SUPPLEMENTARY INFORMATION

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Supplementary Acknowledgements

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phs001218	AA_CAC	GeneSTAR AA_CAC	2	Broad Genomics[a]	HHSN268201500014C
phs001345	AA_CAC	GENOA AA_CAC	2	Broad Genomics[a]	HHSN268201500014C
phs001416	AA_CAC	MESA AA_CAC	2	Broad Genomics[a]	HHSN268201500014C
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phs000956	Amish	Amish	1	Broad Genomics[a]	3R01HL121007-01S1
phs000954	CFS	CFS	1	NWGC[b]	3R01HL098433-05S1
phs000954	CFS	CFS	3.5	NWGC[b]	HHSN268201600032I
phs001368	CHS	CHS	3	Baylor[c]	HHSN268201600033I
phs000974	FHS	FHS	1	Broad Genomics[a]	3U54HG003067-12S2
phs001218	GeneSTAR	GeneSTAR	legacy	Illumina	R01HL112064
phs001218	GeneSTAR	GeneSTAR	2	Psomagen	3R01HL112064-04S1
phs001217	GenSalt	GenSalt	2	Baylor[c]	HHSN268201500015C
phs001359	GOLDN	GOLDN	2	NWGC[b]	3R01HL104135-04S1
phs001345	HyperGEN_ GENOA	GENOA	2	NWGC[b]	3R01HL055673-18S1
phs001293	HyperGEN_ GENOA	HyperGEN	2	NWGC[b]	3R01HL055673-18S1
phs000964	JHS	JHS	1	NWGC[b]	HHSN268201100037C
phs001416	MESA	MESA	2	Broad Genomics[a]	3U54HG003067-13S1
phs001215	SAFS	SAFS	1	Illumina	3R01HL113323-03S1
phs001215	SAFS	SAFS	legacy	Illumina	R01HL113322
phs000972	Samoan	Samoan	1	NWGC[b]	HHSN268201100037C
phs000972	Samoan	Samoan	2	NYGC[d]	HHSN268201500016C
phs001211	VTE	ARIC	2	Baylor[c]	3U54HG003273-12S2, HHSN268201500015C
phs001368	VTE	CHS VTE	2	Baylor[c]	3U54HG003273-12S2, HHSN268201500015C
phs001237	WHI	WHI	2	Broad Genomics[a]	HHSN268201500014C

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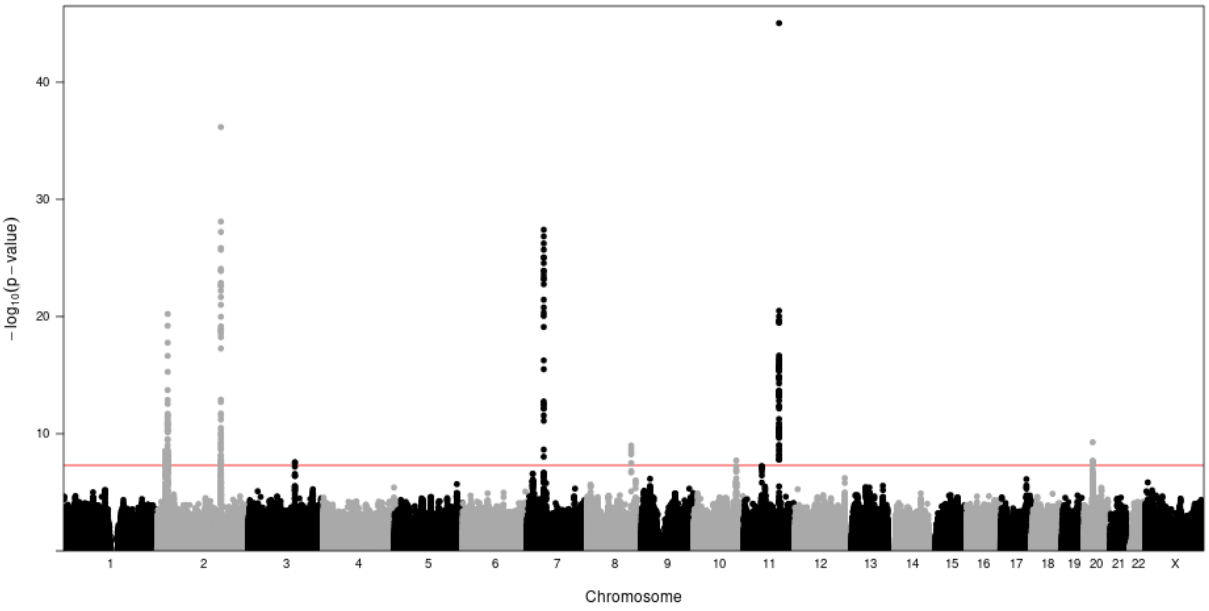
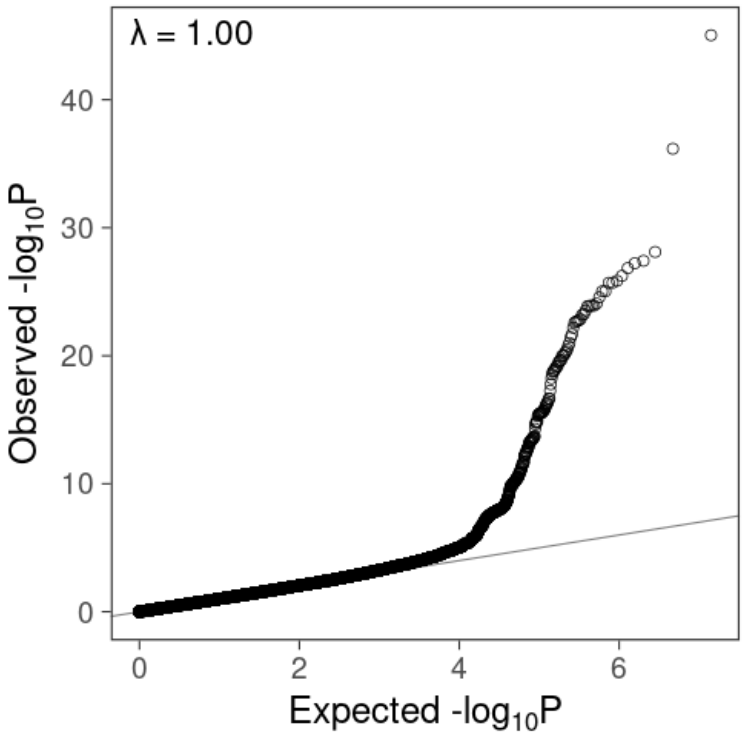
Supplementary Figures

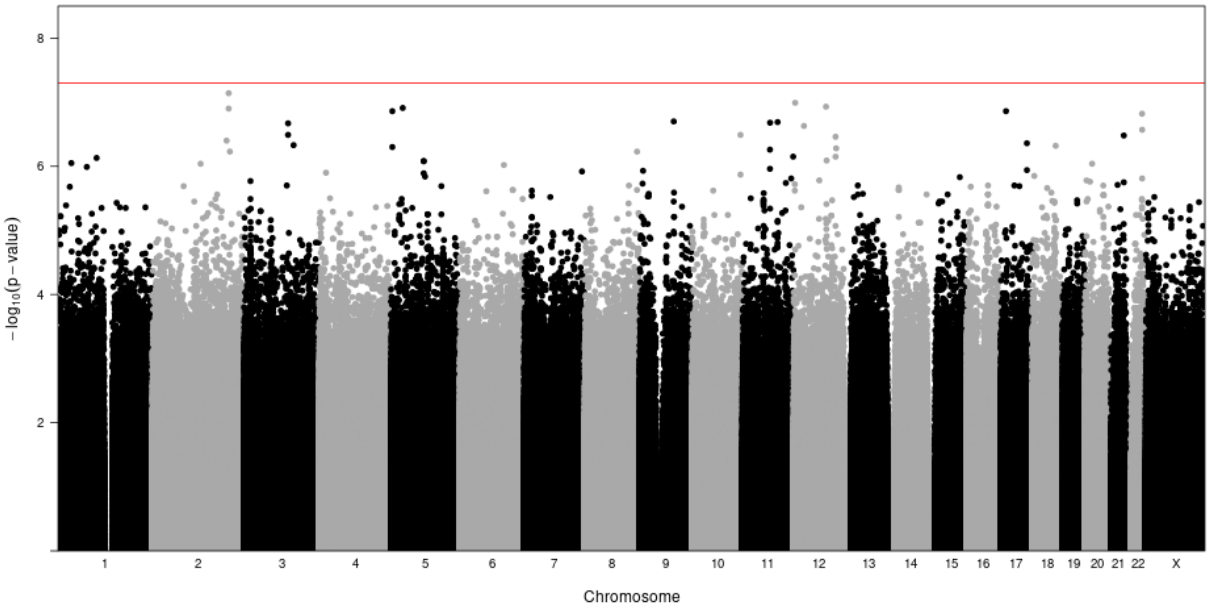
Supplementary Figure 1. Manhattan and QQ plots for pooled single variant analysis with fasting glucose and fasting insulin in TOPMed. The Manhattan plots show the $-\log_{10}$ *P-values* for the variants across the chromosomal positions with a threshold of 5×10^{-8} plotted in red; the QQ-plots show the observed versus expected $-\log_{10}$ *P-values*. The plots are stratified by common (MAF>=0.05) and rare (MAF<0.05) variants for all variants with MAC>=20.

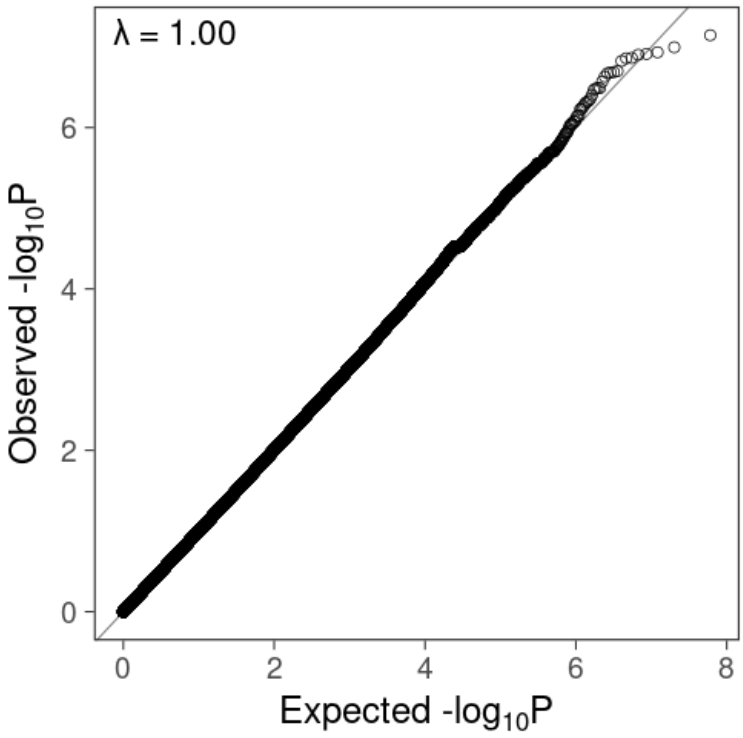
a. Fasting Glucose, MAF>=0.05



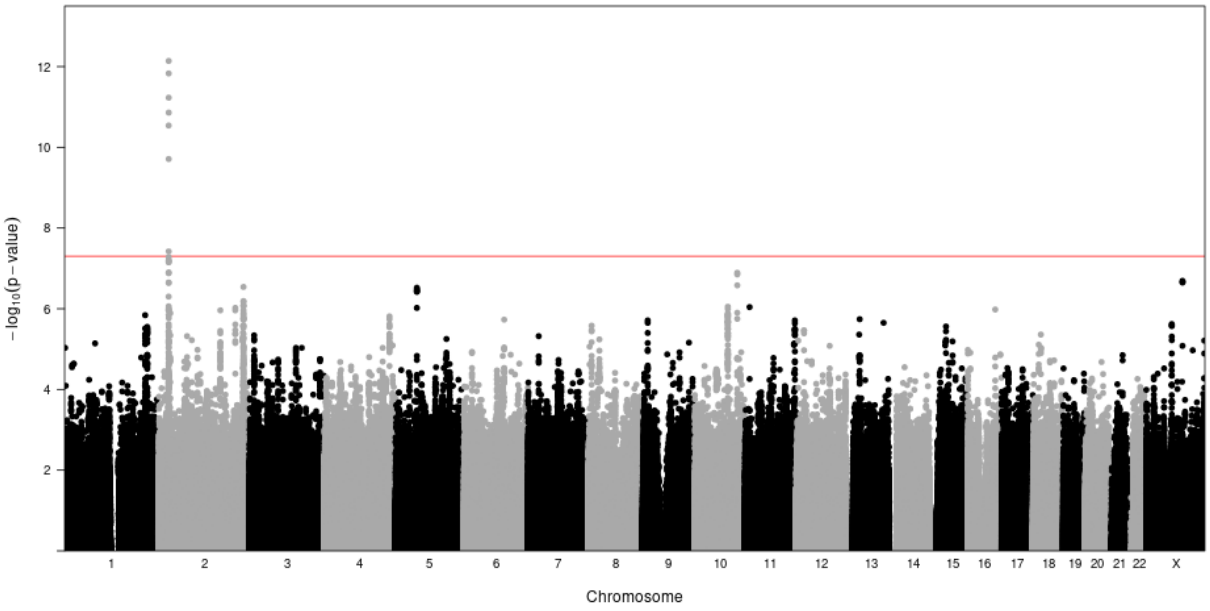


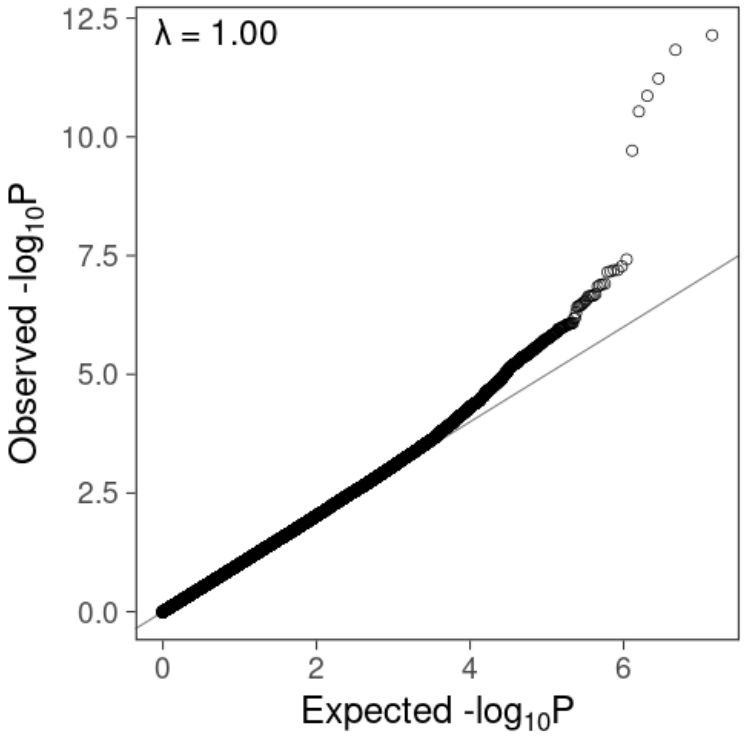
b. Fasting Glucose, MAF<0.05



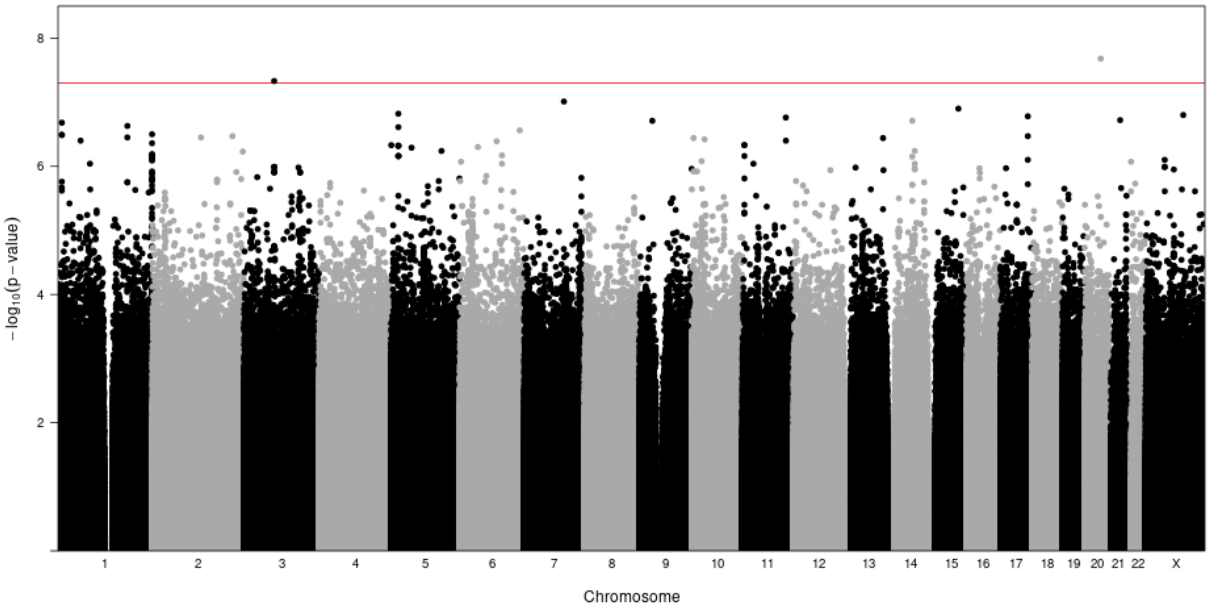


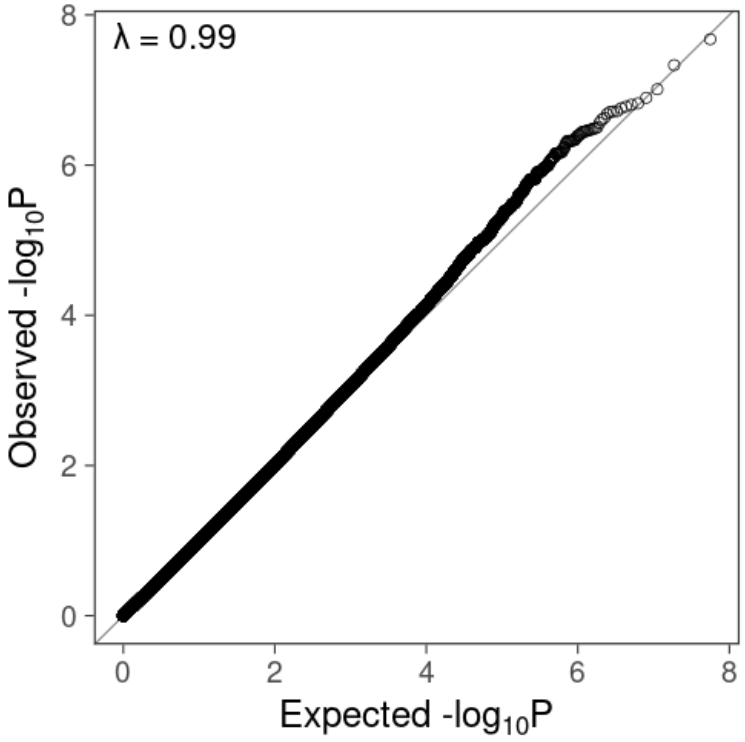
c. Fasting Insulin, MAF>=0.05





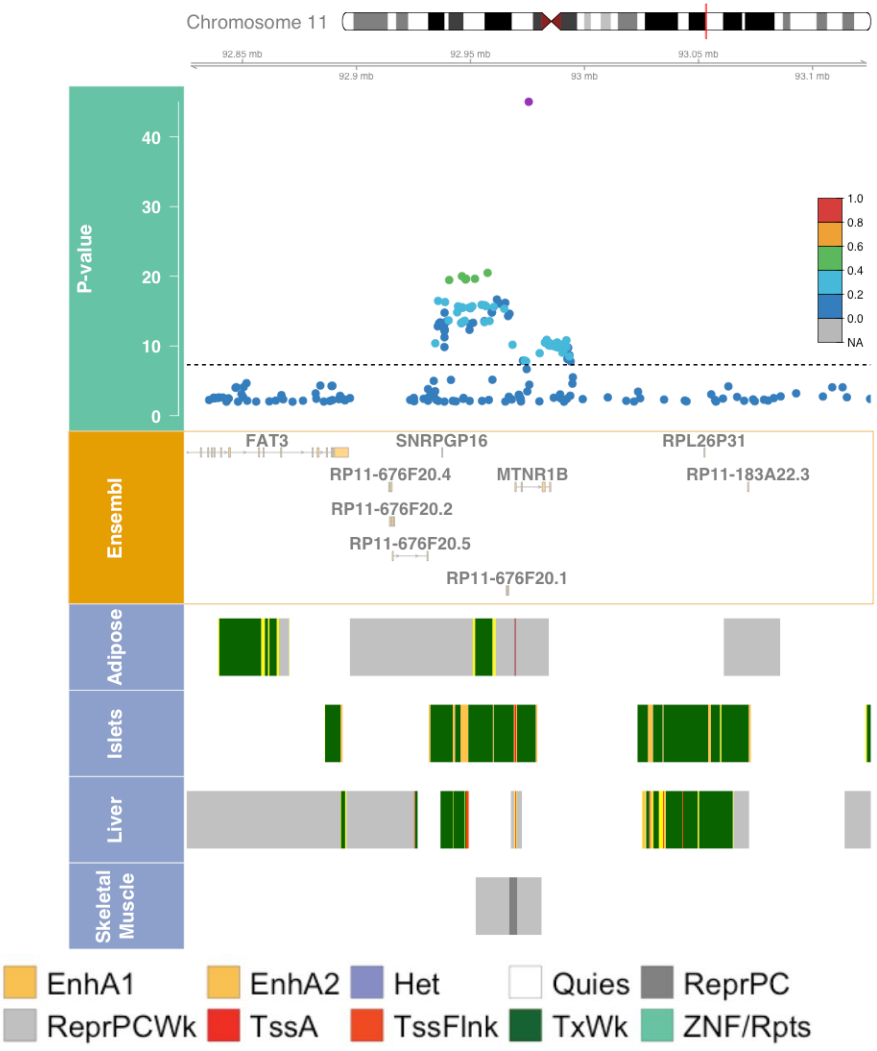
d. Fasting Insulin, MAF<0.05



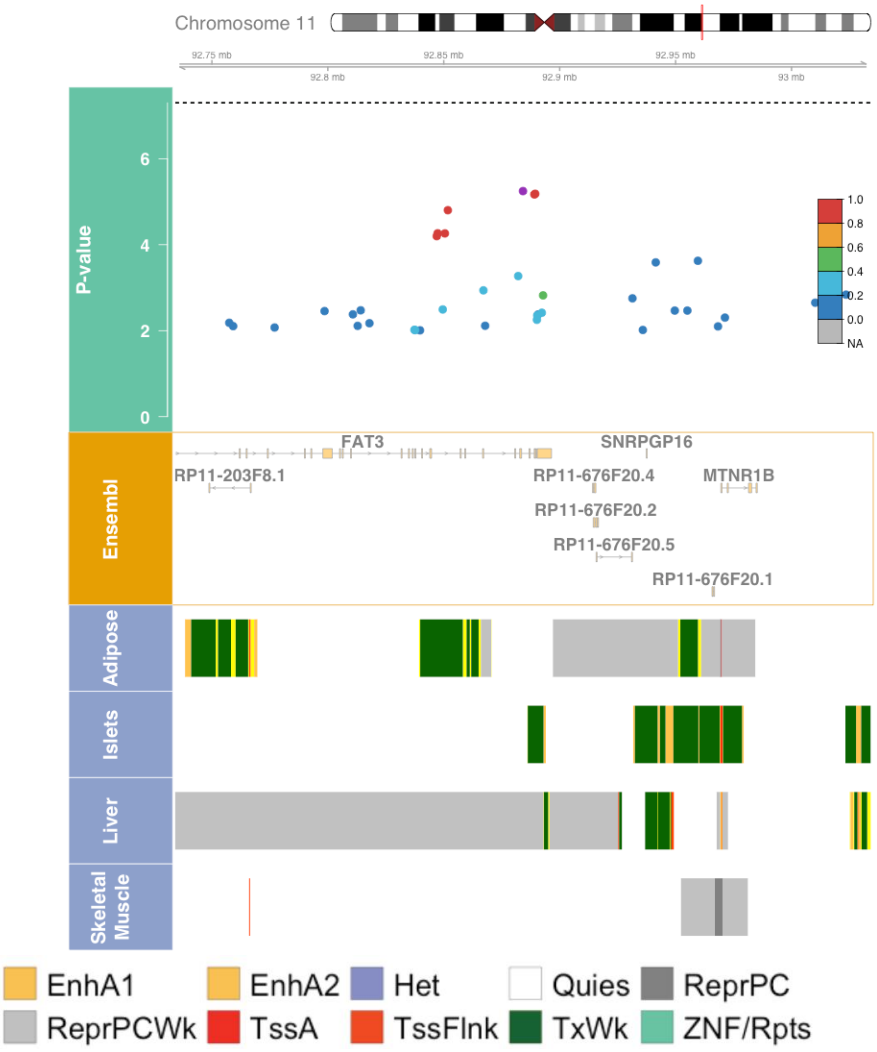


Supplementary Figure 2. Regional locus plots of the twelve loci significantly or suggestively associated in pooled analysis with stepwise conditional analysis. The loci associated with FG (a-b. *MTNR1B,* b. *G6PC2,* c. *GCK,* d. *GCKR,* e. *FOX2A,* f. *SLC30A8,* g. *APOB,* h. *TCF7L2,* i. *ADCY5*) and FI (j. *GCKR,* k. *PTPRT,* l. *ROBO1*). The linkage disequilibrium is given with respect to the index variant and was calculated in the TOPMed analysis sample. Plots denoted by rsID and MarkerID (Chromosome:Position(Hg38):Reference-Allele:Alternative-Allele).

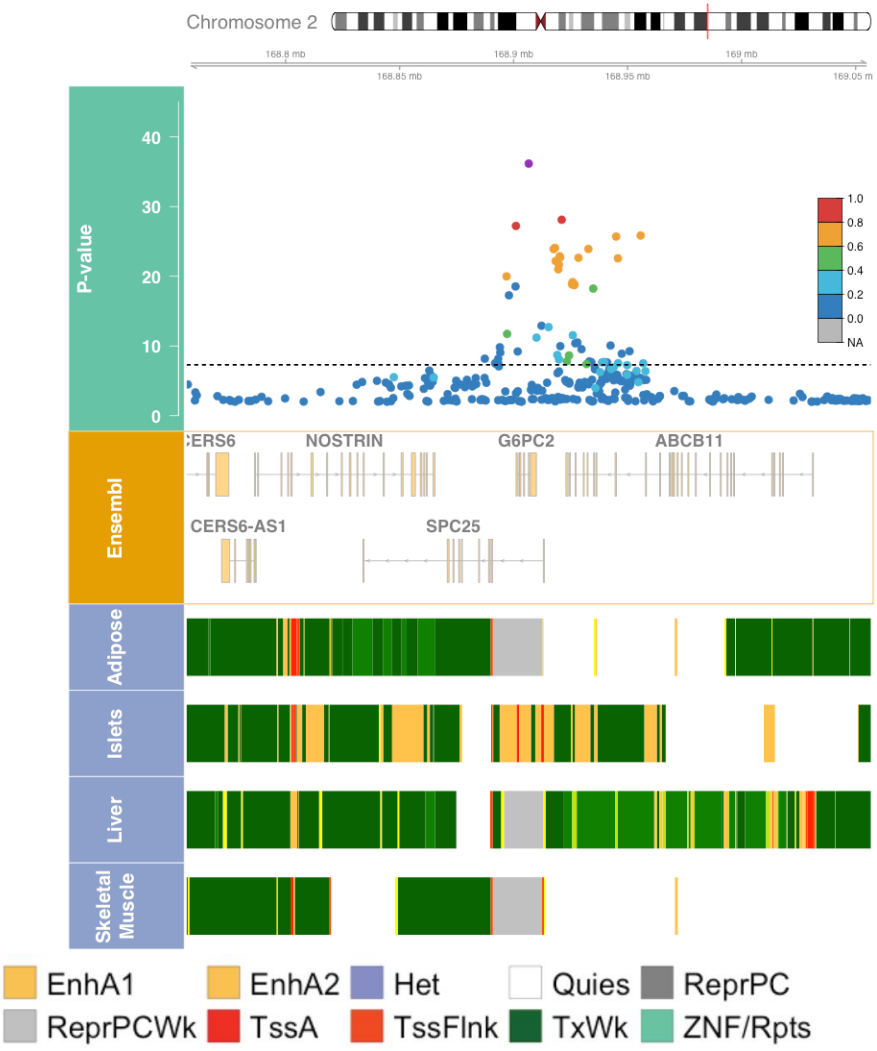
a. *MTNR1B*, rs10830963, 11:92975544:C:G



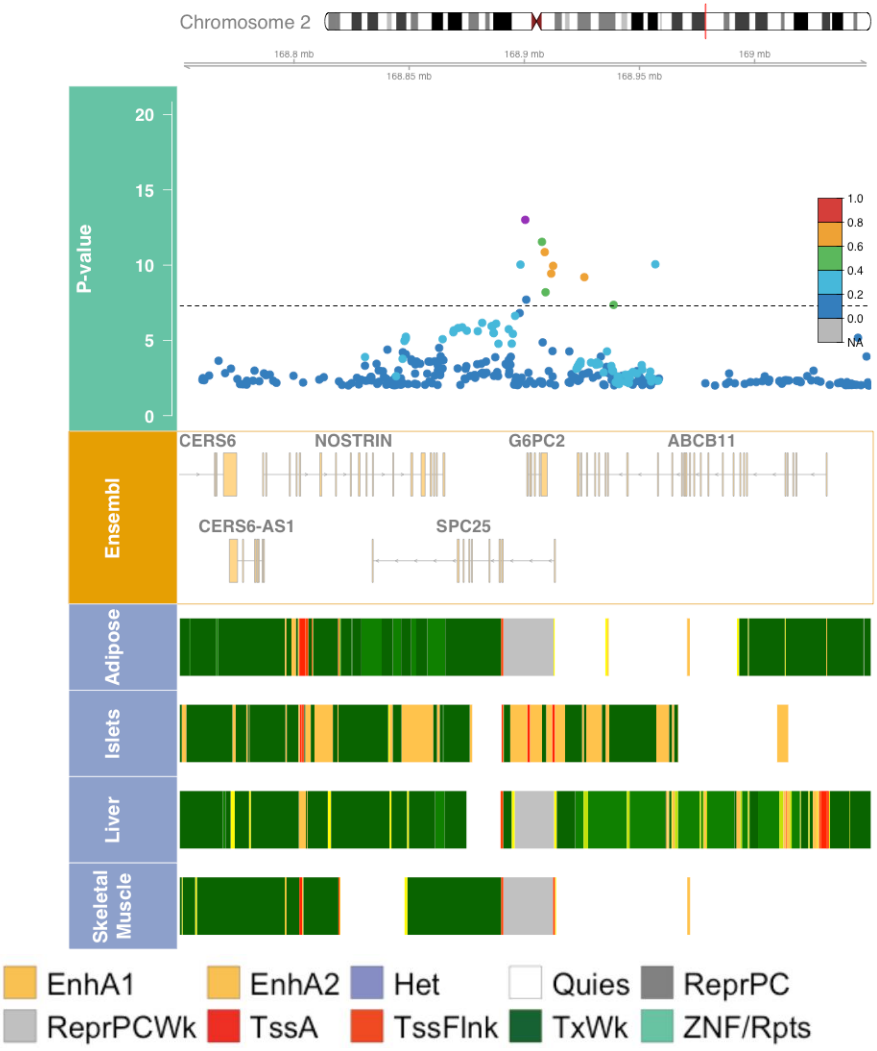
b. *MTNR1B*, rs73560545, 11:92884161:G:A



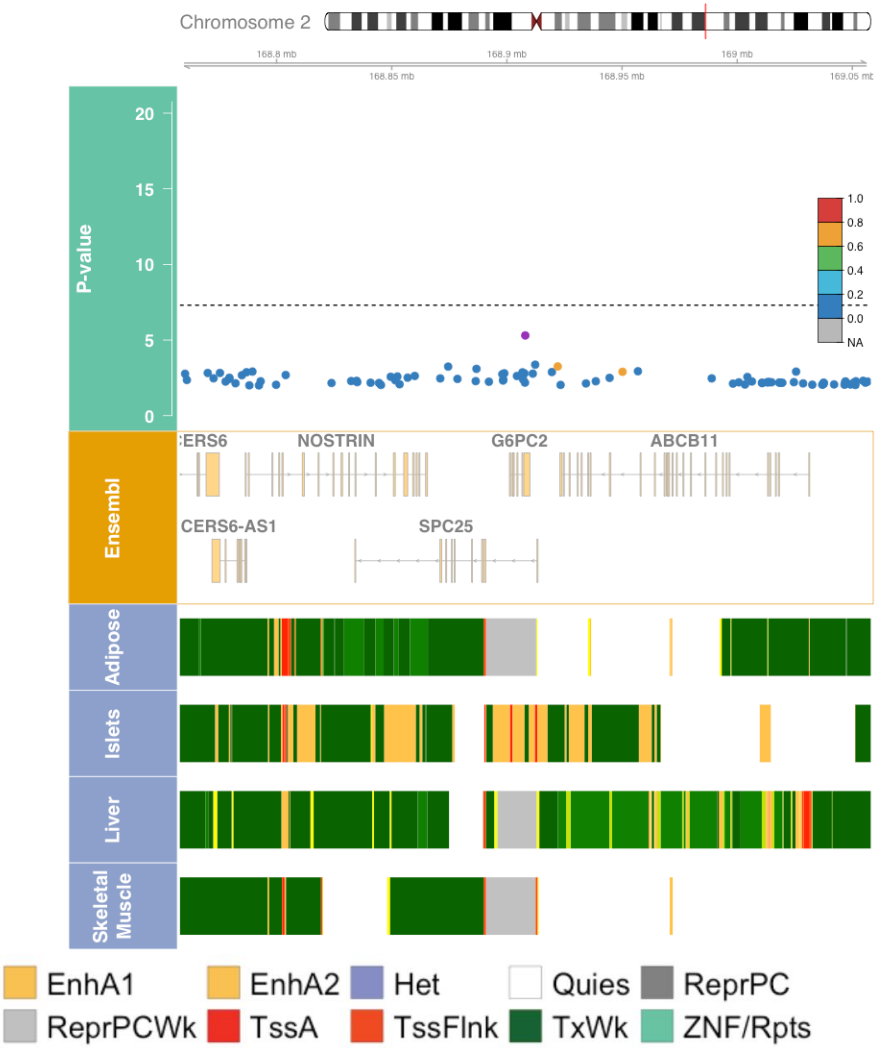
c. *G6PC2*, rs560887, 2:168906638:T:C



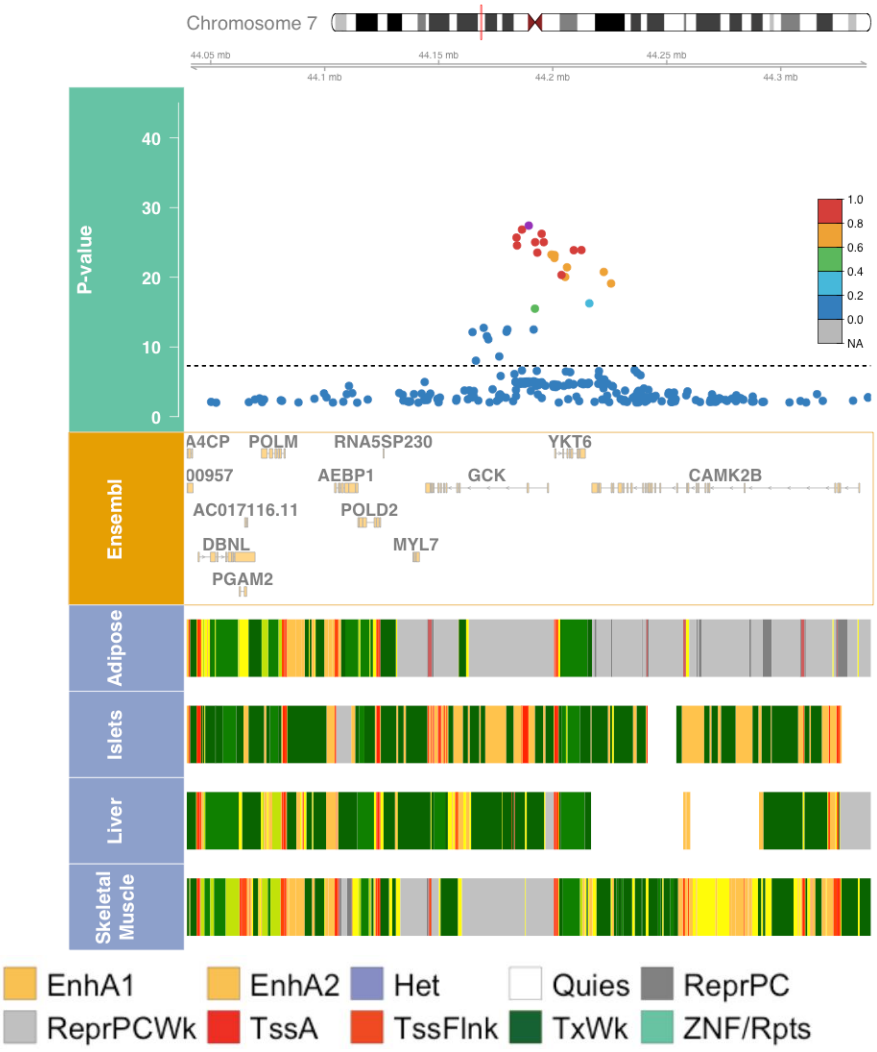
d. *G6PC2*, rs540524, 2:168900420:A:G



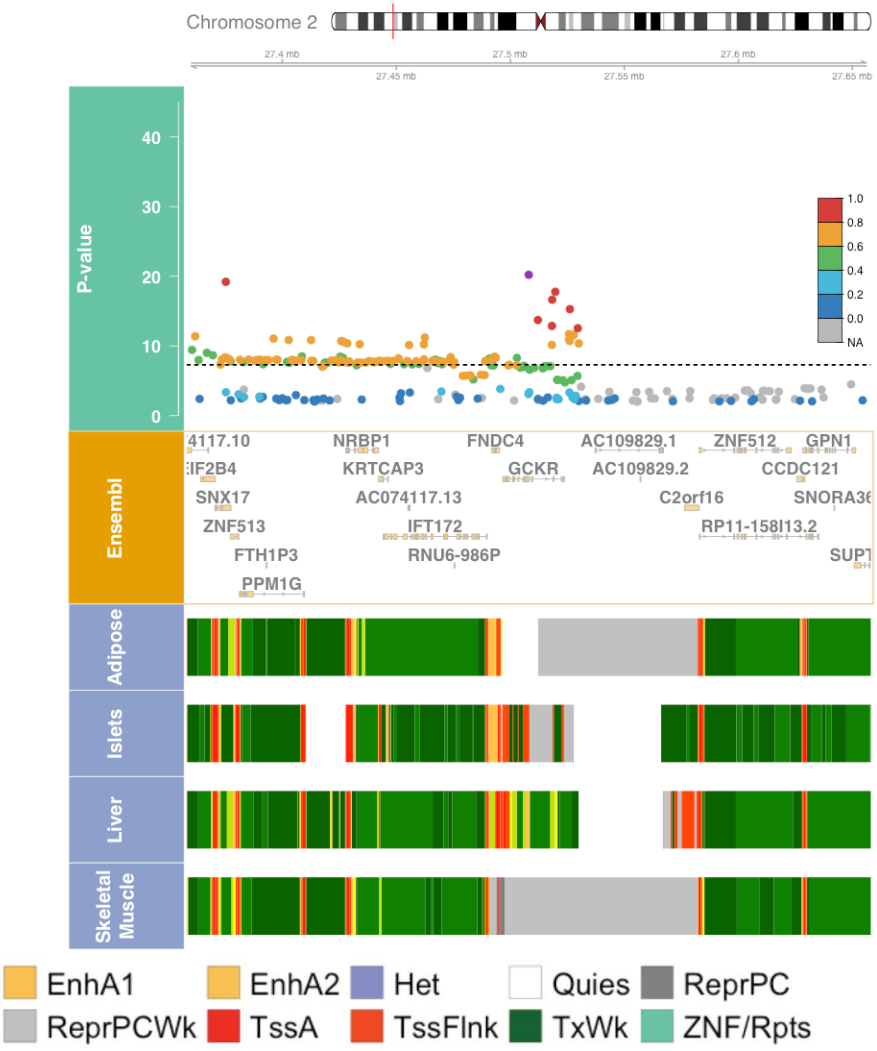
e. *G6PC2*, rs2232326, 2:168907981:T:C



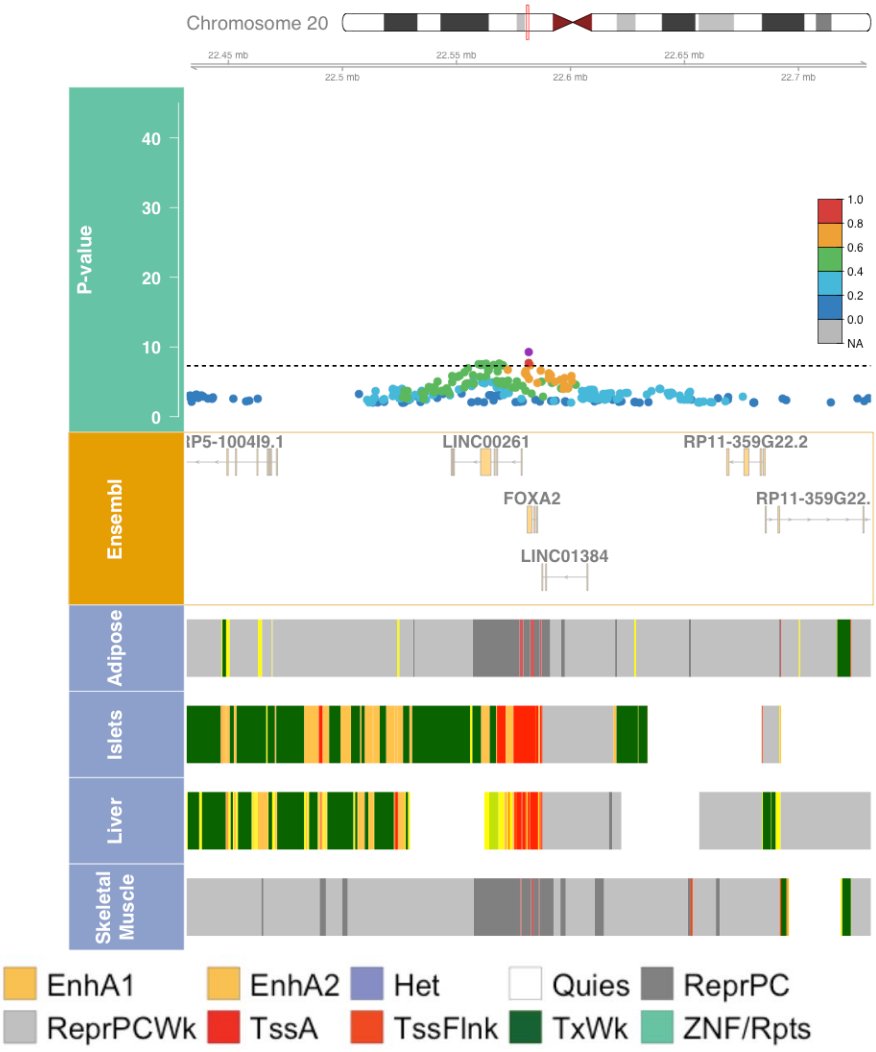
f. *GCK*, rs1799884, 7:44189469:C:T



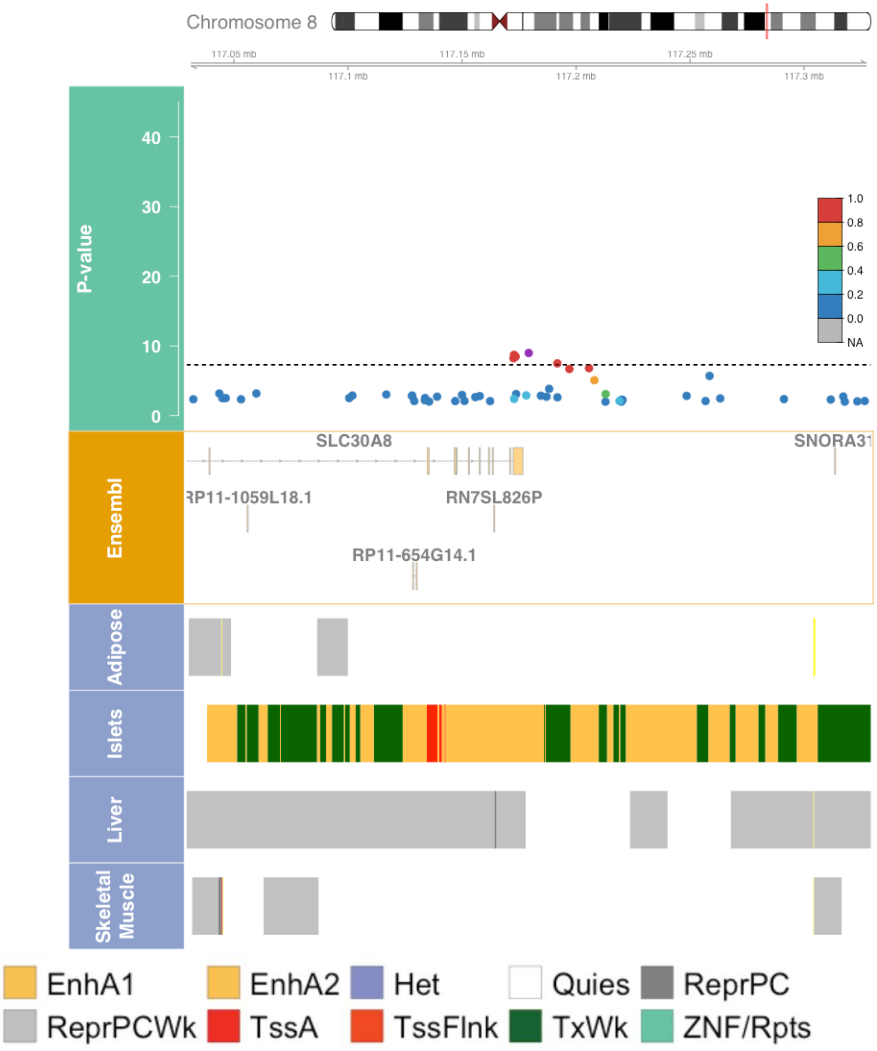
g. *GCKR*, rs1260326, 2:27508073:T:C



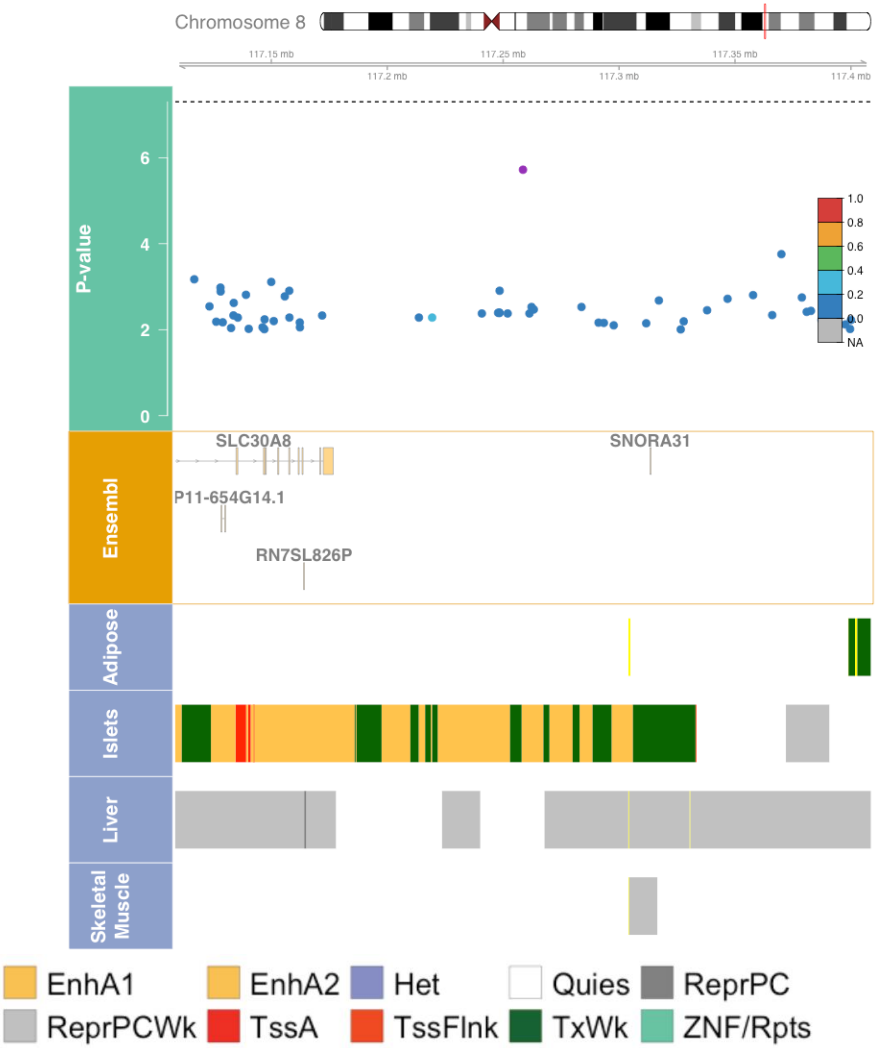
h. *FOXA2*, rs3833331, 20:22581688:A:AG



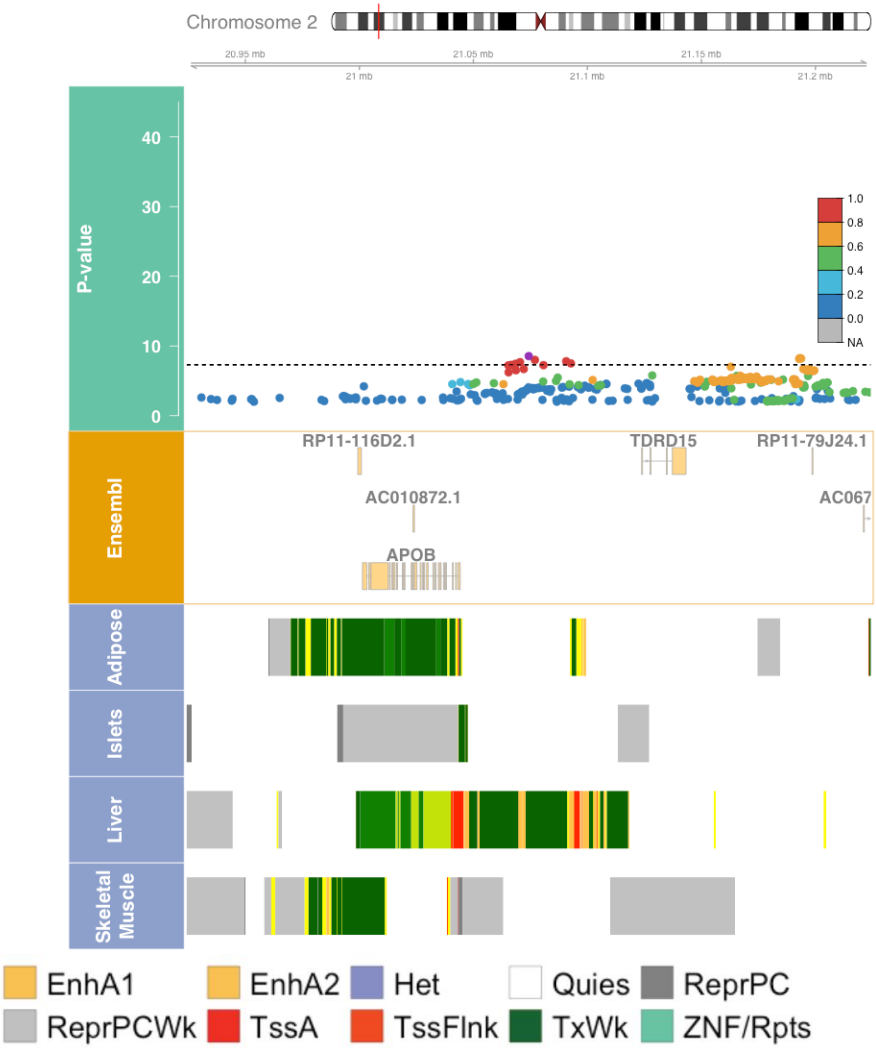
i. *SLC30A8*, rs35859536, 8:117179236:C:T



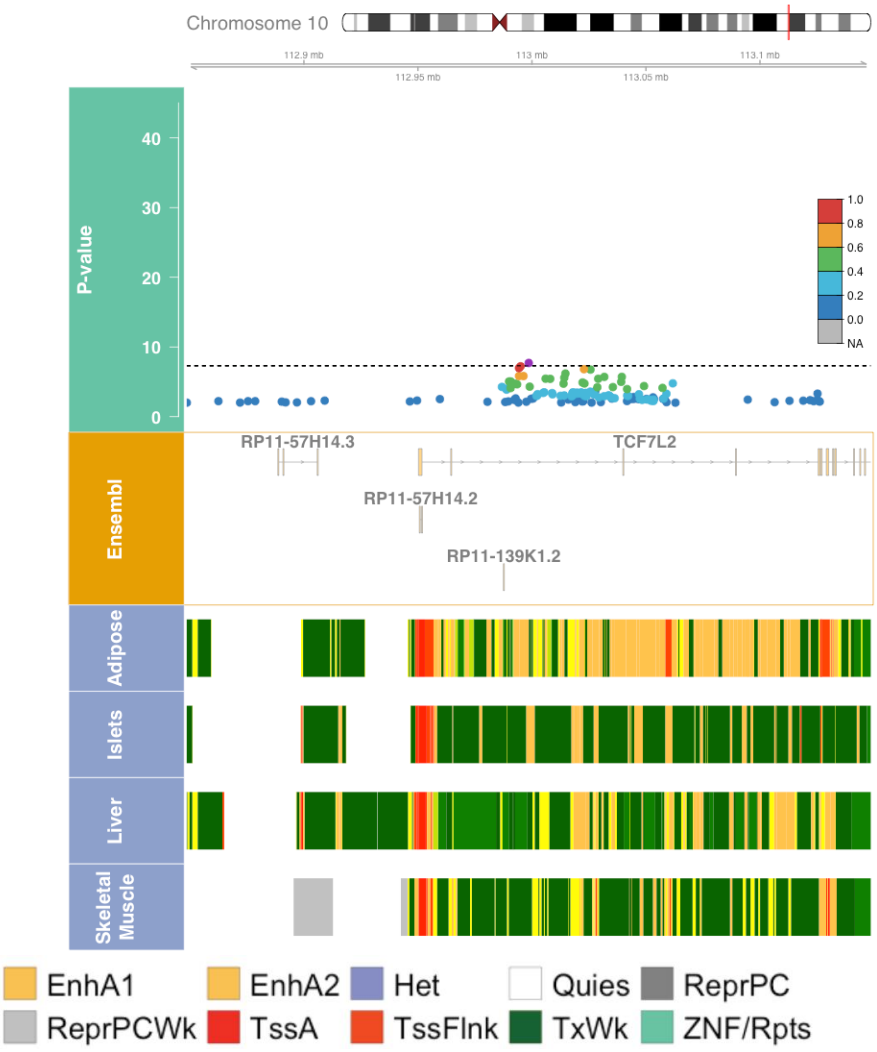
j. *SLC30A8*, rs542965166, 8:117258547:C:T



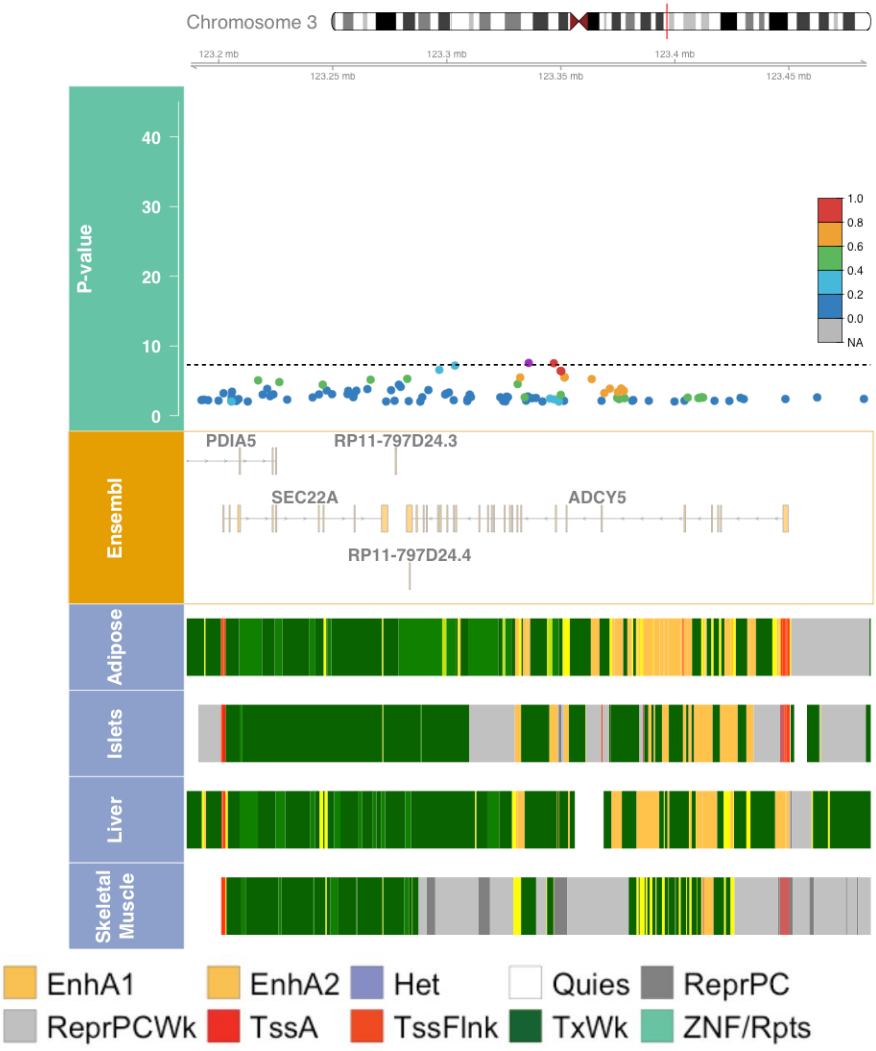
k. *APOB*, rs478588, 2:21074277:A:G



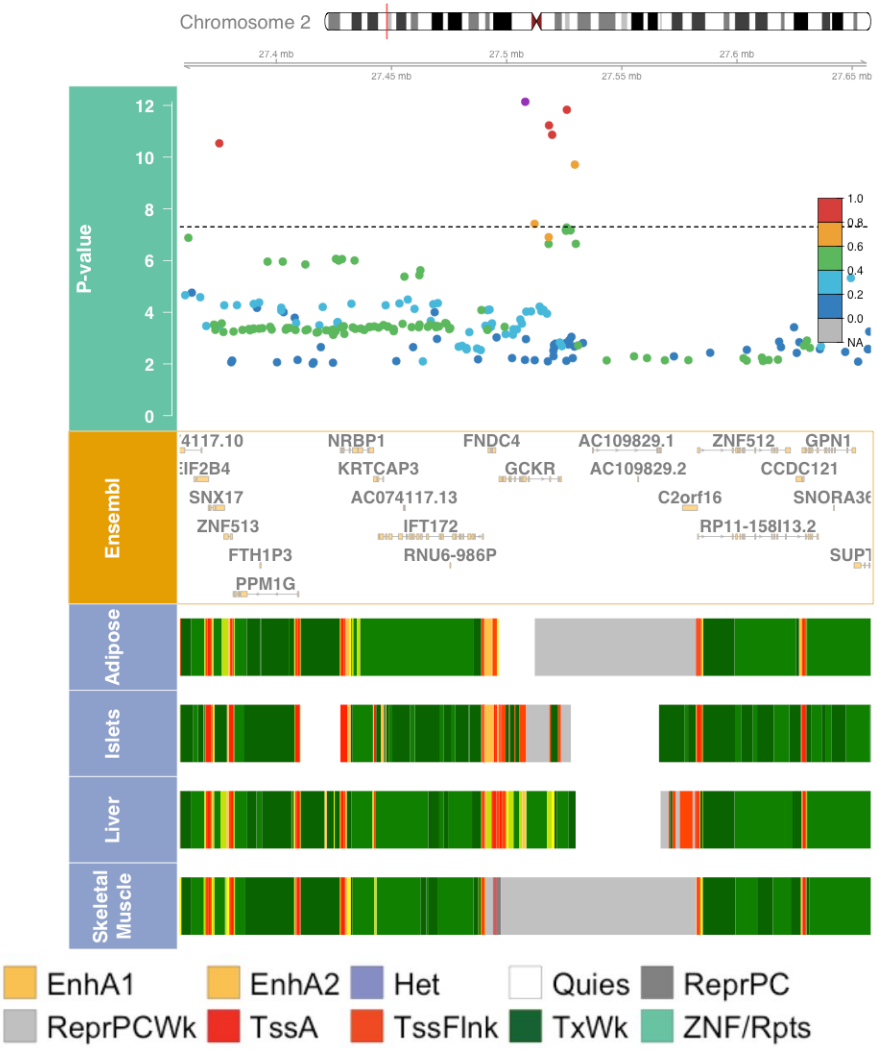
I. *TCF7L2*, rs7903146, 10:112998590:C:T



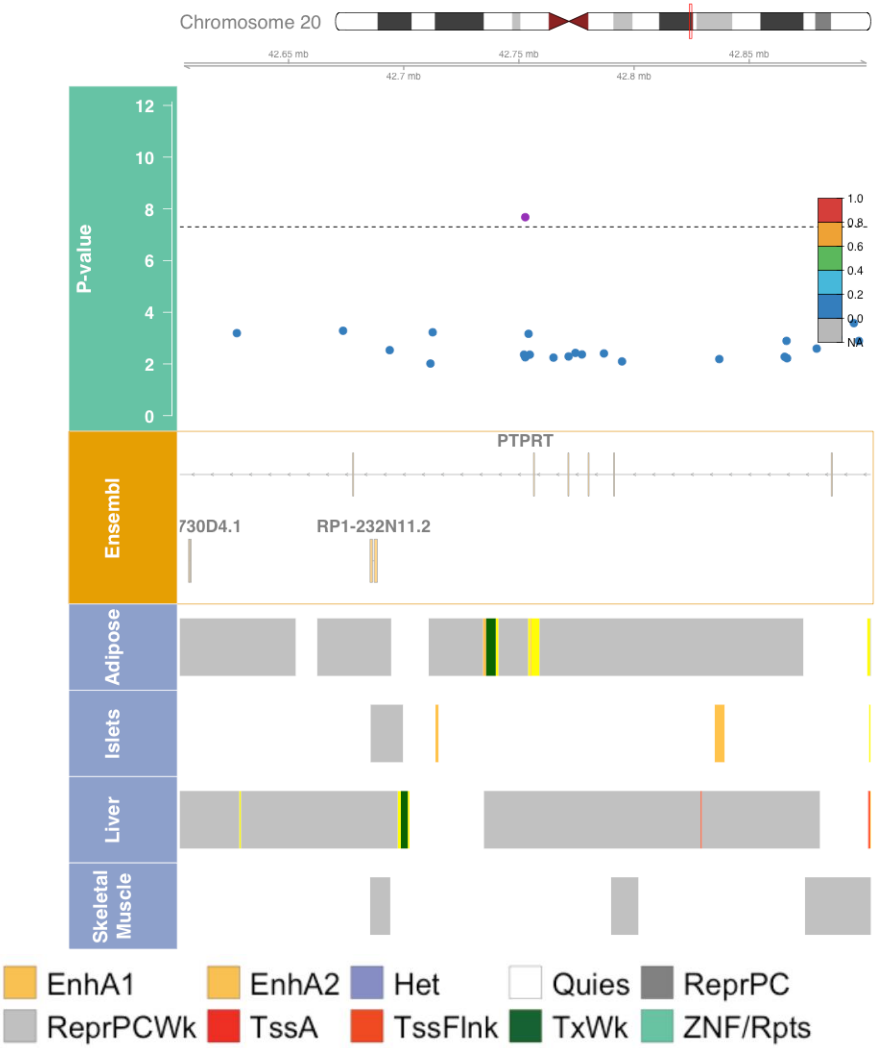
m. *ADCY5*, rs72964564, 3:123335923:A:C



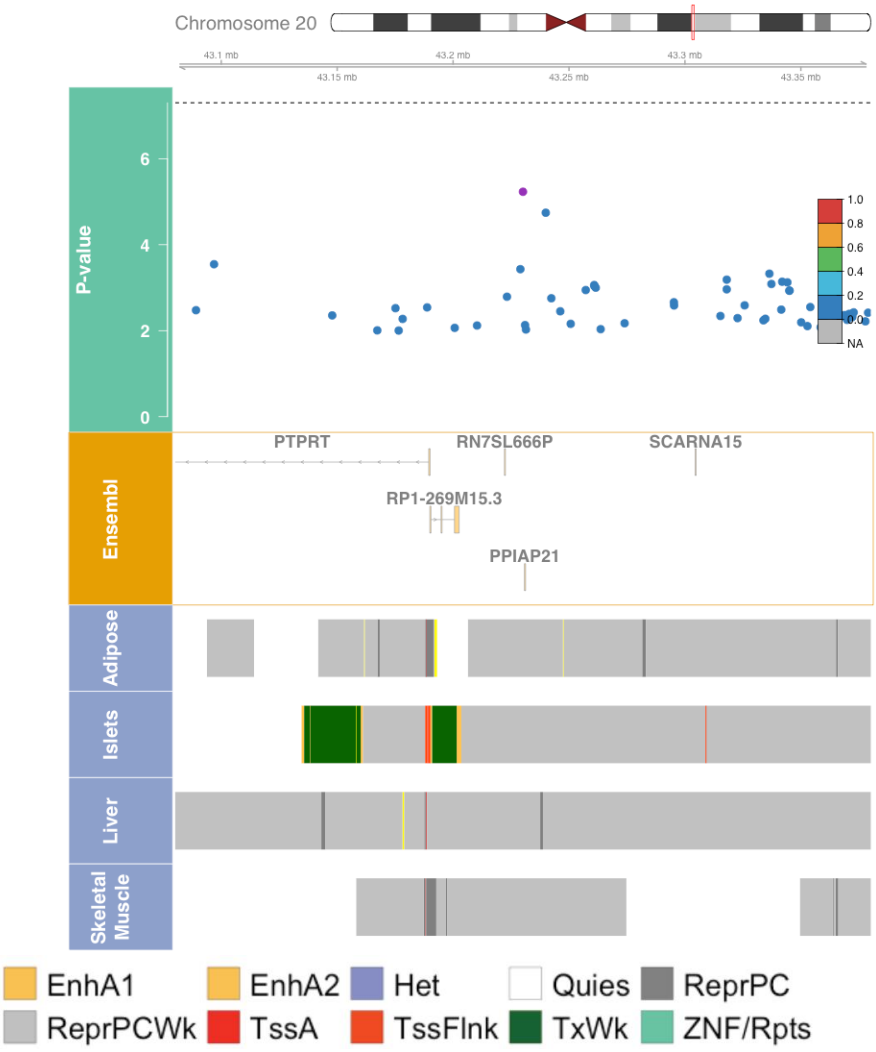
n. *GCKR*, rs1260326, 2:27508073:T:C



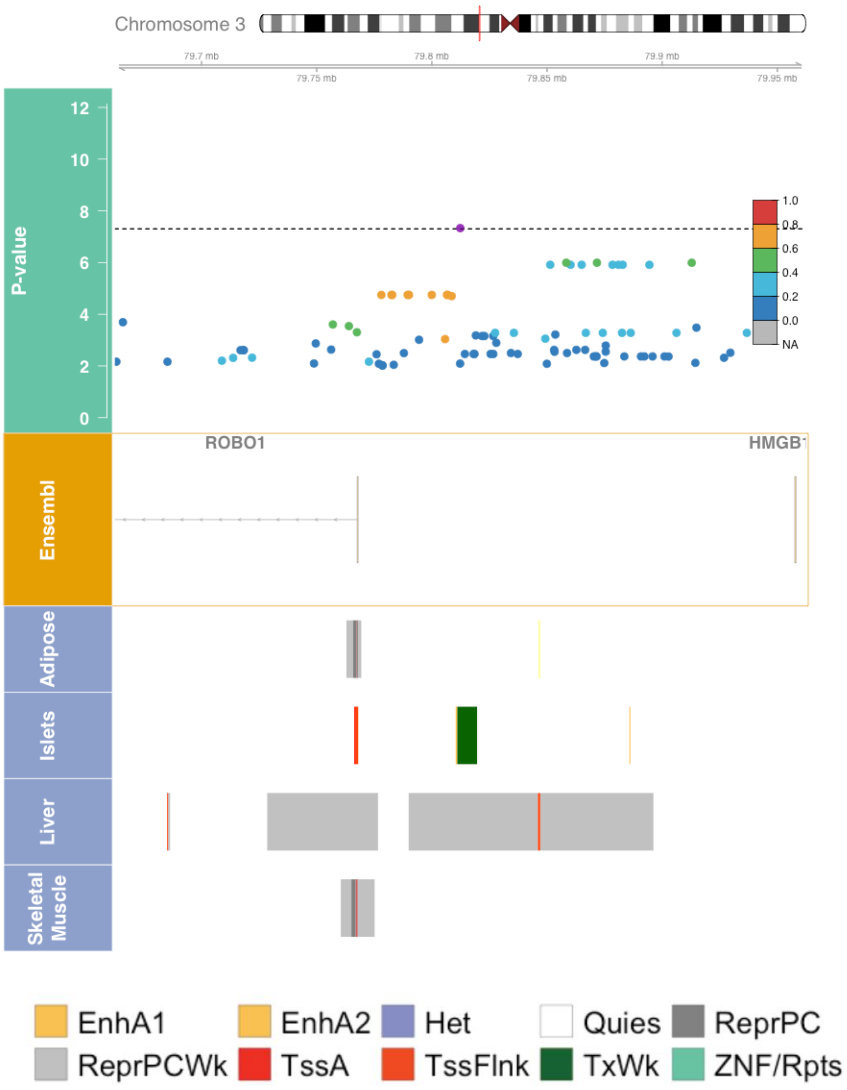
o. *PTPRT*, rs185250851, 20:42752773:G:A



p. *PTPRT*, rs78618809, 20:43230137:C:T



q. *ROBO1*, rs539973028, 3:79812347:C:A



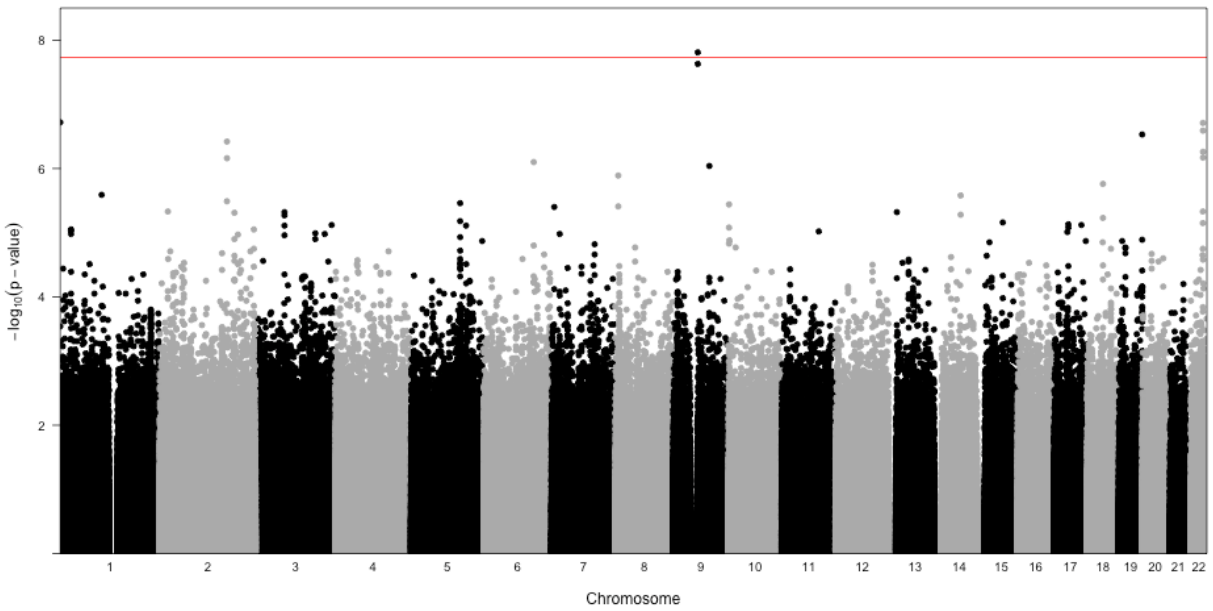
Supplementary Figure 3. Plot of associations with related traits of identified loci in single variant analysis. The plot shows a black indicator for traits that have been previously identified as associated; see also **Supplementary Table 8**.

	FG	FI	HbA1c	T2D	BMI	WHR	HOMA-B
MTNR1B	●		●	●	●		●
G6PC2	●		●				●
GCK	●		●	●			●
GCKR	●	●		●	●		
FOXA2	●			●			
SLC30A8	●		●	●	●		
APOB							
TCF7L2	●	●	●	●	●	●	
ADCY5	●		●	●	●	●	●
PTPRT					●	●	
ROBO1					●	●	

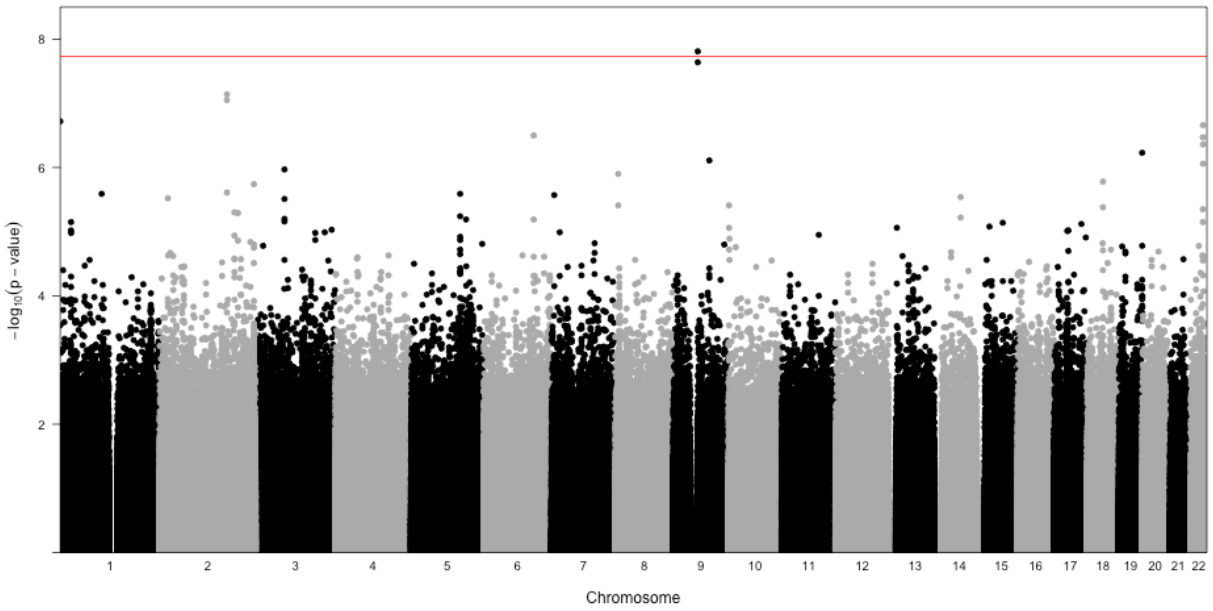
Abbreviations: FG, fasting glucose; FI, fasting insulin; HbA1c, hemoglobin A1c; T2D, Type 2 Diabetes; BMI, body mass index; WHR, waist-hip ratio; HOMA-B, homeostatic model assessment of beta-cell function.

Supplementary Figure 4. Manhattan plots for pooled region-based rare variant aggregate analysis with fasting glucose (a-d) and fasting insulin (e-h) in TOPMed. The Manhattan plot shows the -$\log_{10}$ *P-values* for the variant sets plotted at the starting chromosomal positions, using the burden test and the SKAT test.

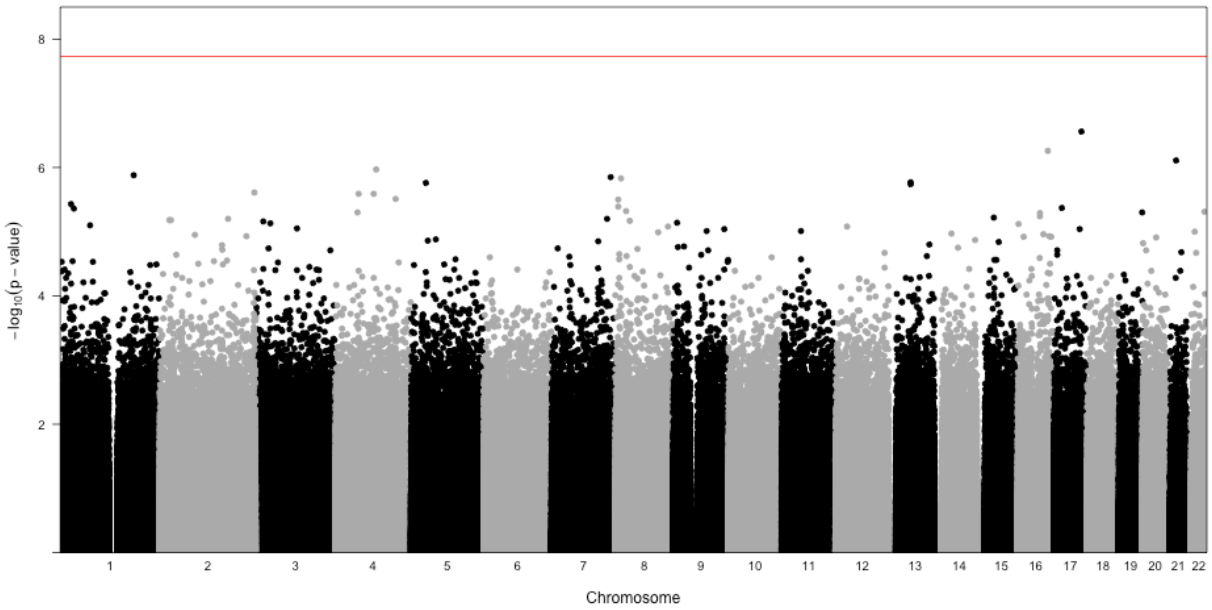
a. Fasting Glucose, SKAT (1,1)



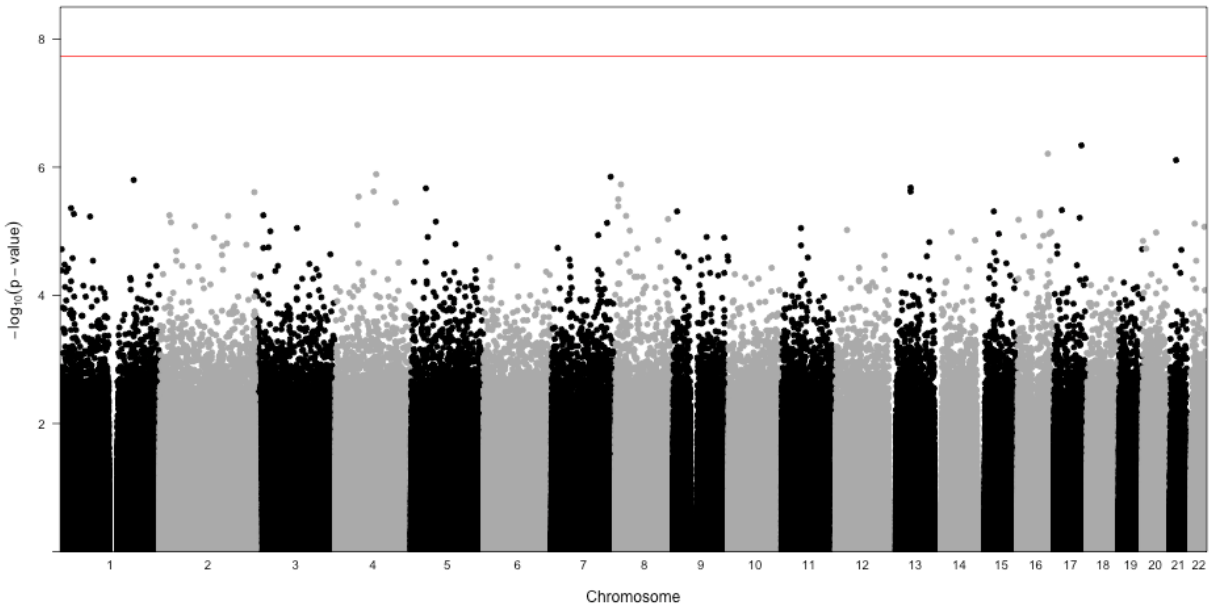
b. Fasting Glucose, SKAT (1,25)



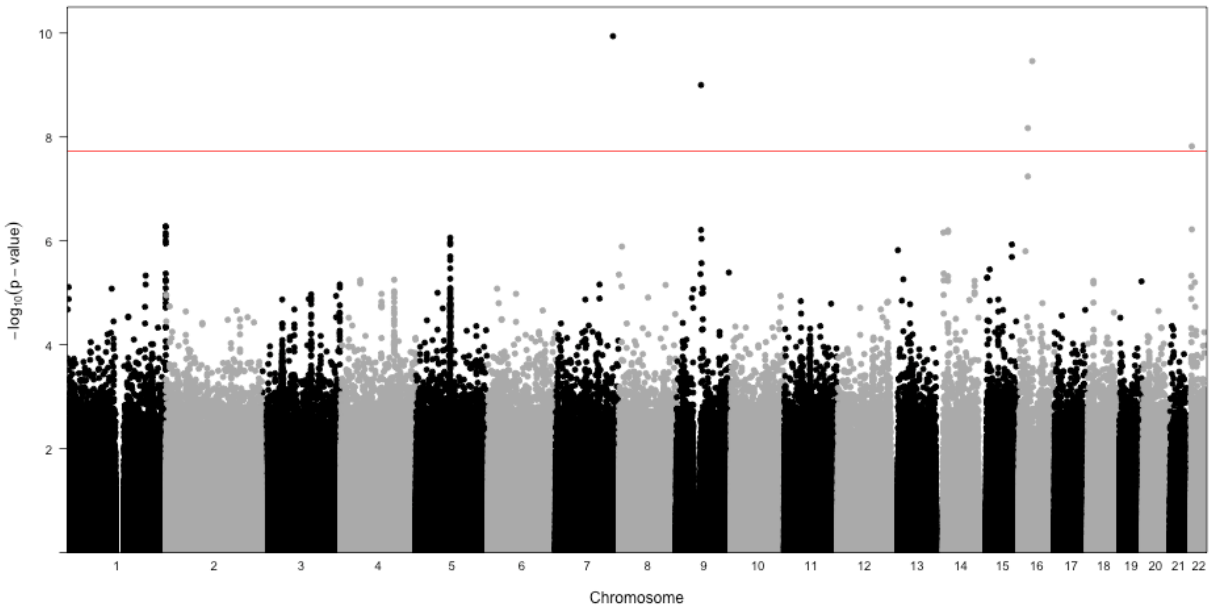
c. Fasting Glucose, Burden (1,1)



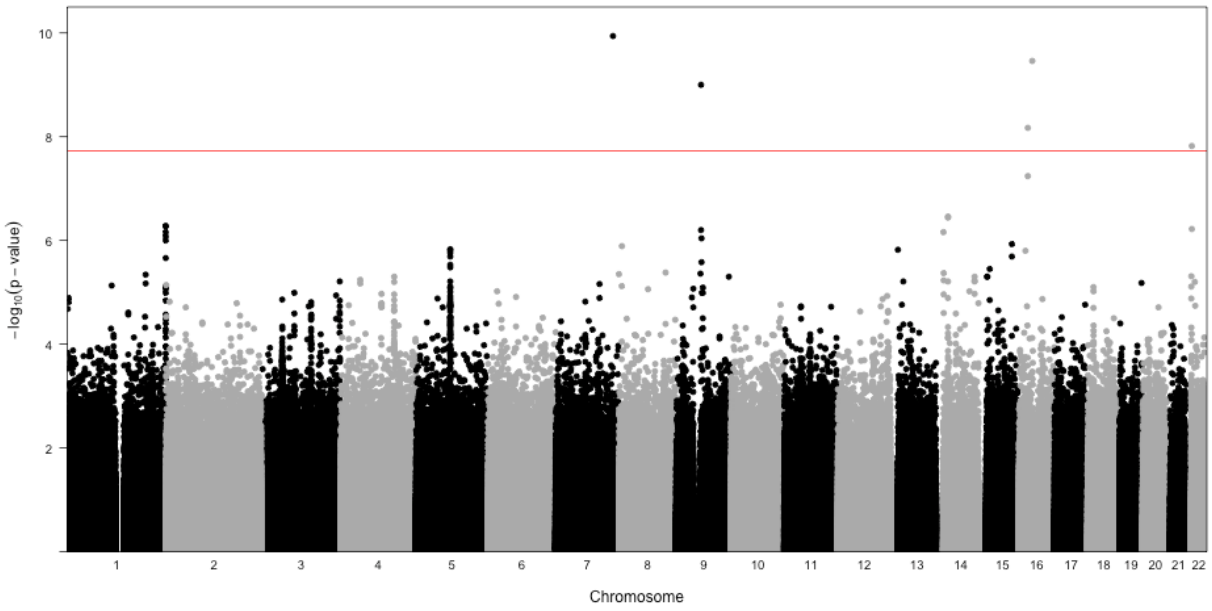
d. Fasting Glucose, Burden (1,25)



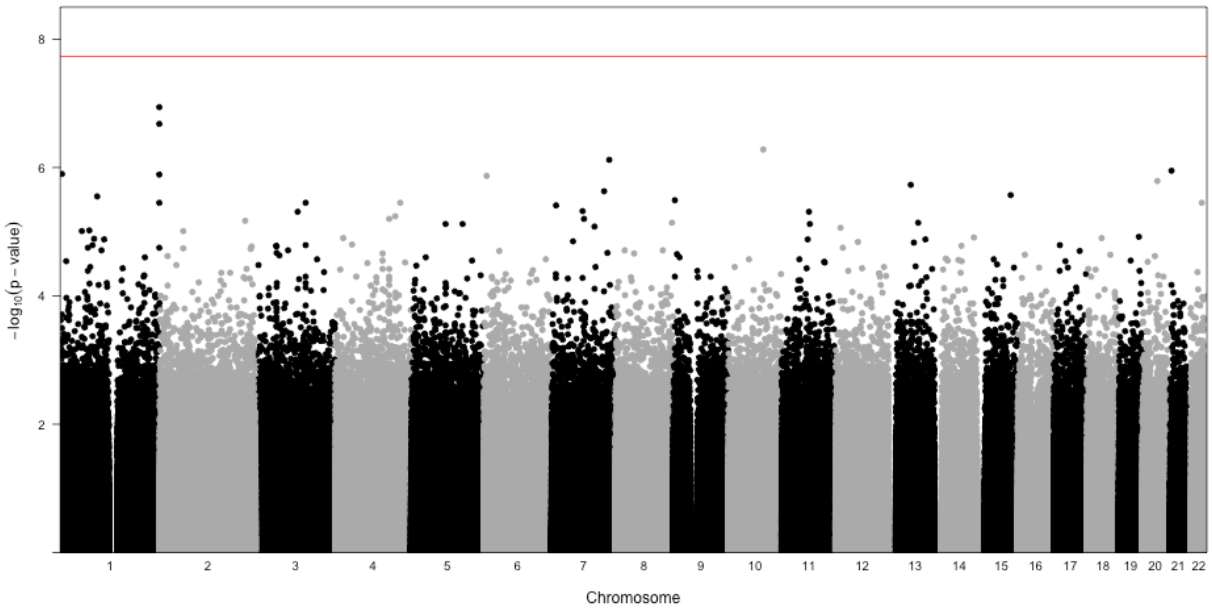
e. Fasting Insulin, SKAT (1,1)



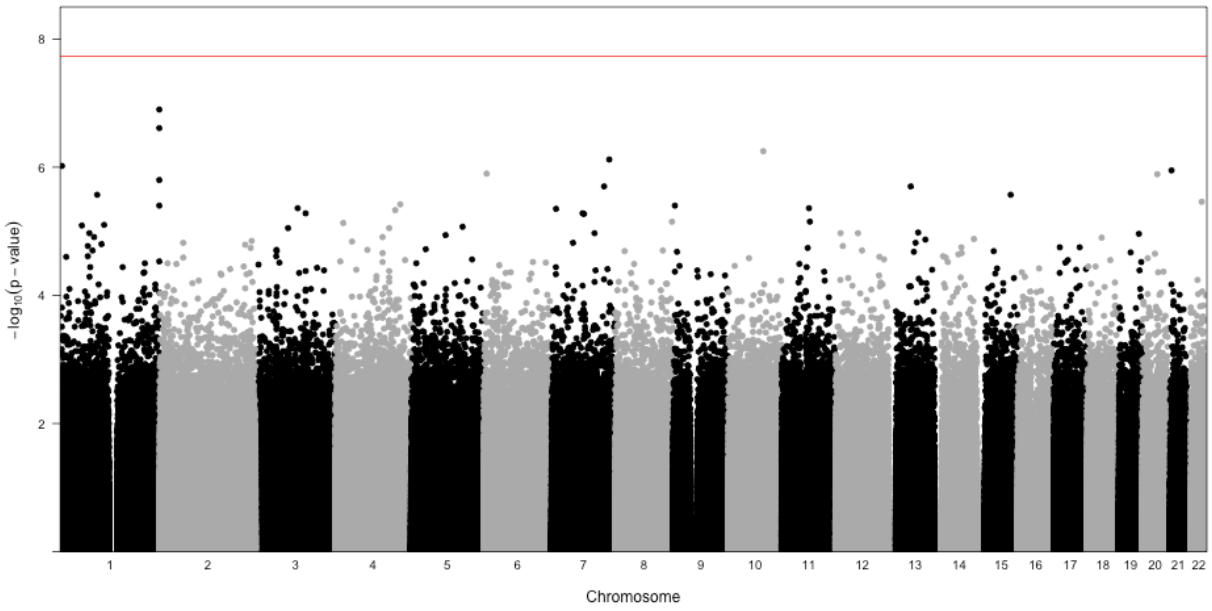
f. Fasting Insulin, SKAT (1,25)



g. Fasting Insulin, Burden (1,1)



h. Fasting Insulin, Burden (1,25)



Supplementary Tables

Supplementary Table 1. Description of TOPMed studies included in glycemic trait analysis

TOPMed Project	TOPMed Accession	Parent Study Accession	TOPMed Study	Study/Cohort Abbreviation	Country	Study Design	FG Unit	FG Source	FI Unit
Amish	phs000956		Genetics of Cardiometabolic Health in the Amish	Amish	USA	Community-based	mmol/l	Plasma	mU/l
AFGen - VTE	phs001211	phs000280	Trans-Omics for Precision Medicine Whole Genome Sequencing Project: ARIC	ARIC	USA	Population-based/ Case-ascertained	mmol/l	Serum	mU/l
CFS	phs000954	phs000284	The Cleveland Family Study (WGS)	CFS	USA	family-based	mmol/l	Plasma	mU/l
VTE	phs001368	phs000287	Cardiovascular Health Study	CHS	USA	Population-based	mmol/l	Plasma	pmol/L
AFGen, FHS	phs000974	phs000007	Whole Genome Sequencing and Related Phenotypes in the Framingham Heart Study	FHS	USA	Population-based	mmol/l	Plasma	mU/l
AA_CAC - GeneSTAR	phs001218	phs001074	GeneSTAR (Genetic Study of Atherosclerosis Risk)	GeneSTAR	USA	Family-based	mmol/l	Serum	pmol/L
AA_CAC - HyperGEN_GENOA	phs001345	phs001238	Genetic Epidemiology Network of Arteriopathy (GENOA)	GENOA	USA	Cohort of sibships enriched for hypertension	mmol/l	Plasma	pmol/L
GenSalt	phs001217	phs000784	Genetic Epidemiology Network of Salt Sensitivity (GenSalt)	GenSalt	China	Longitudinal family study	mmol/l	Plasma	N/A
GOLDN	phs001359	phs000741	Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)	GOLDN	USA	population based	mg/dl	Plasma	mU/l
HyperGEN_GENOA	phs001293		HyperGEN - Genetics of Left Ventricular (LV) Hypertrophy	HyperGEN	USA	population based	mg/d	Plasma	mU/l
JHS	phs000964	phs000286	The Jackson Heart Study	JHS	USA	Population-based	mmol/l	Plasma	pmol/L
AA_CAC - MESA	phs001416	phs000209	MESA and MESA Family AA-CAC	MESA	USA	Population-based	mmol/l	Serum	mU/l
SAFS	phs001215		San Antonio Family Heart Study (WGS)	SAFS	USA	Pedigree-based random ascertainment	mmol/l	Plasma	pmol/l
Samoan	phs000972	phs000914	Genome-wide Association Study of Adiposity in Samoans	Samoan	Samoa	Population-based	mmol/l	Serum	mU/l
WHI	phs001237	phs000200	Women's Health Initiative (WHI)	WHI	USA	Population-based	mmol/l	Serum	pmol/L

Supplementary Table 2. Demographic characteristics of cohorts included in fasting glucose analysis

Study	N	Male (%)	Female (%)	Age (SD)	African (%)	Asian (%)	European (%)	Hispanic / LatinX (%)	Samoan (%)	FG (SD[a])
Amish	908	454 (50%)	454 (50%)	49.7 (16.5)			908 (100%)			4.78 (0.58)
ARIC	2776	1308 (47.1%)	1468 (52.9%)	54.5 (5.7)	148 (5.3%)		2628 (94.7%)			5.43 (0.46)
CFS	427	174 (40.7%)	253 (59.3%)	37.7 (18.1)	236 (55.3%)		191 (44.7%)			5.68 (0.52)
CHS	60	23 (38.3%)	37 (61.7%)	72.9 (5.3)	9 (15%)		51 (85%)			5.43 (0.54)
FHS	2896	1348 (46.5%)	1548 (53.5%)	48.5 (11.9)			2896 (100%)			5.23 (0.51)
GeneSTAR	1371	563 (41.1%)	808 (58.9%)	42.7 (10.4)	587 (42.8%)		784 (57.2%)			4.99 (0.58)
GENOA	807	247 (30.6%)	560 (69.4%)	56.3 (10.7)	807 (100%)					5.18 (0.6)
GenSalt	1635	873 (53.4%)	762 (46.6%)	38.6 (9.5)		1635 (100%)				4.79 (0.58)
GOLDN	807	382 (47.3%)	425 (52.7%)	46.6 (16.3)			807 (100%)			5.42 (0.5)
HyperGEN	1349	516 (38.3%)	833 (61.7%)	44.8 (12.6)	1349 (100%)					5.17 (0.59)
JHS	2321	889 (38.3%)	1432 (61.7%)	54 (13)	2321 (100%)					5.01 (0.5)
MESA	3648	1770 (48.5%)	1878 (51.5%)	60.8 (9.9)	815 (22.3%)	478 (13.1%)	1580 (43.3%)	775 (21.2%)		4.95 (0.57)
SAFS	1004	426 (42.4%)	578 (57.6%)	39.5 (15.7)				1004 (100%)		5.02 (0.55)
Samoan	914	357 (39.1%)	557 (60.9%)	43.3 (11.1)					914 (100%)	4.93 (0.75)
WHI	5884		5884 (100%)	66.7 (6.9)	902 (15.3%)	104 (1.8%)	4668 (79.3%)	210 (3.6%)		5.05 (0.5)
Overall	26807	9330 (34.8%)	17477 (65.2%)	53.8 (14.3)	7174 (26.8%)	2217 (8.3%)	14513 (54.1%)	1989 (7.4%)	914 (3.4%)	5.09 (0.57)

[a] SD, standard deviation

Supplementary Table 3. Demographic characteristics of cohorts included in fasting insulin analysis

Study	N	Male (%)	Female (%)	Age (SD)	African (%)	Asian (%)	European (%)	Hispanic / LatinX (%)	Samoan (%)	FG (SD[a])
Amish	898	448 (49.9%)	450 (50.1%)	49.7 (16.6)			898 (100%)			2.18 (0.48)
ARIC	2712	1278 (47.1%)	1434 (52.9%)	54.4 (5.7)	135 (5%)		2577 (95%)			2.11 (0.65)
CFS	424	173 (40.8%)	251 (59.2%)	37.7 (18.1)	236 (55.7%)		188 (44.3%)			2.28 (0.6)
CHS	59	23 (39%)	36 (61%)	73 (5.3)	9 (15.3%)		50 (84.7%)			2.6 (0.44)
FHS	2730	1275 (46.7%)	1455 (53.3%)	48.6 (12)			2730 (100%)			3.31 (0.39)
GeneSTAR	449	175 (39%)	274 (61%)	48.2 (7.9)	257 (57.2%)		192 (42.8%)			2.05 (0.65)
GENOA	806	246 (30.5%)	560 (69.5%)	56.3 (10.7)	806 (100%)					2.24 (0.75)
GOLDN	805	380 (47.2%)	425 (52.8%)	46.6 (16.3)			805 (100%)			2.46 (0.47)
HyperGEN	1347	517 (38.4%)	830 (61.6%)	44.8 (12.6)	1347 (100%)					2.01 (0.7)
JHS	2310	888 (38.4%)	1422 (61.6%)	54 (13)	2310 (100%)					2.62 (0.53)
MESA	3648	1770 (48.5%)	1878 (51.5%)	60.8 (9.9)	815 (22.3%)	478 (13.1%)	1580 (43.3%)	775 (21.2%)		1.65 (0.62)
SAFS	660	257 (38.9%)	403 (61.1%)	43.9 (15.2)				660 (100%)		2.76 (0.59)
Samoan	914	357 (39.1%)	557 (60.9%)	43.3 (11.1)					914 (100%)	2.41 (0.79)
WHI	5449		5449 (100%)	66.5 (7)	888 (16.3%)	94 (1.7%)	4261 (78.2%)	206 (3.8%)		2.01 (0.59)
Overall	23211	7787 (33.5%)	15424 (66.5%)	55.5 (13.5)	6803 (29.3%)	572 (2.5%)	13281 (57.2%)	1641 (7.1%)	914 (3.9%)	2.25 (0.76)

[a] SD, standard deviation

Supplementary Table 4. Haplotype analysis of the *G6PC2* locus

Marginal Effects with Respect to Effect Allele									
Position[a]	**Signal**	**RSID**	**EA[b]**	**EAF[c]**	**EAC[d]**	**N**	**P-Value**	**Beta**	**SE**
2:168906638:T:C	GWAS, Primary signal	rs560887	C	0.82	43730	26807	6.8E-37	0.0717	0.0057
2:168900420:A:G	Secondary signal	rs540524	A	0.66	35607	26807	8.4E-02	0.0080	0.0046
2:168907981:T:C	Tertiary/Rare Variant signal	rs2232326	T	0.99	53345	26807	3.8E-05	0.1346	0.0327
2:168907631:A:C	Rare Variant signal, Mahajan - p.Tyr207Ser	rs2232323	A	0.99	53302	26807	1.8E-04	0.1038	0.0277
2:168906752:C:T	Mahajan - p.His177Tyr	rs138726309	C	0.99	53511	26807	2.9E-02	0.1000	0.0458
2:168907666:G:C	Mahajan - p.Val219Leu	rs492594	C	0.41	22387	26807	9.9E-01	0.0001	0.0044

Previous Haplotype Variants				Secondary	Tertiary/Rare Variant			
2:168906638 rs560887	**2:168906752 rs138726309**	**2:168907631 rs2232323**	**2:168907666 rs492594**	**2:168900420 rs540524**	**2:168907981 rs2232326**	**Frequency**	**Beta**	**SE**
C	C	A	C[e]	G[e]	T	0.32	Baseline	
				A	T	0.01	0.03	3.9E-03
				G[e]	C[e]	0.001	-0.15	2.4E-05
T[e]	C	A	G	A	T	0.19	-0.05	5.8E-03
C	C	A	G	A	C[e]	0.003	-0.09	4.1E-05
				A	T	0.37	0.04	4.9E-03
				G[e]	T	0.02	0.04	1.6E-04
T[e]	C	C[e]	G	A	T	0.006	-0.11	7.5E-05
C	T[e]	A	C[e]	A	T	0.002	-0.09	3.3E-05

[a] Format: Chromosome, Position (Hg38), Reference Allele, Alternate Allele
[b] Effect Allele
[c] Effect Allele Frequency
[d] Effect Allele Count
[e] Glucose Lowering

Supplementary Table 5. Validation lookups of significant and suggestive novel signals in the UKBB

Trait	Gene	Chr[a]	Position (HG38)	Ref[b]	Alt[c]	rsID	Imputation r^2	N	ALT.AC[d]	MAC[e]	MAF[f]	P-value	Beta (Alt allele)	SE[g] Beta
Fasting Glucose	*MTNR1B*	11	9288161	G	A	rs73560545	1.00	12,798	3459	3459	0.14	9.3E-01	-7.7E-04	9.4E-03
	SLC30A8	8	117179236	C	T	rs35859536	1.00	12,798	8105	8105	0.32	4.6E-05	-2.8E-02	6.9E-03
	APOB	2	21074277	A	G	rs478588	1.00	12,798	20539	5057	0.80	1.1E-02	2.0E-02	8.1E-03
	ADCY5	3	123335923	A	C	rs72964564	0.99	12,798	6438	6438	0.25	1.0E-07	-3.9E-02	7.4E-03
	HS6ST3/UGGT2	13	96407609	A	G	rs1328056	1.00	12,798	1536	1536	0.06	5.7E-01	7.8E-03	1.4E-02
	CTD-2199O4.4/ ATPSCKMT/CCT5	5	10169711	T	C	rs13361160	1.00	12,798	11095	11095	0.43	6.3E-01	3.1E-03	6.4E-03

[a] Chromosome, [b] Reference Allele, [c] Alternative Allele, [d] Alternative Allele Count, [e] Minor Allele Count, [f] Minor Allele Frequency, [g] Standard Error

Supplementary Table 6. Validation lookups of significant and suggestive novel signals in METSIM cohorts

Trait	Gene	Chr[a]	Position (HG38)	Ref[b]	Alt[c]	rsID	Imputation r^2	N	ALT.AC[d]	MAC[e]	MAF[f]	P-value	Beta (Alt allele)	SE[g] Beta
Fasting Glucose	*MTNR1B*	11	92884161	G	A	rs73560545	0.99	10058	3201.42	3201	0.16	0.853	0.004	0.021
	SLC30A8	8	117179236	C	T	rs35859536	0.99	10058	7898.28	7898	0.39	0.000	-0.073	0.016
	SLC30A8	8	117258547	C	T	rs542965166	0.01	10058	0.29	0.29	0.00001	NA	NA	NA
	APOB	2	21074277	A	G	rs478588	0.99	10058	15779.39	4336.	0.22	0.128	-0.029	0.019
	ADCY5	3	123335923	A	C	rs72964564	0.99	10058	3231.05	3231	0.16	0.071	-0.037	0.021
	HS6ST3	13	96407609	A	G	rs1328056	0.95	10058	1425.58	1425	0.07	0.526	0.019	0.030
	CTD-2199C04.4	5	10169711	T	C	rs13361160	0.99	10058	8288.41	8288	0.41	0.875	0.002	0.015
Fasting Insulin	*PTPRT*	20	42752773	G	A	rs185250851	0.98	10058	8.77	8	0.0004	0.051	0.351	0.180
	PTPRT	20	43230137	C	T	rs78618809	0.29	10058	0.56	0.56	0.00003	0.514	-0.862	1.321
	ROBO1	3	79812347	C	A	rs539973028	0	10058	0	0	0	NA	NA	NA
	LINC00704, LINC00705	10	4656482	GAAAAT	G	rs775018107	0.05	10058	0.82	0.82	0.00004	0.575	-0.870	1.553
	RP11/IGSF11	3	118656074	T	G	rs117592405	0.99	10058	131.47	131	0.007	0.438	-0.036	0.047

[a] Chromosome, [b] Reference Allele, [c] Alternative Allele, [d] Alternative Allele Count, [e] Minor Allele Count, [f] Minor Allele Frequency, [g] Standard Error

Supplementary Table 7. Validation lookups of novel suggestive signals in the Samoan cohort

Trait	Gene	Chr[a]	Position (HG38)	Ref[b]	Alt[c]	rsID	Imputation r^2	N	ALT.AC[d]	MAC[e]	MAF[f]	P-value	Beta (Alt allele)	SE[g] Beta
Fasting Insulin	*RP11/IGSF11*	3	118656074	T	G	rs117592405	0.98	1401	22	22	0.008	0.089	-0.233	0.137

[a] Chromosome, [b] Reference Allele, [c] Alternative Allele, [d] Alternative Allele Count, [e] Minor Allele Count, [f] Minor Allele Frequency, [g] Standard Error

Supplementary Table 8. Enrichment of Chromatin States at significant and suggestive Fasting Glucose signals

Tissue	Chromatin State	1000G Reference Population for LD	#SNPs in Chrom State	Expected #SNPS in Chrom State	P-Value
Islets	Active Enhancer 2	AF	6	1.4	0.0011
Islets	Active Enhancer 2	AS	7	2.6	0.0036
Islets	Active Enhancer 2	EU	8	2.8	0.0014
Islets	Active Enhancer 2	HS	7	2.6	0.0056
Islets	Weak Transcription	AF	10	5.2	0.0064
Islets	Weak Transcription	AS	12	6.5	0.0013
Islets	Weak Transcription	EU	11	6.7	0.013
Islets	Weak Transcription	HS	12	6.3	0.0012
Islets	Genic Enhancer	HS	3	0.6	0.014
Islets	Genic Enhancer	AS	1	0.0	0.022

Supplementary Table 9. Number of rare variant sets by phenotype and set-type

Mask	Number of tests - FG	Number of tests - FI
Enhancer	58677	58642
Missense	18256	18237
Putative loss of function	13723	13161
Promoter	20525	20496
Synonymous	18199	18182
All Masks	129380	128718

Supplementary Data 1. 95% Credible Sets for all Reported Loci
See Supplementary Data Excel Sheet

Supplementary Data 2. 99% Credible Sets for Reported Loci from Pooled Analysis with <50 Variants
See Supplementary Data Excel Sheet

Supplementary Data 3. References for previous identification of variants in this study
See Supplementary Data Excel Sheet

Supplementary Data 4. Reference for previous identification of gene regions in this study
See Supplementary Data Excel Sheet

Supplementary Data 5. Lookups in related traits of identified loci in TOPMed projects
See Supplementary Data Excel Sheet

Supplementary Data 6. Significant Results of genome wide Fasting Glucose gene-centric rare variant aggregate tests
See Supplementary Data Excel Sheet

Supplementary Data 7. Significant Results of genome wide Fasting Glucose genetic-regions (sliding window) rare variant aggregate tests
See Supplementary Data Excel Sheet

Supplementary Data 8. Significant Results of genome wide log Fasting Insulin gene-centric rare variant aggregate tests.
See Supplementary Data Excel Sheet

Supplementary Data 9. Significant Results of genome wide log Fasting Insulin genetic-regions (sliding window) rare variant aggregate tests
See Supplementary Data Excel Sheet