	0.131	<b>0.0298</b>	<b>0.258</b>	-1.06	-0.934	0.162	<b>0.273</b>	NA	-0.934	0.162	<b>0.273</b>	NA
COX17	0.504	<b>0.0599</b>	NA	<b>5.29</b>	-2.01	NA	NA	NA	-2.01	NA	NA	NA
CYP4F11	0.13	-0.0051	<b>0.0832</b>	0.379	-0.172	<b>0.0965</b>	0.078	<b>0.254</b>	-0.172	<b>0.0965</b>	0.078	<b>0.254</b>
GART	-0.0756	0.005	<b>0.18</b>	-0.103	-0.066	<b>0.209</b>	<b>0.181</b>	0.13	-0.066	<b>0.209</b>	<b>0.181</b>	0.13
HADH	-0.0802	<b>0.0141</b>	<b>0.111</b>	-4.19	0.487	0.095	<b>0.118</b>	0.148	0.487	0.095	<b>0.118</b>	0.148
HAS2	0.057	0.0099	<b>0.228</b>	0.337	0.258	<b>0.221</b>	<b>0.221</b>	NA	0.258	<b>0.221</b>	<b>0.221</b>	NA
HSD11B1	-0.599	-0.134	<b>0.226</b>	2.12	-2.22	<b>0.27</b>	<b>0.246</b>	NA	-2.22	<b>0.27</b>	<b>0.246</b>	NA
LGR5	-0.966	0.0036	<b>0.0516</b>	-3.86	1.62	<b>0.0737</b>	<b>0.0529</b>	<b>-0.217</b>	1.62	<b>0.0737</b>	<b>0.0529</b>	<b>-0.217</b>
MC4R	<b>0.726</b>	<b>0.0502</b>	-0.114	<b>1.61</b>	0.317	-0.0805	-0.119	0.035	0.317	-0.0805	-0.119	0.035
PER2	0.0619	-0.0032	<b>0.338</b>	-0.316	-0.117	<b>0.35</b>	<b>0.309</b>	0.0468	-0.117	<b>0.35</b>	<b>0.309</b>	0.0468
PPARG	0.341	<b>-0.148</b>	<b>0.22</b>	<b>-5.96</b>	-0.642	<b>0.327</b>	0.198	0.215	-0.642	<b>0.327</b>	0.198	0.215
PRKAB1	0.259	0.0189	<b>0.17</b>	<b>2.43</b>	-1.23	<b>0.196</b>	0.163	NA	-1.23	<b>0.196</b>	0.163	NA
RPN2	-0.164	0.0084	<b>0.233</b>	0.711	1.33	<b>0.28</b>	<b>0.225</b>	0.111	1.33	<b>0.28</b>	<b>0.225</b>	0.111
TMEM154	-0.109	0.0532	<b>0.209</b>	3.31	<b>-1.25</b>	<b>0.213</b>	<b>0.216</b>	-0.0871	<b>-1.25</b>	<b>0.213</b>	<b>0.216</b>	-0.0871

Table 28: Grey zone genes with a pattern of associations characteristic of the obesity cluster (effect sizes)

Gene	T2D P-value	T2D Effect	BMI P-value	BMI Effect	HipC P-value	HipC Effect	Height P-value	Height Effect	HOMA-B P-value	HOMA-B Effect	WaistC P-value	WaistC Effect
HNF1A	<b>0.0219</b>	<b>0.206</b>	0.217	-0.0083	<b>0.00193</b>	<b>-4.78</b>	0.649	-0.858	<b>0.0332</b>	<b>-0.368</b>	<b>0.00792</b>	<b>-4.37</b>
UGT2B15	0.159	-0.595	<b>0.00127</b>	<b>-0.0891</b>	<b>0.00162</b>	<b>-7.15</b>	0.986	0.491	0.931	-0.0152	<b>0.00877</b>	<b>-6.56</b>
LAMA1	0.72	-0.0702	<b>0.024</b>	<b>-0.0043</b>	<b>0.0166</b>	<b>-1.27</b>	0.69	-0.295	0.927	-0.0123	<b>0.000324</b>	<b>-1.58</b>
GIPR	0.786	-0.202	<b>0.000163</b>	<b>-0.018</b>	<b>0.013</b>	<b>-1.47</b>	0.362	-1.34	0.45	-0.0756	<b>0.0154</b>	<b>-1.35</b>
GALE	0.795	0.299	<b>0.00166</b>	<b>-0.0281</b>	<b>0.0137</b>	<b>-2.41</b>	0.116	-1.7	0.319	-0.168	<b>0.00942</b>	<b>-2.53</b>

Table 29: Grey zone genes with a pattern of associations characteristic of the proinsulin cluster