

# S1 APPENDIX

## GENOME-WIDE ASSOCIATION STUDIES IN SAMOANS GIVE INSIGHT INTO THE GENETIC ETIOLOGY OF FASTING SERUM LIPID LEVELS

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## 1. AUTHOR CONTRIBUTIONS

R.L.M. performed the genotype quality control and association analyses, with guidance from D.E.W.; J.C.C. created the figures and wrote the relevant sections of the manuscript with guidance from D.E.W, R.L.M, S.T.M, and N.L.H; D.E.W. carried out the MAGENTA and INRICH analyses and assembled the Supplementary Information; N.L.H. led the field work data collection and phenotype analyses with guidance from S.T.M. G.S. led and directed genotyping experiments (using the Affymetrix 6.0 chip) and assay development for validation and replication (using the TaqMan platform) with guidance from R.D. H.C. participated extensively in DNA extraction, genotyping, and quality control of the data under the supervision of G.S. and R.D. M.S.R. and J.T. facilitated fieldwork in Samoa and American Samoa. T.N. contributed to the discussion of the public health implications of the findings. All authors contributed to this work, discussed the results, and critically reviewed and revised the manuscript.

## 2. TOTAL CHOLESTEROL (TC)

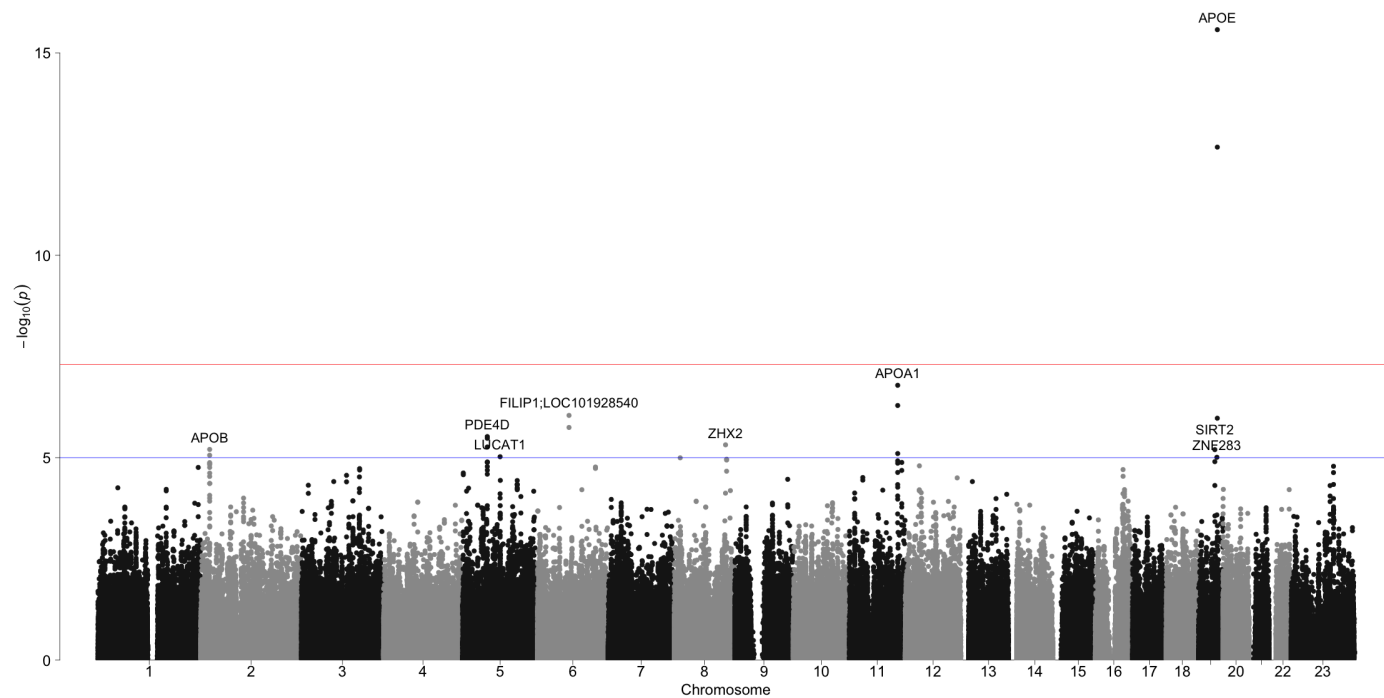


FIGURE S1. TC: genome-wide association scan

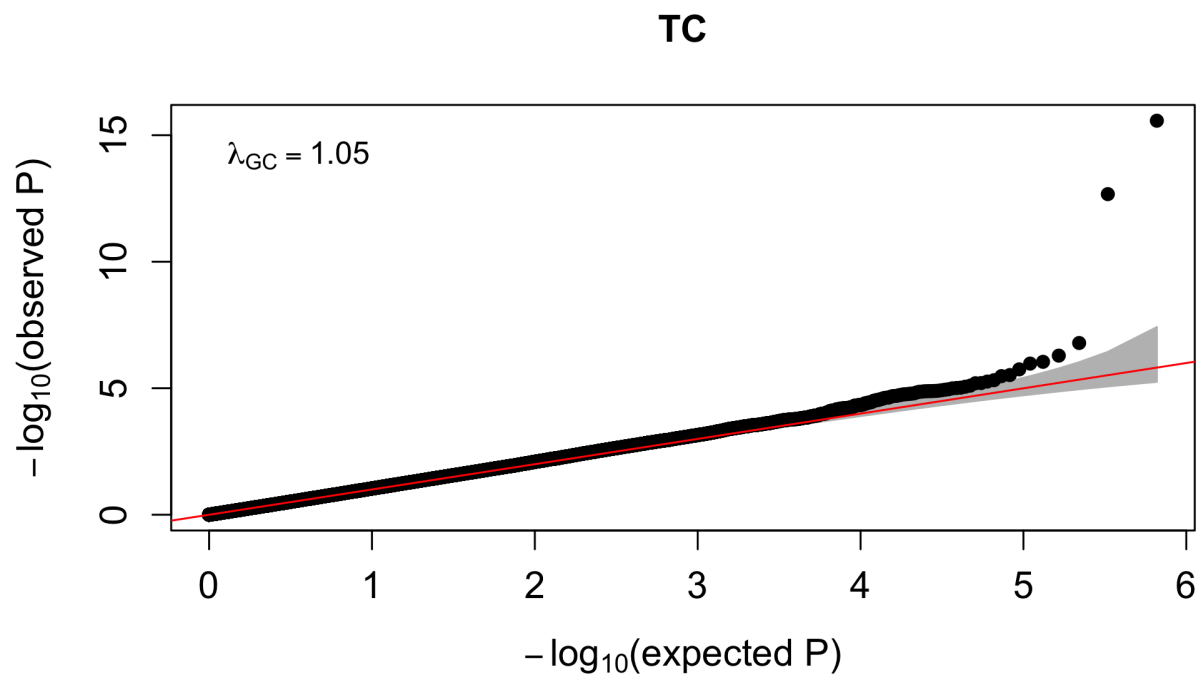


FIGURE S2. TC: QQ plot

TABLE S1. TC results. See Table S2 for a description of the column contents. Significant P values less than  $5 \times 10^{-8}$  are in **bold**, while suggestive P values between  $1 \times 10^{-5}$  and  $5 \times 10^{-8}$  are in *dark red italics*.

Label	SNP	CHR	POS	$P_D$	$P_U$	$P_A$	$P_R$	$P_{DR}$
APOE	rs1160985	19	45403412	<b>2.13E-13</b>	8.74E-05	<i>9.34E-06</i>	<b>3.36E-09</b>	<b>4.29E-21</b>
APOA1	rs964184	11	116648917	5.37E-05	0.007	0.237	0.009	<i>1.72E-06</i>
APOB	rs754523	2	21311691	<i>6.25E-06</i>	0.116	0.647	0.178	1.20E-05
ZHX2	rs7841763	8	123971081	<i>4.82E-06</i>	0.517	0.925	0.631	1.03E-04
PDE4D	rs7711093	5	59593138	<i>3.01E-06</i>	0.810	0.542	0.747	5.37E-04
FILIP1;LOC101928540	rs2951921	6	76165524	<i>9.04E-07</i>	NA	NA	NA	NA
SIRT2	rs10405150	19	39387919	<i>6.34E-06</i>	NA	NA	NA	NA
LUCAT1	rs10072084	5	90539203	<i>9.48E-06</i>	NA	NA	NA	NA
ZNF283	rs16976816	19	44339377	<i>9.78E-06</i>	NA	NA	NA	NA

Label	SNP	CHR	POS	$z_D$	$z_U$	$z_A$	Dir	$n_D$	$n_U$	$n_A$	$n_R$	$n_{DR}$
APOE	rs1160985	19	45403412	7.34	3.92	4.43	+++	2849	704	1077	1781	4630
APOA1	rs964184	11	116648917	4.04	2.68	1.18	+++	2849	710	1080	1790	4639
APOB	rs754523	2	21311691	4.52	1.57	0.46	+++	2848	709	1078	1787	4635
ZHX2	rs7841763	8	123971081	4.57	0.65	0.09	+++	2849	708	1078	1786	4635
PDE4D	rs7711093	5	59593138	4.67	0.24	-0.61	++-	2849	706	1079	1785	4634
FILIP1;LOC101928540	rs2951921	6	76165524	4.91	NA	NA	+??	2849	NA	NA	NA	NA
SIRT2	rs10405150	19	39387919	4.52	NA	NA	+??	2849	NA	NA	NA	NA
LUCAT1	rs10072084	5	90539203	4.43	NA	NA	+??	2849	NA	NA	NA	NA
ZNF283	rs16976816	19	44339377	4.42	NA	NA	+??	2849	NA	NA	NA	NA

Label	SNP	CHR	POS	eafD	eafU	eafA	SAM	EAS	SAS	EUR	AMR	AFR	eA	oA
APOE	rs1160985	19	45403412	0.732	0.712	0.709	0.724	0.659	0.590	0.554	0.447	0.378	C	T
APOA1	rs964184	11	116648917	0.430	0.453	0.457	0.440	0.240	0.229	0.162	0.277	0.221	G	C
APOB	rs754523	2	21311691	0.254	0.248	0.228	0.247	0.265	0.140	0.309	0.306	0.201	G	A
ZHX2	rs7841763	8	123971081	0.040	0.047	0.047	0.043	0.023	0.146	0.102	0.058	0.169	T	C
PDE4D	rs7711093	5	59593138	0.509	0.522	0.488	0.506	0.643	0.553	0.856	0.775	0.852	G	A
FILIP1;LOC101928540	rs2951921	6	76165524	0.073	NA	NA	0.073	0.022	0.063	0.015	0.030	0.293	T	C
SIRT2	rs10405150	19	39387919	0.056	NA	NA	0.056	0.147	0.144	0.081	0.117	0.774	C	T
LUCAT1	rs10072084	5	90539203	0.541	NA	NA	0.541	0.559	0.422	0.232	0.429	0.822	C	T
ZNF283	rs16976816	19	44339377	0.977	NA	NA	0.977	0.970	0.994	0.987	0.976	0.864	G	A

Label	SNP	CHR	POS	known	traitW	GeneUp	DistanceUp	GeneDown	DistanceDown
APOE	rs1160985	19	45403412	APOE	C H L T	TOMM40	0	TOMM40	0
APOA1	rs964184	11	116648917	APOA1	C H L T	ZPR1	0	ZPR1	0
APOB	rs754523	2	21311691	APOB	C H L T	APOB	44746	TDRD15	35166
ZHX2	rs7841763	8	123971081	NA	NA	ZHX2	0	ZHX2	0
PDE4D	rs7711093	5	59593138	NA	NA	PDE4D	0	PDE4D	0
FILIP1;LOC101928540	rs2951921	6	76165524	NA	NA	FILIP1;LOC101928540	0	FILIP1;LOC101928540	0
SIRT2	rs10405150	19	39387919	NA	NA	SIRT2	0	SIRT2	0
LUCAT1	rs10072084	5	90539203	NA	NA	ADGRV1	79170	LUCAT1	59599
ZNF283	rs16976816	19	44339377	NA	NA	ZNF283	0	ZNF283	0

Label	SNP	CHR	POS	$P_D$	$P_R$	$P_{DR}$	gwasPeak	gwasP
APOE	rs1160985	19	45403412	<b>2.13E-13</b>	<b>3.36E-09</b>	<b>4.29E-21</b>	rs4420638	<b>2.67E-16</b>
APOA1	rs964184	11	116648917	5.37E-05	0.009	<i>1.72E-06</i>	rs3741298	<i>1.63E-07</i>
APOB	rs754523	2	21311691	<i>6.25E-06</i>	0.178	1.20E-05	NA	NA
ZHX2	rs7841763	8	123971081	<i>4.82E-06</i>	0.631	1.03E-04	NA	NA
PDE4D	rs7711093	5	59593138	<i>3.01E-06</i>	0.747	5.37E-04	NA	NA
FILIP1;LOC101928540	rs2951921	6	76165524	<i>9.04E-07</i>	NA	NA	NA	NA
SIRT2	rs10405150	19	39387919	<i>6.34E-06</i>	NA	NA	NA	NA
LUCAT1	rs10072084	5	90539203	<i>9.48E-06</i>	NA	NA	NA	NA
ZNF283	rs16976816	19	44339377	<i>9.78E-06</i>	NA	NA	NA	NA

TABLE S2. Descriptions of the columns in the GWAS results tables.

Column	Description
Label	Label for the locus derived from the list of known loci as labeled by Teslovich et al. and Willer et al., or if novel, the nearest gene.
SNP	SNP RS ID
CHR	chromosome
POS	physical position (hg19) in base pairs
$P_D$	p-value in the GWAS Samoans from the 2010s (the discovery cohort)
$P_U$	p-value in the unrelated Samoans from 1990s (the 1990-95 replication cohort)
$P_A$	p-value in the adult Samoans from the 2000s (the 2002-03 replication cohort)
$P_R$	meta-analysis p-value of the 1990s and 2000s samples
$P_{DR}$	meta-analysis p-value of the 1990s, 2000s and 2010s samples.
$z_D$	z-score, computed from the p-value, in the GWAS (all z-scores are for the transformed trait)
$z_U$	z-score, computed from the p-value, in the unrelated Samoans from the 1990s

$z_A$	z-score, computed from the p-value, in the adult Samoans from the 2000s
Dir	direction of the effect in each of the four samples (+ indicates the effect allele is increasing the trait value on the raw scale)
$n_D$	sample size in the GWAS Samoans from the 2010s
$n_U$	sample size in the unrelated Samoans from 1990s
$n_A$	sample size in the adult Samoans from the 2000s
$n_R$	meta-analysis sample size of the 1990s and 2000s samples
$n_{DR}$	meta-analysis sample size of the 1990s, 2000s and 2010s samples.
eafD	effect allele frequency in the GWAS Samoans from the 2010s
eafU	effect allele frequency in the unrelated Samoans from 1990s
eafA	effect allele frequency in the adult Samoans from the 2000s
SAM	effect allele frequency in all Samoans
EAS	effect allele frequency in individuals of East Asian descent from the 1000 Genomes Project
SAS	effect allele frequency in individuals of South Asian descent from the 1000 Genomes Project
EUR	effect allele frequency in individuals of European descent from the 1000 Genomes Project
AMR	effect allele frequency in individuals of admixed American descent from the 1000 Genomes Project
AFR	effect allele frequency in individuals of African descent from the 1000 Genomes Project
eA	effect allele (the effect allele is the one associated with a poorer health outcome)
oA	other allele
known	known lipid-levels locus from Teslovich et al. 2010 and Willer et al. 2013
traitW	traits associated with the locus listed in the 'known' column (C = Cholesterol, H = HDL, L = LDL, T = Triglycerides)
GeneUp	nearest gene upstream of the SNP
DistanceUp	distance in base pairs to nearest upstream gene (if 0 the SNP is within the transcription boundaries of the gene(s))
GeneDown	nearest gene downstream of the SNP
DistanceDown	distance in base pairs to nearest downstream gene (if 0 the SNP is within the transcription boundaries of the gene(s))
gwasPeak	sometimes the most significant SNP at a particular locus was not examined using OpenArray, if another SNP at that same locus was more strongly associated with another trait. E.g., rs4420638 was the peak SNP associated with total cholesterol at the APOE locus. However, rs1160985, a SNP also at the APOE locus was associated with LDL with a smaller p value. We selected a single SNP at each locus to replicate across all the traits and so we replicated rs1160985 for total cholesterol. This column (gwasPeak) contains the SNP that was the peak SNP at this locus for this trait if it is other than the SNP that was replicated.
gwasP	GWAS p value for gwasPeak

TABLE S3. MAGENTA pathway analysis of TC. See Table S4 for a description of the column contents.

Database	Gene Set	Effective Gene Set Size	FDR (95% cutoff)	Exp. # Genes (>95% cutoff)	Obs. # Genes (>95% cutoff)	Trait-specific Known Genes
GOTERM	high-density lipoprotein particle remodeling	10	0.0186	1	5	APOA1, APOE, CETP, LIPC, LIPG
GOTERM	reverse cholesterol transport	13	0.03866667	1	5	ABCA1, APOA1, APOE, CETP, LIPC, HNF1A, LIPG

TABLE S4. Descriptions of the columns in the MAGENTA results tables.

Column	Description
Database	Pathway database
Gene Set	Gene set name
Effective Gene Set Size	Effective number of genes per gene set analyzed by GSEA, after removing genes that were not assigned a gene score (e.g. no SNPs in their region), or after adjusting for physical clustering of genes in a given gene set (removing all but one gene from a subset of genes assigned the same best SNP, keeping the gene with the most significant gene score)
FDR (95% cutoff)	Estimated false discovery rate (q-value) using the 95 percentile enrichment cutoff
Exp. # Genes (>95% cutoff)	Expected number of genes with a corrected gene p-value above the 95 percentile enrichment cutoff
Obs. # Genes (>95% cutoff)	Observed number of genes with a corrected gene p-value above the 95 percentile enrichment cutoff
Trait-specific Known Genes	Genes in the trait-specific list of known genes from Willer et al (2013) that belong to each gene set



TABLE S5. INRICH analysis of TC. See Table S6 for a description of the INRICH parameters used.

Gene Set Size	Number overlapping	Empirical P value	Corrected P value	Gene Set	Known overlapping genes
68	4	0.002931	0.00379981	Known TC genes	APOB, TRIB1, APOA1, APOE
67	6	3.5e-05	9.9995e-05	Known HDL genes	APOB, TRIB1, APOA1, SCARB1, LCAT, APOE
52	4	0.000792999	0.00164992	Known LDL genes	APOB, TRIB1, APOA1, APOE
41	4	0.000705999	0.00119994	Known TG genes	APOB, TRIB1, APOA1, APOE

TABLE S6. INRICH parameter settings.

Parameter	Value	Comment
gene-list (-g)	entrez_gene.hg19.map	Entrez genes
background-genes (-b)	--no background set--	
range-file (-x)	--no ranges--	
compact (-k)	YES	
target size-filter (-i,j)	2..200	
min-obs threshold (-z)	2	
test-type (-l)	INTERVALS	
top-N-regions (-n)	--all--	
kb-window (-w)	50000	Extend target gene regions 50 kb up/downstream
match-density (-d)	0.1	Allow mapping SNP density of 90-110%
pre-compute (-c)	YES	
match-genes (-e)	YES	
num-replicates (-r)	1000000	
num-bootstraps (-q)	20000	
display-p (-p)	1	

### 3. HDL

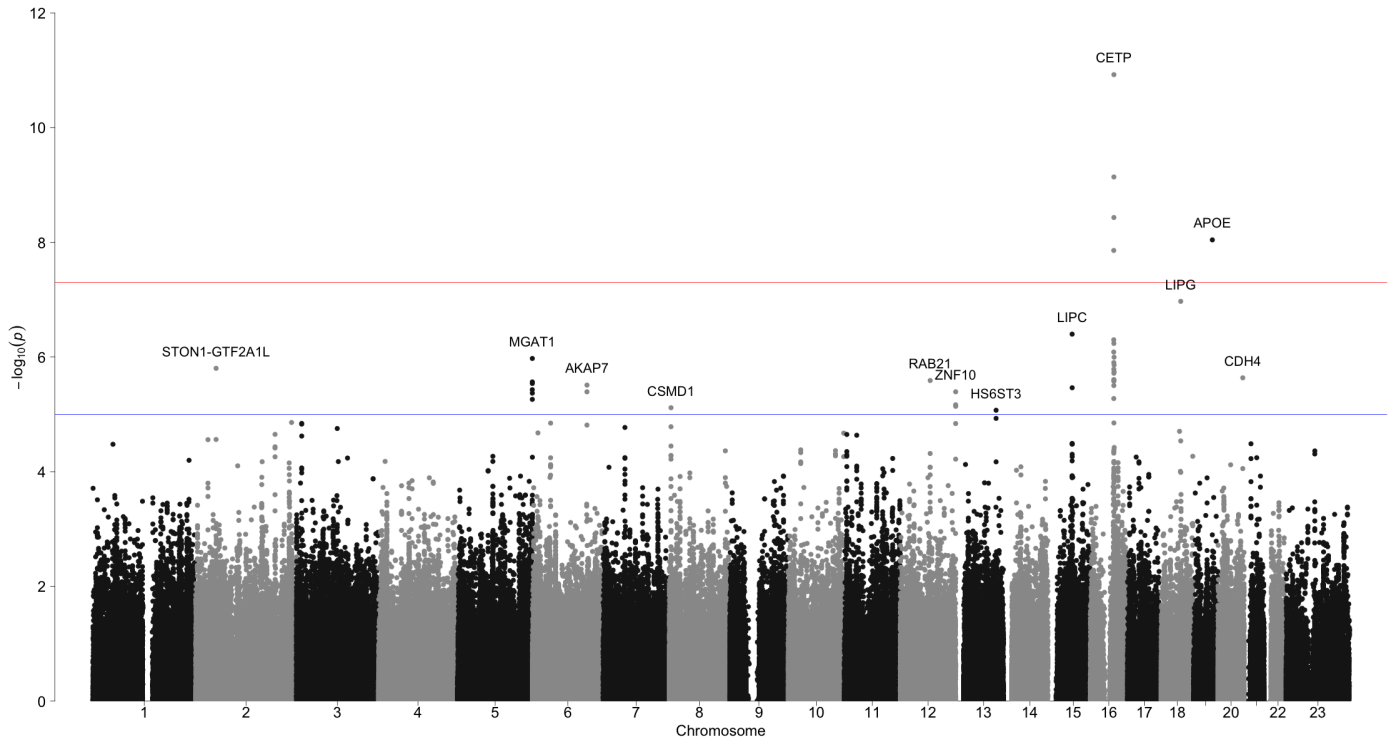


FIGURE S3. HDL: genome-wide association scan

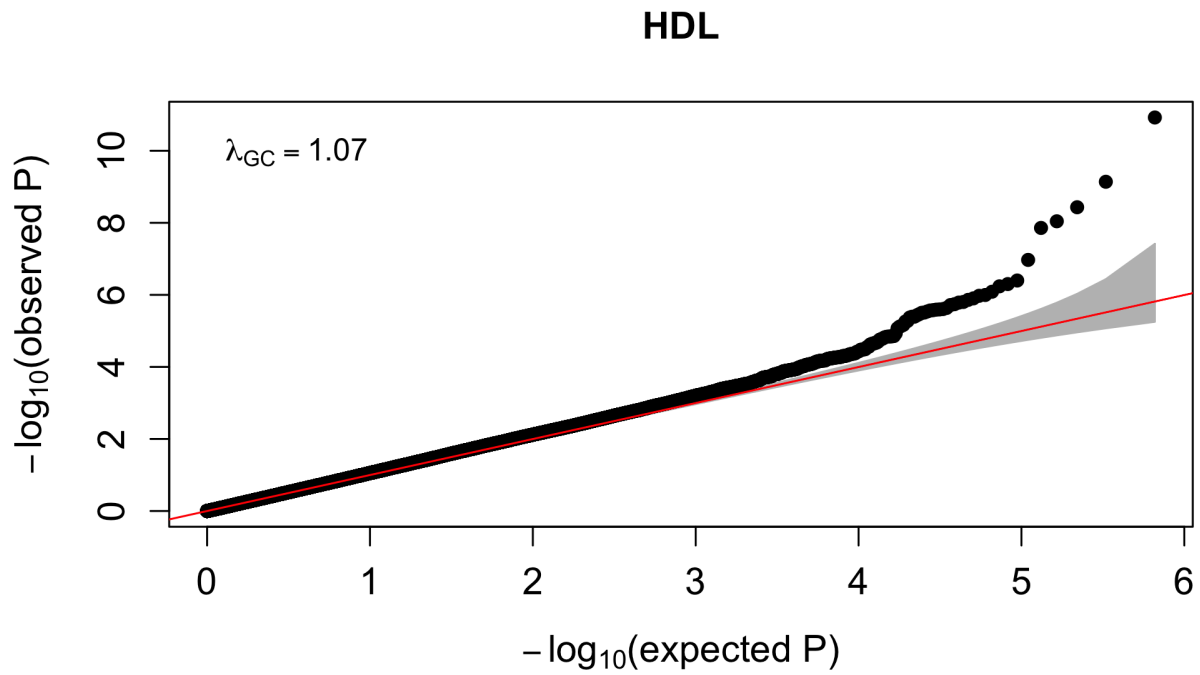


FIGURE S4. HDL: QQ plot

TABLE S7. HDL results. See Table S2 for a description of the column contents. Significant P values less than  $5 \times 10^{-8}$  are in **bold**, while suggestive P values between  $1 \times 10^{-5}$  and  $5 \times 10^{-8}$  are in *dark red italics*.

Label	SNP	CHR	POS	$P_D$	$P_U$	$P_A$	$P_R$	$P_{DR}$
MGAT1	rs1038143	5	180213878	<i>3.72E-06</i>	0.010	0.301	0.016	<i>2.91E-07</i>
RAB21	rs328733	12	72197574	<i>2.57E-06</i>	0.011	0.517	0.036	<i>5.92E-07</i>
LIPC	rs10438284	15	58629424	<i>4.00E-07</i>	0.905	0.043	0.133	<i>9.15E-07</i>
CDH4	rs817687	20	59753355	<i>2.31E-06</i>	0.206	0.615	0.237	<i>8.77E-06</i>
AKAP7	rs3777486	6	131584648	<i>3.09E-06</i>	0.050	0.212	0.808	4.37E-04
APOE	rs1160985	19	45403412	0.003	0.722	0.133	0.342	0.004
CETP	rs289708	16	57038162	<b>1.19E-11</b>	NA	NA	NA	NA
LIPG	rs16950739	18	47138509	<i>1.07E-07</i>	NA	NA	NA	NA
STON1-GTF2A1L	rs6739536	2	48831901	<i>1.58E-06</i>	NA	NA	NA	NA
ZNF10	rs2292029	12	133734113	<i>4.05E-06</i>	NA	NA	NA	NA
CSMD1	rs1626142	8	4345284	<i>7.67E-06</i>	NA	NA	NA	NA
HS6ST3	rs16953620	13	97508453	<i>8.48E-06</i>	NA	NA	NA	NA

Label	SNP	CHR	POS	$z_D$	$z_U$	$z_A$	Dir	$n_D$	$n_U$	$n_A$	$n_R$	$n_{DR}$
MGAT1	rs1038143	5	180213878	-4.63	-2.57	-1.04	---	2849	695	1071	1766	4615
RAB21	rs328733	12	72197574	-4.70	-2.55	-0.65	---	2849	697	1076	1773	4622
LIPC	rs10438284	15	58629424	-5.07	0.12	-2.02	-+-	2847	697	1077	1774	4621
CDH4	rs817687	20	59753355	-4.72	-1.27	-0.50	---	2840	678	1074	1752	4592
AKAP7	rs3777486	6	131584648	-4.67	1.96	-1.25	-+-	2847	682	1077	1759	4606
APOE	rs1160985	19	45403412	-2.96	0.36	-1.50	-+-	2849	692	1075	1767	4616
CETP	rs289708	16	57038162	-6.78	NA	NA	-??	2849	NA	NA	NA	NA
LIPG	rs16950739	18	47138509	-5.31	NA	NA	-??	2849	NA	NA	NA	NA
STON1-GTF2A1L	rs6739536	2	48831901	-4.80	NA	NA	-??	2847	NA	NA	NA	NA
ZNF10	rs2292029	12	133734113	-4.61	NA	NA	-??	2848	NA	NA	NA	NA
CSMD1	rs1626142	8	4345284	-4.47	NA	NA	-??	2756	NA	NA	NA	NA
HS6ST3	rs16953620	13	97508453	-4.45	NA	NA	-??	2847	NA	NA	NA	NA

Label	SNP	CHR	POS	eafD	eafU	eafA	SAM	EAS	SAS	EUR	AMR	AFR	eA	oA
MGAT1	rs1038143	5	180213878	0.310	0.303	0.311	0.309	0.110	0.137	0.148	0.081	0.013	A	G
RAB21	rs328733	12	72197574	0.788	0.799	0.782	0.788	0.626	0.700	0.869	0.738	0.611	T	C
LIPC	rs10438284	15	58629424	0.290	0.289	0.276	0.286	0.326	0.173	0.272	0.199	0.047	A	G
CDH4	rs817687	20	59753355	0.985	0.987	0.989	0.986	0.924	0.945	0.967	0.855	0.610	C	T
AKAP7	rs3777486	6	131584648	0.975	0.978	0.976	0.976	0.909	0.898	0.858	0.793	0.949	T	C
APOE	rs1160985	19	45403412	0.732	0.712	0.709	0.724	0.659	0.590	0.554	0.447	0.378	C	T
CETP	rs289708	16	57038162	0.905	NA	NA	0.905	0.815	0.800	0.860	0.823	0.597	G	A
LIPG	rs16950739	18	47138509	0.019	NA	NA	0.019	0.058	0.190	0.057	0.140	0.004	T	C
STON1-GTF2A1L	rs6739536	2	48831901	0.762	NA	NA	0.762	0.676	0.837	0.918	0.842	0.609	T	A
ZNF10	rs2292029	12	133734113	0.179	NA	NA	0.179	0.112	0.254	0.245	0.156	0.008	T	C
CSMD1	rs1626142	8	4345284	0.612	NA	NA	0.612	0.400	0.435	0.298	0.392	0.654	G	A
HS6ST3	rs16953620	13	97508453	0.968	NA	NA	0.968	0.950	0.949	0.848	0.911	0.836	A	G

Label	SNP	CHR	POS	known	traitW	GeneUp	DistanceUp	GeneDown	DistanceDown
MGAT1	rs1038143	5	180213878	NA	NA	OR2Y1	46820	MGAT1	3662
RAB21	rs328733	12	72197574	NA	NA	RAB21	10318	TBC1D15	35912
LIPC	rs10438284	15	58629424	LIPC	C H T	AQP9	151314	LIPC	94750
CDH4	rs817687	20	59753355	NA	NA	LINC01718	98120	CDH4	74126
AKAP7	rs3777486	6	131584648	NA	NA	AKAP7	0	AKAP7	0
APOE	rs1160985	19	45403412	APOE	C H L T	TOMM40	0	TOMM40	0
CETP	rs289708	16	57038162	CETP	C H L T	NLRC5	0	NLRC5	0
LIPG	rs16950739	18	47138509	LIPG	C H	LIPG	19230	ACAA2	171364
STON1-GTF2A1L	rs6739536	2	48831901	NA	NA	STON1-GTF2A1L	0	STON1-GTF2A1L	0
ZNF10	rs2292029	12	133734113	NA	NA	ZNF10	0	ZNF10	0
CSMD1	rs1626142	8	4345284	NA	NA	CSMD1	0	CSMD1	0
HS6ST3	rs16953620	13	97508453	NA	NA	HS6ST3	16637	LINC00359	85081

Label	SNP	CHR	POS	$P_D$	$P_R$	$P_{DR}$	gwasPeak	gwasP
MGAT1	rs1038143	5	180213878	<i>3.72E-06</i>	0.016	<i>2.91E-07</i>	rs249356	<i>1.06E-06</i>
RAB21	rs328733	12	72197574	<i>2.57E-06</i>	0.036	<i>5.92E-07</i>	NA	NA
LIPC	rs10438284	15	58629424	<i>4.00E-07</i>	0.133	<i>9.15E-07</i>	NA	NA
CDH4	rs817687	20	59753355	<i>2.31E-06</i>	0.237	<i>8.77E-06</i>	NA	NA
AKAP7	rs3777486	6	131584648	<i>3.09E-06</i>	0.808	4.37E-04	NA	NA
APOE	rs1160985	19	45403412	0.003	0.342	0.004	rs4420638	<b>9.07E-09</b>
CETP	rs289708	16	57038162	<b>1.19E-11</b>	NA	NA	NA	NA
LIPG	rs16950739	18	47138509	<i>1.07E-07</i>	NA	NA	NA	NA
STON1-GTF2A1L	rs6739536	2	48831901	<i>1.58E-06</i>	NA	NA	NA	NA
ZNF10	rs2292029	12	133734113	<i>4.05E-06</i>	NA	NA	NA	NA
CSMD1	rs1626142	8	4345284	<i>7.67E-06</i>	NA	NA	NA	NA
HS6ST3	rs16953620	13	97508453	<i>8.48E-06</i>	NA	NA	NA	NA

TABLE S8. MAGENTA pathway analysis of HDL. See Table S4 for a description of the column contents.

Database	Gene Set	Effective Gene Set Size	FDR (95% cutoff)	Exp. # Genes (>95% cutoff)	Obs. # Genes (>95% cutoff)	Trait-specific Known Genes
GOTERM	high-density lipoprotein particle remodeling	10	0	1	8	APOA1, APOE, SCARB1, CETP, LCAT, LIPC, LIPG
GOTERM	reverse cholesterol transport	13	0	1	9	ABCA1, APOA1, APOE, SCARB1, CETP, LCAT, LIPC, LIPG
GOTERM	high-density lipoprotein particle	15	3.333333e-05	1	8	APOA1, APOE, CETP, LCAT, LIPC
REACTOME	LIPOPROTEIN METABOLISM	24	8e-04	1	9	ABCA1, APOA1, APOB, APOE, SCARB1, CETP, LCAT, LIPC, LPL
REACTOME	HDL MEDIATED LIPID TRANSPORT	11	0.00315	1	5	ABCA1, APOA1, SCARB1, CETP, LCAT
GOTERM	cholesterol homeostasis	36	0.00508	2	10	ABCA1, APOA1, APOB, APOE, SCARB1, CETP, LCAT, LIPC, LIPG
GOTERM	phospholipid efflux	7	0.005225	0	4	ABCA1, APOA1, APOE

GOTERM	cholesterol efflux	16	0.006466667	1	6	ABCA1, APOA1, APOE, SCARB1
GOTERM	cholesterol transporter activity	12	0.007114286	1	5	ABCA1, APOA1, APOB, APOE, CETP, STARD3
GOTERM	cholesterol transport	12	0.0090625	1	5	APOA1, APOB, CETP, LCAT
GOTERM	cholesterol binding	18	0.009444444	1	6	ABCA1, APOA1, CETP, STARD3
Ingenuity	LXR.RXR.Activation	34	0.0129	2	8	ABCA1, APOA1, APOE, CETP, LCAT, LPL, PLTP
PANTHER BIOLOGICAL PROCESS	Other apoptosis	10	0.0146	1	4	SCARB1
REACTOME	CHYLOMICRON MEDIATED LIPID TRANSPORT	14	0.01463333	1	5	APOA1, APOB, APOE, LIPC, LPL
GOTERM	cholesterol catabolic process	10	0.0215	1	4	APOE, SCARB1
PANTHER MOLECULAR FUNCTION	Apolipoprotein	15	0.025	1	5	APOA1, APOB, APOE

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TABLE S9. INRICH analysis of HDL. See Table S6 for a description of the INRICH parameters used.

Gene Set Size	Number overlapping	Empirical P value	Corrected P value	Gene Set	Known overlapping genes
68	7	7.99999e-06	4.99975e-05	Known TC genes	RAF1, GPAM, APOA1, LIPC, CETP, LIPG, APOE
67	7	3.5e-05	9.9995e-05	Known HDL genes	VEGFA, APOA1, LIPC, CETP, LCAT, LIPG, APOE
52	4	0.002151	0.00654967	Known LDL genes	GPAM, APOA1, CETP, APOE
41	5	9.59999e-05	0.000349983	Known TG genes	VEGFA, APOA1, LIPC, CETP, APOE

#### 4. LDL

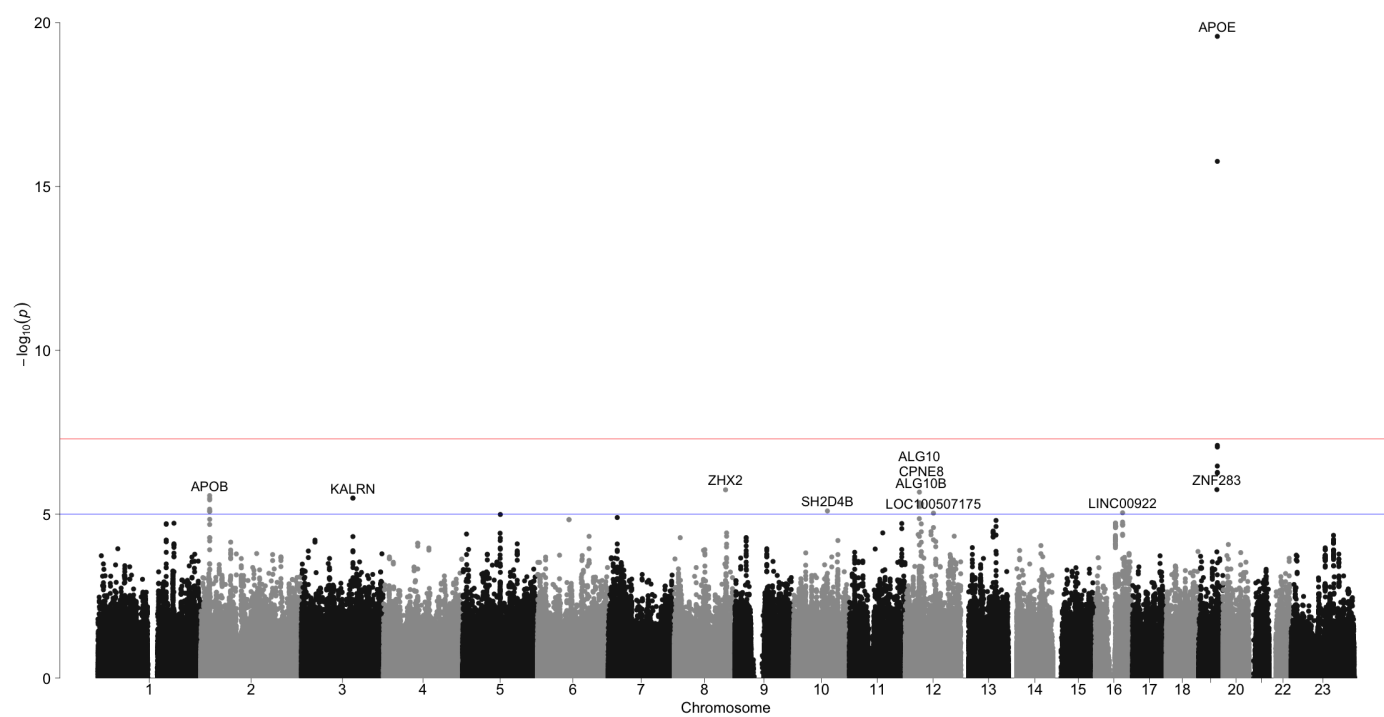


FIGURE S5. LDL: genome-wide association scan

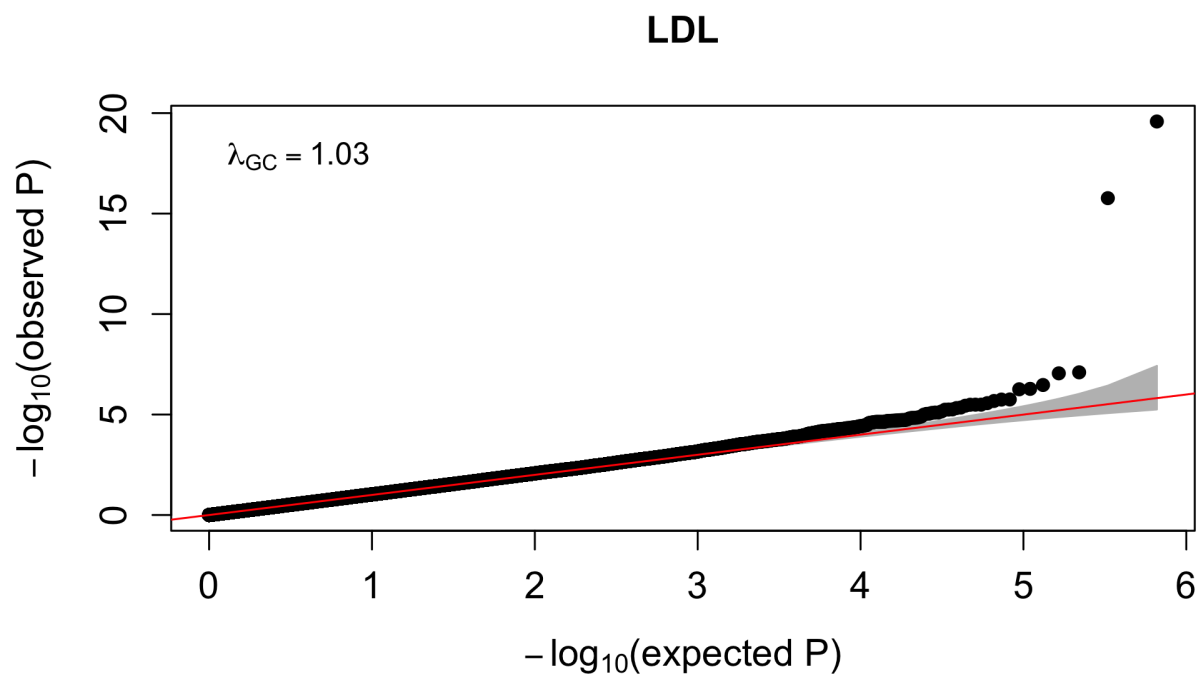


FIGURE S6. LDL: QQ plot

TABLE S10. LDL results. See Table S2 for a description of the column contents. Significant P values less than  $5 \times 10^{-8}$  are in **bold**, while suggestive P values between  $1 \times 10^{-5}$  and  $5 \times 10^{-8}$  are in *dark red italics*.

Label	SNP	CHR	POS	$P_D$	$P_U$	$P_A$	$P_R$	$P_{DR}$
APOE	rs1160985	19	45403412	<b>2.61E-20</b>	0.001	<i>7.88E-07</i>	<b>5.07E-09</b>	<b>1.53E-27</b>
APOB	rs754523	2	21311691	<i>3.25E-06</i>	0.247	0.381	0.158	<i>5.81E-06</i>
ZHX2	rs7841763	8	123971081	<i>1.80E-06</i>	0.293	0.920	0.557	3.78E-05
ALG10	rs3912355	12	34079616	<i>2.12E-06</i>	0.514	0.801	0.544	3.97E-05
CPNE8	rs11169807	12	39244161	<i>4.77E-06</i>	0.464	0.654	0.418	4.13E-05
KALRN	rs6789134	3	123942339	<i>3.22E-06</i>	0.497	0.667	0.925	1.96E-04
ZNF283	rs16976816	19	44339377	<i>1.78E-06</i>	NA	NA	NA	NA
ALG10B	rs10880642	12	38554152	<i>5.56E-06</i>	NA	NA	NA	NA
SH2D4B	rs10509415	10	82473065	<i>7.96E-06</i>	NA	NA	NA	NA
LINC00922	rs254371	16	65943650	<i>9.04E-06</i>	NA	NA	NA	NA
LINC02408	rs17104016	12	67969929	<i>9.29E-06</i>	NA	NA	NA	NA

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Label	SNP	CHR	POS	$z_D$	$z_U$	$z_A$	Dir	$n_D$	$n_U$	$n_A$	$n_R$	$n_{DR}$
APOE	rs1160985	19	45403412	9.23	3.19	4.94	+++	2842	692	1047	1739	4581
APOB	rs754523	2	21311691	4.65	1.16	0.88	+++	2841	697	1048	1745	4586
ZHX2	rs7841763	8	123971081	4.78	1.05	-0.10	++-	2842	696	1048	1744	4586
ALG10	rs3912355	12	34079616	4.74	0.65	0.25	+++	2833	688	1046	1734	4567
CPNE8	rs11169807	12	39244161	4.58	0.73	0.45	+++	2842	695	1050	1745	4587
KALRN	rs6789134	3	123942339	4.66	0.68	-0.43	++-	2842	692	1049	1741	4583
ZNF283	rs16976816	19	44339377	4.78	NA	NA	+??	2842	NA	NA	NA	NA
ALG10B	rs10880642	12	38554152	4.54	NA	NA	+??	2830	NA	NA	NA	NA
SH2D4B	rs10509415	10	82473065	4.47	NA	NA	+??	2842	NA	NA	NA	NA
LINC00922	rs254371	16	65943650	4.44	NA	NA	+??	2842	NA	NA	NA	NA
LINC02408	rs17104016	12	67969929	4.43	NA	NA	+??	2806	NA	NA	NA	NA

Label	SNP	CHR	POS	eafD	eafU	eafA	SAM	EAS	SAS	EUR	AMR	AFR	eA	oA
APOE	rs1160985	19	45403412	0.732	0.712	0.709	0.724	0.659	0.590	0.554	0.447	0.378	C	T
APOB	rs754523	2	21311691	0.254	0.247	0.229	0.247	0.265	0.140	0.309	0.306	0.201	G	A
ZHX2	rs7841763	8	123971081	0.040	0.047	0.049	0.043	0.023	0.146	0.102	0.058	0.169	T	C
ALG10	rs3912355	12	34079616	0.855	0.856	0.857	0.855	0.872	0.651	0.605	0.732	0.863	C	T
CPNE8	rs11169807	12	39244161	0.802	0.760	0.794	0.794	0.644	0.536	0.505	0.408	0.898	C	T
KALRN	rs6789134	3	123942339	0.079	0.074	0.076	0.078	0.161	0.120	0.046	0.118	0.212	G	A
ZNF283	rs16976816	19	44339377	0.977	NA	NA	0.977	0.970	0.994	0.987	0.976	0.864	G	A
ALG10B	rs10880642	12	38554152	0.802	NA	NA	0.802	0.715	0.555	0.481	0.532	0.299	A	G
SH2D4B	rs10509415	10	82473065	0.706	NA	NA	0.706	0.510	0.735	0.758	0.808	0.708	A	C
LINC00922	rs254371	16	65943650	0.555	NA	NA	0.555	0.698	0.650	0.599	0.693	0.884	T	C
LINC02408	rs17104016	12	67969929	0.574	NA	NA	0.574	0.734	0.924	0.853	0.906	0.838	A	T

Label	SNP	CHR	POS	known	traitW	GeneUp	DistanceUp	GeneDown	DistanceDown
APOE	rs1160985	19	45403412	APOE	C H L T	TOMM40	0	TOMM40	0
APOB	rs754523	2	21311691	APOB	C H L T	APOB	44746	TDRD15	35166
ZHX2	rs7841763	8	123971081	NA	NA	ZHX2	0	ZHX2	0
ALG10	rs3912355	12	34079616	NA	NA	SYT10	486862	ALG10	95599
CPNE8	rs11169807	12	39244161	NA	NA	CPNE8	0	CPNE8	0
KALRN	rs6789134	3	123942339	NA	NA	KALRN	0	KALRN	0
ZNF283	rs16976816	19	44339377	NA	NA	ZNF283	0	ZNF283	0
ALG10B	rs10880642	12	38554152	NA	NA	ALG10	4372916	ALG10B	156404
SH2D4B	rs10509415	10	82473065	NA	NA	SH2D4B	66749	NRG3	1162004
LINC00922	rs254371	16	65943650	NA	NA	LINC00922	333447	CDH5	456859
LINC02408	rs17104016	12	67969929	NA	NA	LINC02408	9018	DYRK2	72582

Label	SNP	CHR	POS	$P_D$	$P_R$	$P_{DR}$	gwasPeak	gwasP
APOE	rs1160985	19	45403412	<b>2.61E-20</b>	<b>5.07E-09</b>	<b>1.53E-27</b>	NA	NA
APOB	rs754523	2	21311691	<i>3.25E-06</i>	0.158	<i>5.81E-06</i>	rs1469513	<i>2.71E-06</i>
ZHX2	rs7841763	8	123971081	<i>1.80E-06</i>	0.557	3.78E-05	NA	NA
ALG10	rs3912355	12	34079616	<i>2.12E-06</i>	0.544	3.97E-05	NA	NA
CPNE8	rs11169807	12	39244161	<i>4.77E-06</i>	0.418	4.13E-05	NA	NA
KALRN	rs6789134	3	123942339	<i>3.22E-06</i>	0.925	1.96E-04	NA	NA
ZNF283	rs16976816	19	44339377	<i>1.78E-06</i>	NA	NA	NA	NA
ALG10B	rs10880642	12	38554152	<i>5.56E-06</i>	NA	NA	NA	NA
SH2D4B	rs10509415	10	82473065	<i>7.96E-06</i>	NA	NA	NA	NA
LINC00922	rs254371	16	65943650	<i>9.04E-06</i>	NA	NA	NA	NA
LINC02408	rs17104016	12	67969929	<i>9.29E-06</i>	NA	NA	NA	NA

TABLE S11. MAGENTA pathway analysis of LDL. See Table S4 for a description of the column contents.

Database	Gene Set	Effective Gene Set Size	FDR (95% cutoff)	Exp. # Genes (>95% cutoff)	Obs. # Genes (>95% cutoff)	Trait-specific Known Genes
PANTHER MOLECULAR FUNCTION	Amylase	4	0.19	0	2	-

TABLE S12. INRICH analysis of LDL. See Table S6 for a description of the INRICH parameters used.

Gene Set Size	Number overlapping	Empirical P value	Corrected P value	Gene Set	Known overlapping genes
68	5	8.29999e-05	0.000249988	Known TC genes	APOB, CMTM6, DNAH11, TRIB1, APOE
67	3	0.00803399	0.0148493	Known HDL genes	APOB, TRIB1, APOE
52	6	3e-06	4.99975e-05	Known LDL genes	APOB, CMTM6, DNAH11, TRIB1, APOE, SPTLC3
41	3	0.00177	0.00439978	Known TG genes	APOB, TRIB1, APOE

## 5. TRIGLYCERIDES (TG)

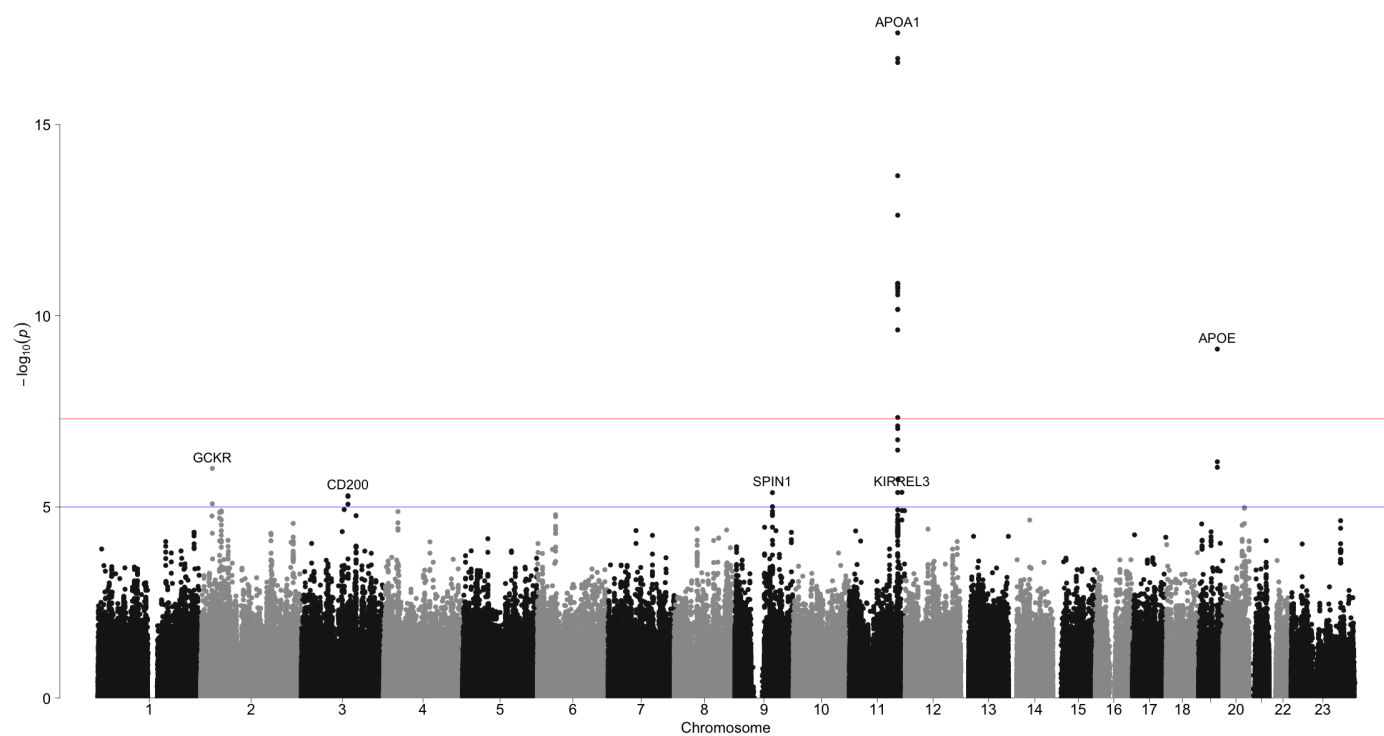


FIGURE S7. TG: genome-wide association scan

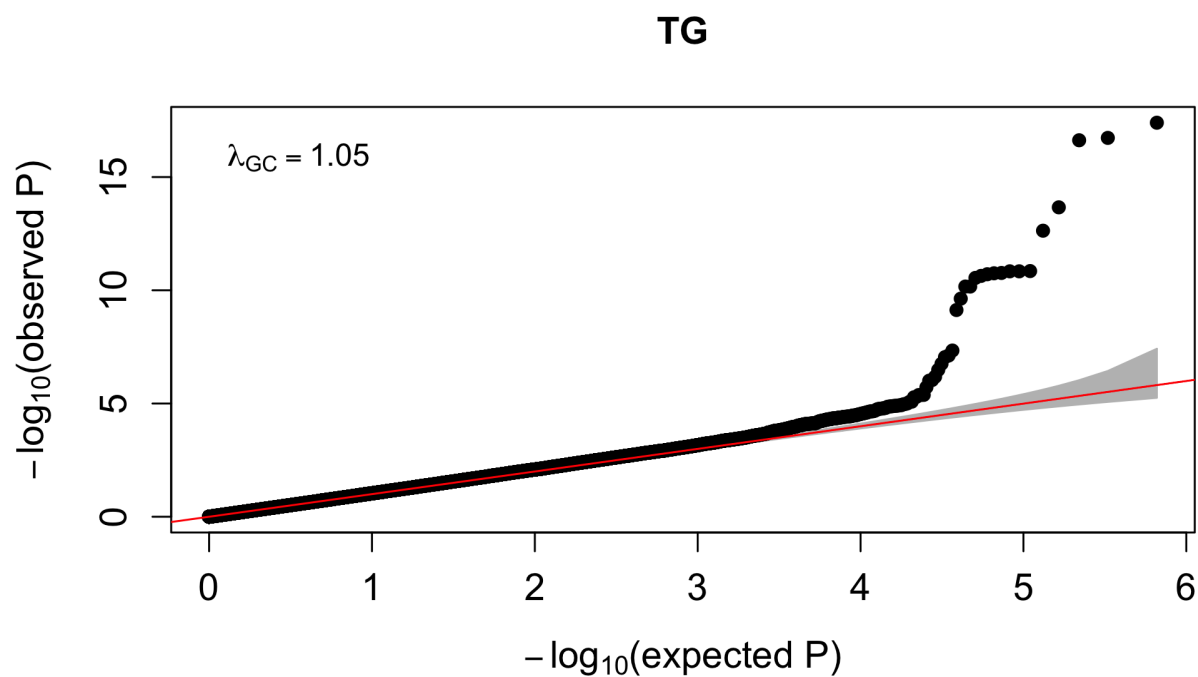


FIGURE S8. TG: QQ plot



TABLE S13. TG results. See Table S2 for a description of the column contents. Significant P values less than  $5 \times 10^{-8}$  are in **bold**, while suggestive P values between  $1 \times 10^{-5}$  and  $5 \times 10^{-8}$  are in *dark red italics*.

Label	SNP	CHR	POS	$P_D$	$P_U$	$P_A$	$P_R$	$P_{DR}$
APOA1	rs964184	11	116648917	<b>2.37E-17</b>	<i>7.27E-07</i>	<b>2.39E-08</b>	<b>8.97E-14</b>	<b>1.81E-29</b>
GCKR	rs780094	2	27741237	<i>9.84E-07</i>	0.016	0.175	0.010	<i>5.62E-08</i>
CD200	rs2399416	3	112059213	<i>5.12E-06</i>	0.635	0.353	0.668	9.29E-04
APOE	rs1160985	19	45403412	0.312	0.672	0.940	0.836	0.507
KIRREL3	rs3018434	11	126805881	<i>4.16E-06</i>	NA	NA	NA	NA
SPIN1	rs7861888	9	90886340	<i>4.24E-06</i>	NA	NA	NA	NA

Label	SNP	CHR	POS	$z_D$	$z_U$	$z_A$	Dir	$n_D$	$n_U$	$n_A$	$n_R$	$n_{DR}$
APOA1	rs964184	11	116648917	8.47	4.95	5.58	+++	2849	710	1080	1790	4639
GCKR	rs780094	2	27741237	4.90	2.40	1.36	+++	2847	710	1080	1790	4637
CD200	rs2399416	3	112059213	4.56	0.47	-0.93	++-	2832	692	1078	1770	4602
APOE	rs1160985	19	45403412	1.01	-0.42	0.08	+ - +	2849	704	1077	1781	4630
KIRREL3	rs3018434	11	126805881	4.60	NA	NA	+??	2844	NA	NA	NA	NA
SPIN1	rs7861888	9	90886340	4.60	NA	NA	+??	2816	NA	NA	NA	NA

Label	SNP	CHR	POS	eafD	eafU	eafA	SAM	EAS	SAS	EUR	AMR	AFR	eA	oA
APOA1	rs964184	11	116648917	0.430	0.453	0.457	0.440	0.240	0.229	0.162	0.277	0.221	G	C
GCKR	rs780094	2	27741237	0.332	0.347	0.331	0.334	0.476	0.198	0.411	0.360	0.132	T	C
CD200	rs2399416	3	112059213	0.020	0.015	0.028	0.021	0.148	0.140	0.393	0.272	0.101	A	G
APOE	rs1160985	19	45403412	0.268	0.288	0.291	0.276	0.341	0.410	0.446	0.553	0.623	T	C
KIRREL3	rs3018434	11	126805881	0.916	NA	NA	0.916	0.803	0.920	0.866	0.857	0.974	G	A
SPIN1	rs7861888	9	90886340	0.706	NA	NA	0.706	0.719	0.897	0.921	0.842	0.989	A	G

Label	SNP	CHR	POS	known	traitW	GeneUp	DistanceUp	GeneDown	DistanceDown
APOA1	rs964184	11	116648917	APOA1	C H L T	ZPR1	0	ZPR1	0
GCKR	rs780094	2	27741237	GCKR	C T	GCKR	0	GCKR	0
CD200	rs2399416	3	112059213	NA	NA	CD200	0	CD200	0
APOE	rs1160985	19	45403412	APOE	C H L T	TOMM40	0	TOMM40	0
KIRREL3	rs3018434	11	126805881	NA	NA	KIRREL3	0	KIRREL3	0
SPIN1	rs7861888	9	90886340	NA	NA	SPATA31C2	136440	SPIN1	116956

Label	SNP	CHR	POS	$P_D$	$P_R$	$P_{DR}$	gwasPeak	gwasP
APOA1	rs964184	11	116648917	<b>2.37E-17</b>	<b>8.97E-14</b>	<b>1.81E-29</b>	rs6589566	<b>3.98E-18</b>
GCKR	rs780094	2	27741237	<i>9.84E-07</i>	0.010	<i>5.62E-08</i>	NA	NA
CD200	rs2399416	3	112059213	<i>5.12E-06</i>	0.668	9.29E-04	NA	NA
APOE	rs1160985	19	45403412	0.312	0.836	0.507	rs4420638	<b>7.44E-10</b>
KIRREL3	rs3018434	11	126805881	<i>4.16E-06</i>	NA	NA	NA	NA
SPIN1	rs7861888	9	90886340	<i>4.24E-06</i>	NA	NA	NA	NA

TABLE S14. MAGENTA pathway analysis of TG. See Table S4 for a description of the column contents.

Database	Gene Set	Effective Gene Set Size	FDR (95% cutoff)	Exp. # Genes (>95% cutoff)	Obs. # Genes (>95% cutoff)	Trait-specific Known Genes
GOTERM	cholesterol efflux	15	0.0018	1	7	APOA1, APOE
GOTERM	reverse cholesterol transport	13	0.00405	1	6	APOA1, APOE, CETP, LIPC
GOTERM	phospholipid efflux	7	0.005866667	0	4	APOA1, APOE
GOTERM	thyroid hormone receptor binding	24	0.030375	1	7	JMJD1C
GOTERM	ligand-dependent nuclear receptor transcription coactivator activity	26	0.0389	1	7	-
GOTERM	high-density lipoprotein particle remodeling	10	0.04408	1	4	APOA1, APOE, CETP, LIPC
GOTERM	fatty acid biosynthetic process	48	0.04907143	2	10	LIPC, LPL

TABLE S15. INRICH analysis of TG. See Table S6 for a description of the INRICH parameters used.

Gene Set Size	Number overlapping	Empirical P value	Corrected P value	Gene Set	Known overlapping genes
68	5	0.000306	0.00039998	Known TC genes	GCKR, SOX17, TRIB1, APOA1, APOE
67	5	0.000446	0.00099995	Known HDL genes	VEGFA, TRIB1, APOA1, SCARB1, APOE
52	4	0.000987999	0.00214989	Known LDL genes	SOX17, TRIB1, APOA1, APOE
41	5	2.4e-05	0.000149993	Known TG genes	GCKR, VEGFA, TRIB1, APOA1, APOE

## 6. LOCUSZOOM PLOTS

### 6.1. Total Cholesterol LocusZoom plots.

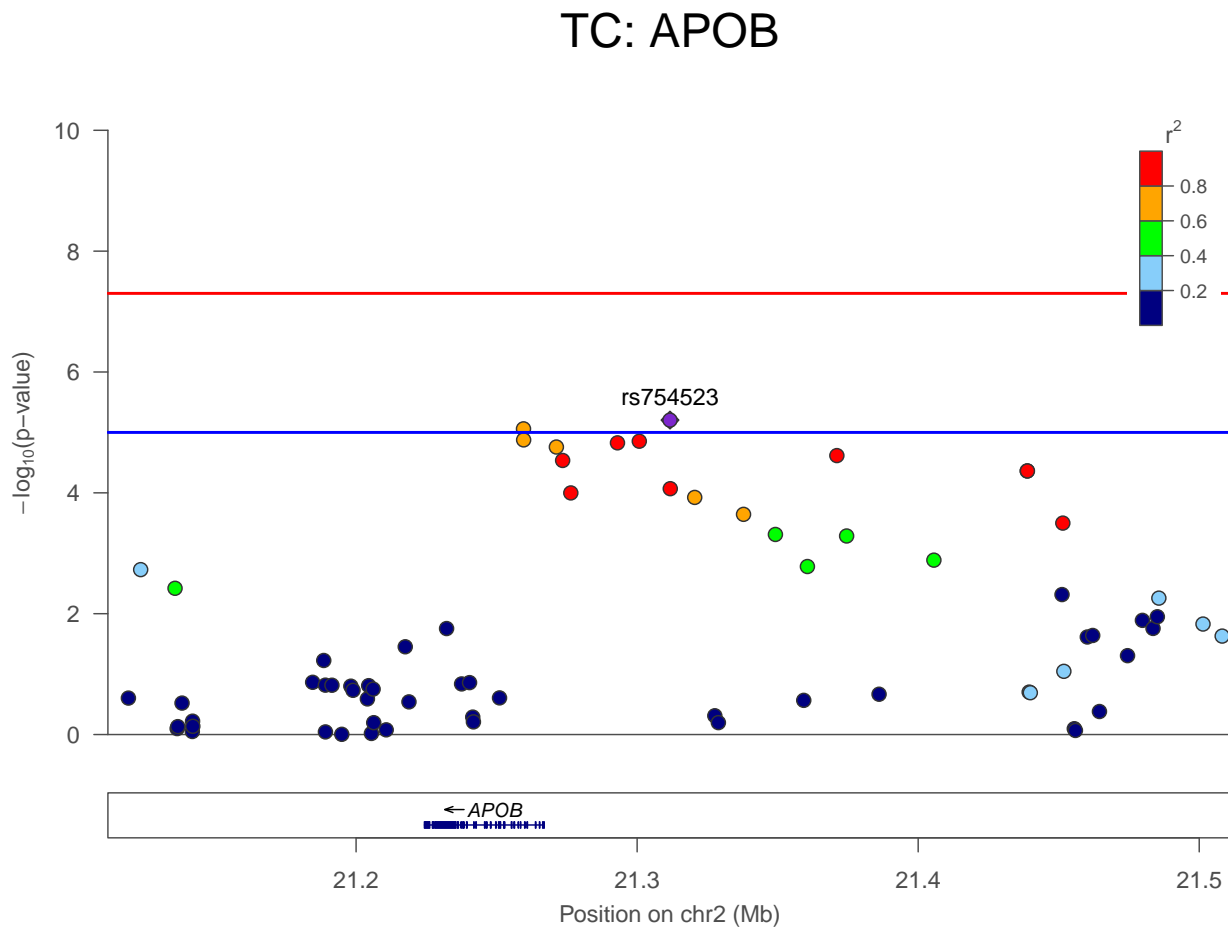


FIGURE S9. TC on chromosome 2 positions 21111691-21511691

# TC: PDE4D

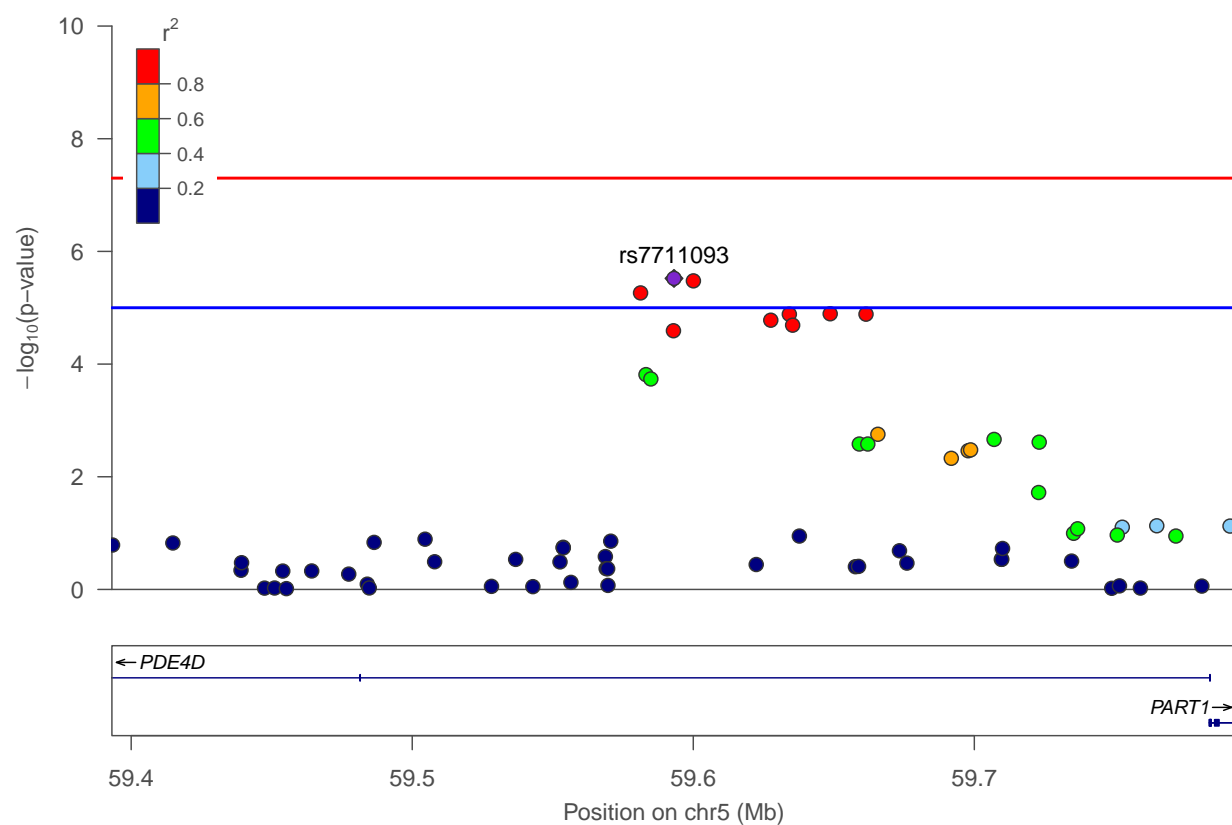


FIGURE S10. TC on chromosome 5 positions 59393138-59793138

# TC: LUCAT1

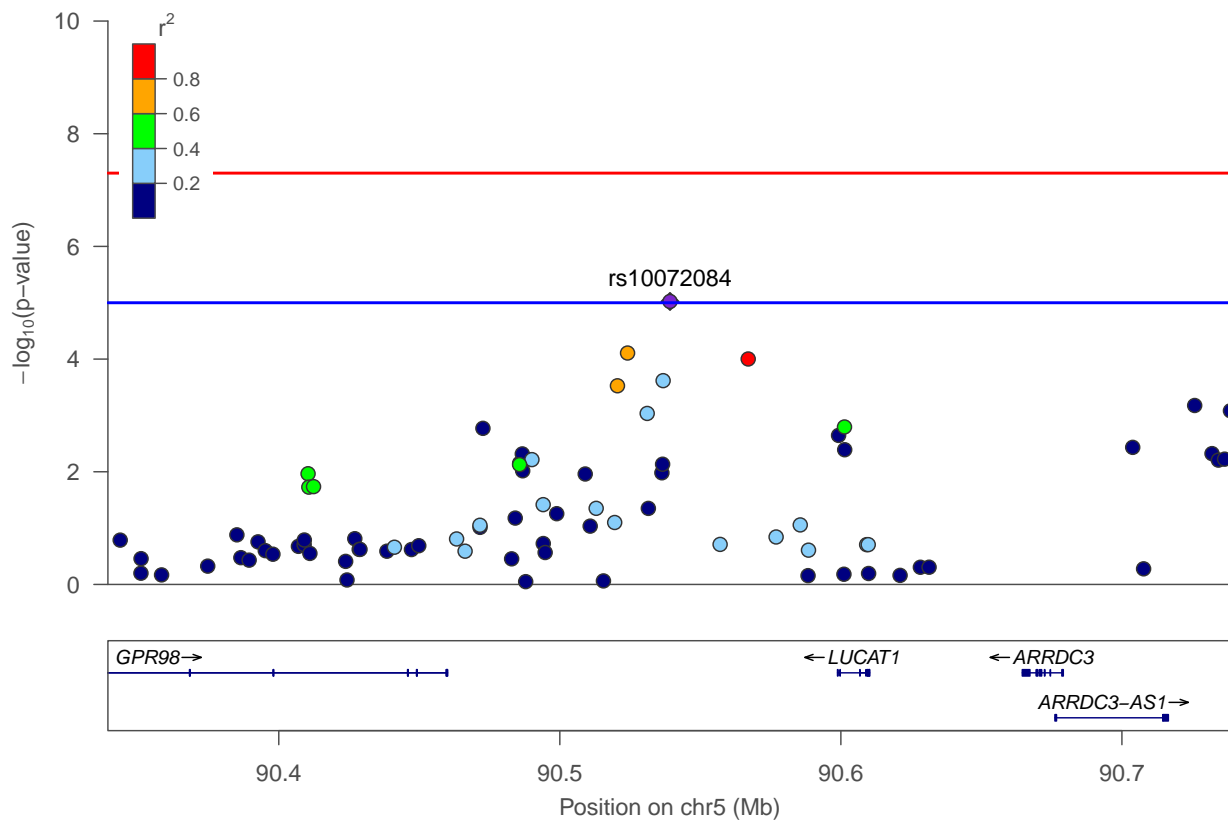


FIGURE S11. TC on chromosome 5 positions 90339203-90739203

# TC: FILIP1;LOC101928540

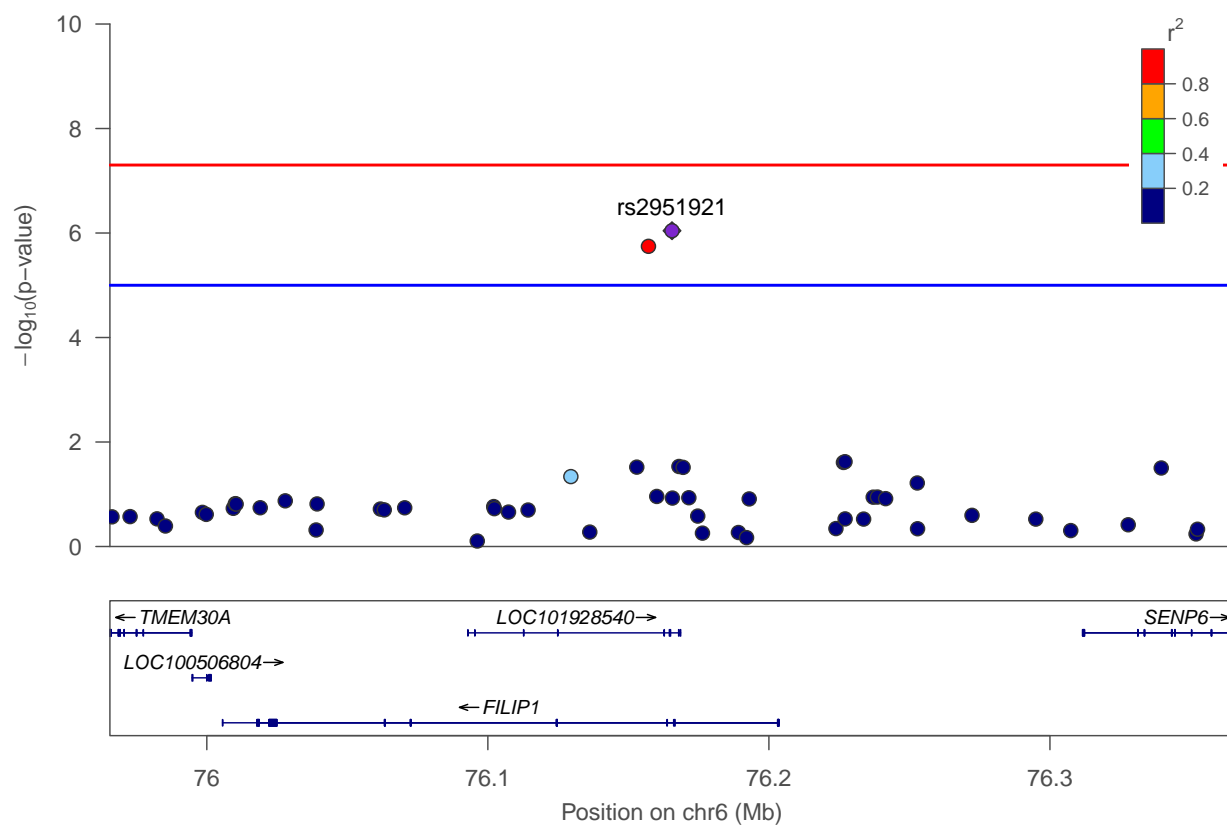


FIGURE S12. TC on chromosome 6 positions 75965524-76365524



# TC: ZHX2

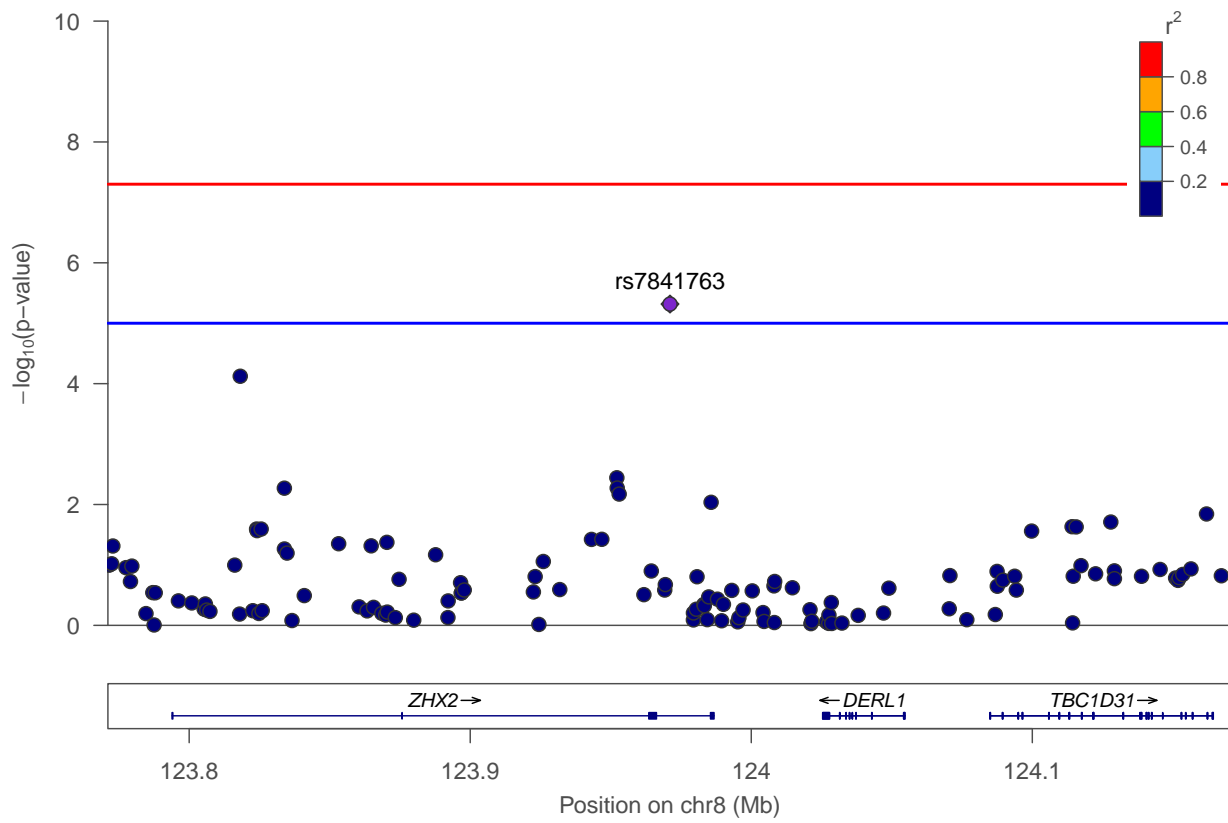


FIGURE S13. TC on chromosome 8 positions 123771081-124171081

# TC: APOA1

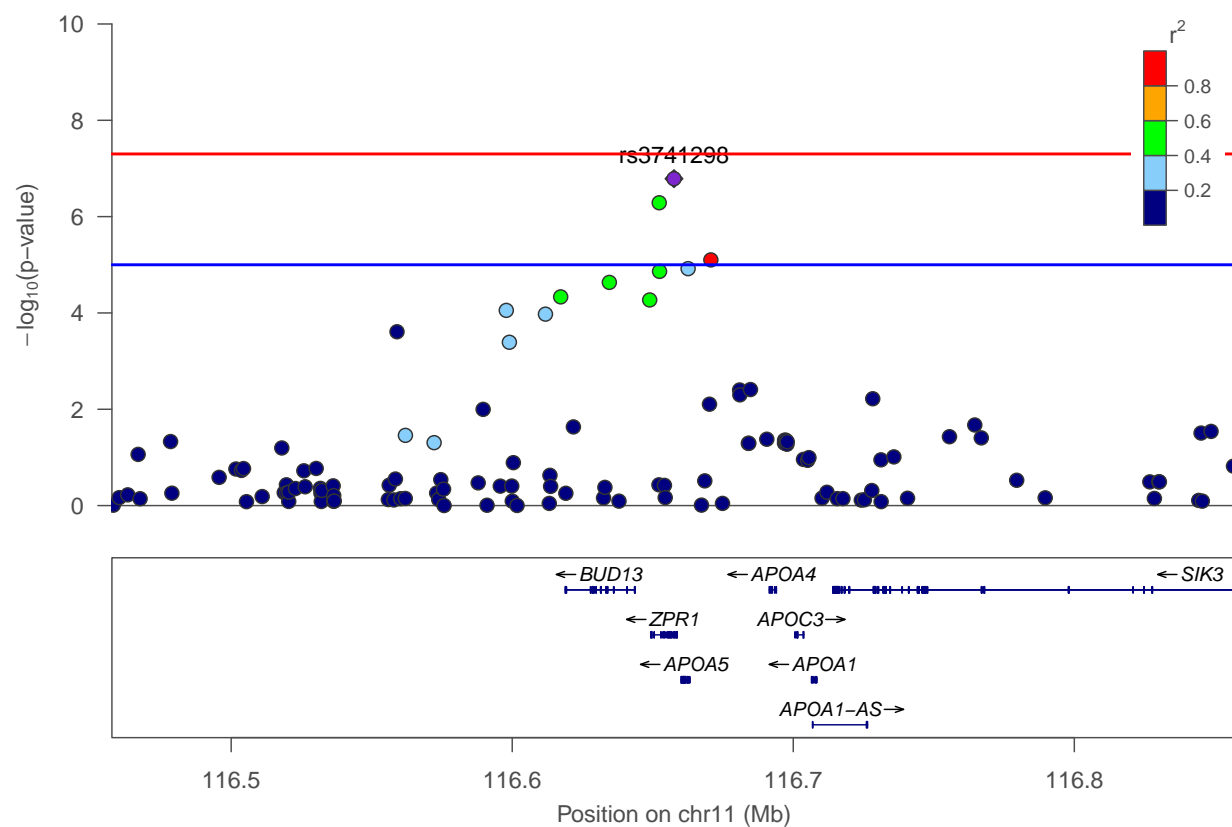


FIGURE S14. TC on chromosome 11 positions 116457561-116857561

# TC: SIRT2

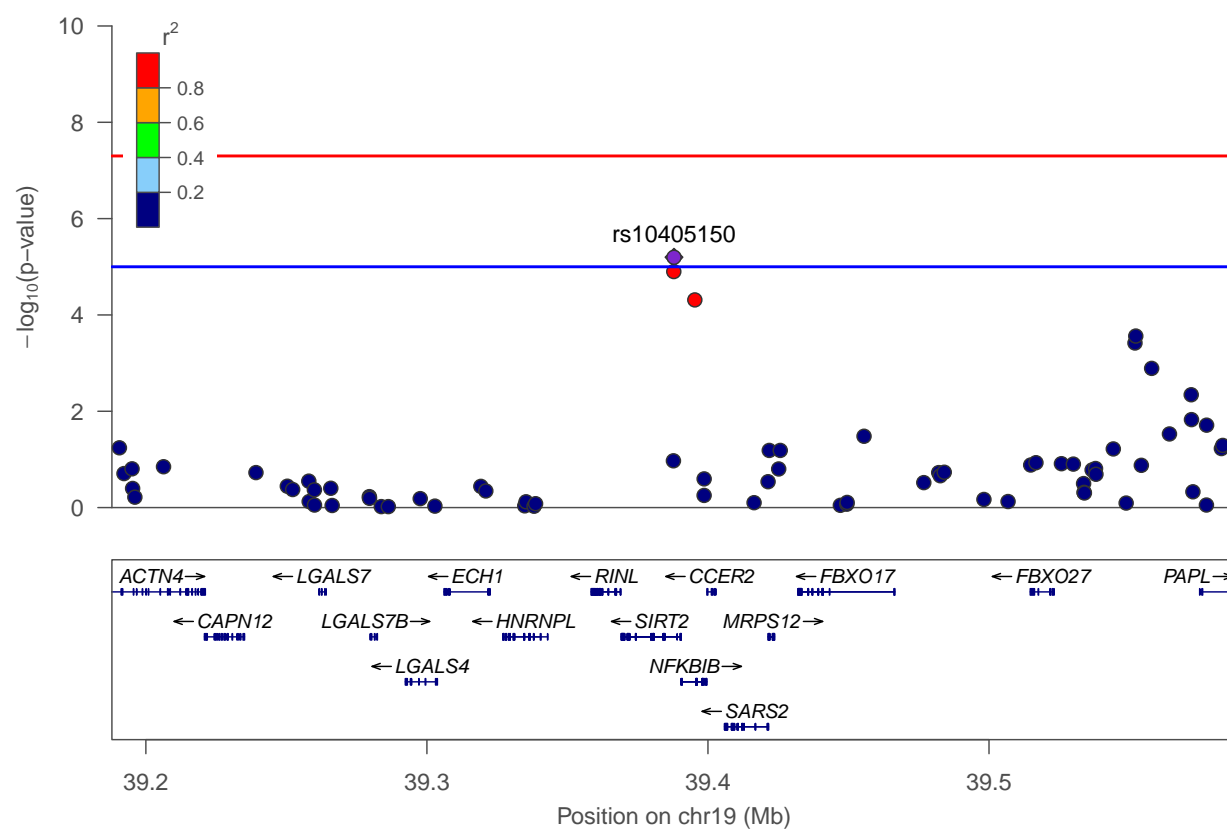


FIGURE S15. TC on chromosome 19 positions 39187919-39587919

# TC: ZNF283

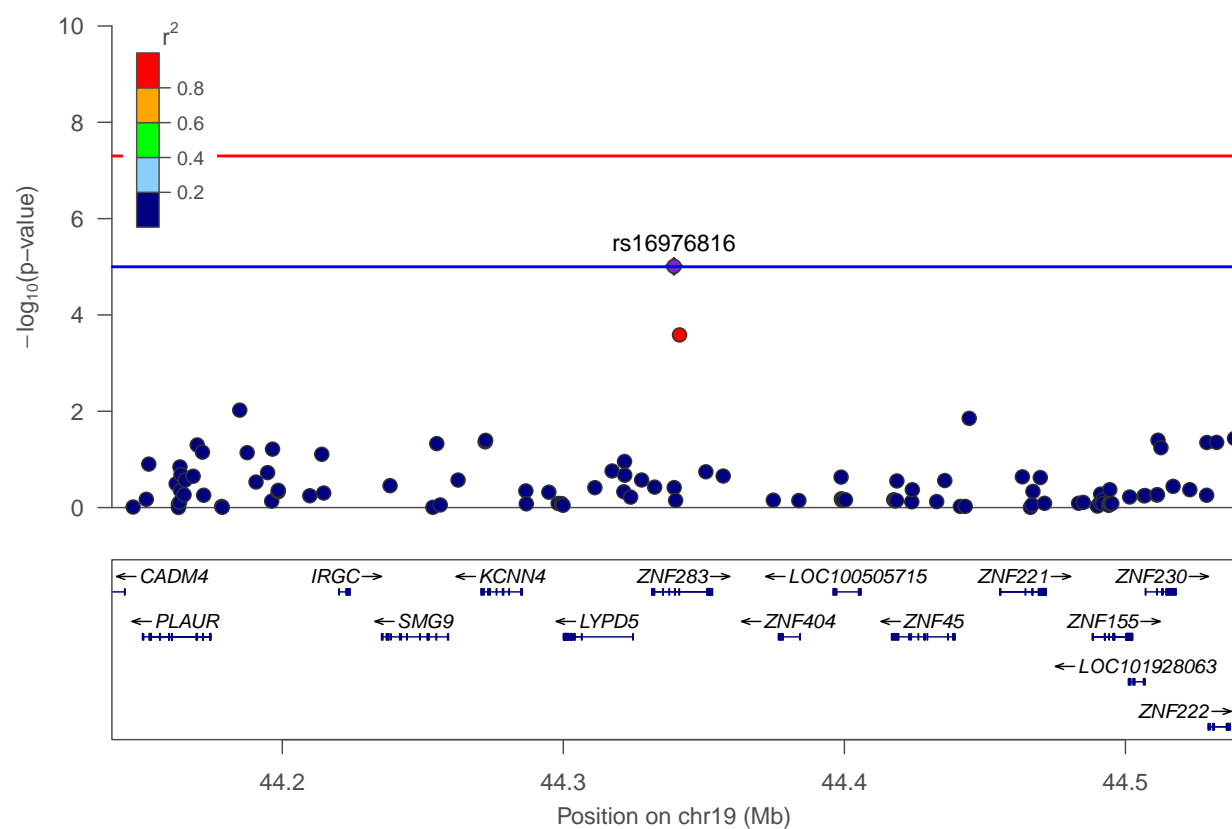


FIGURE S16. TC on chromosome 19 positions 44139377-44539377

# TC: APOE

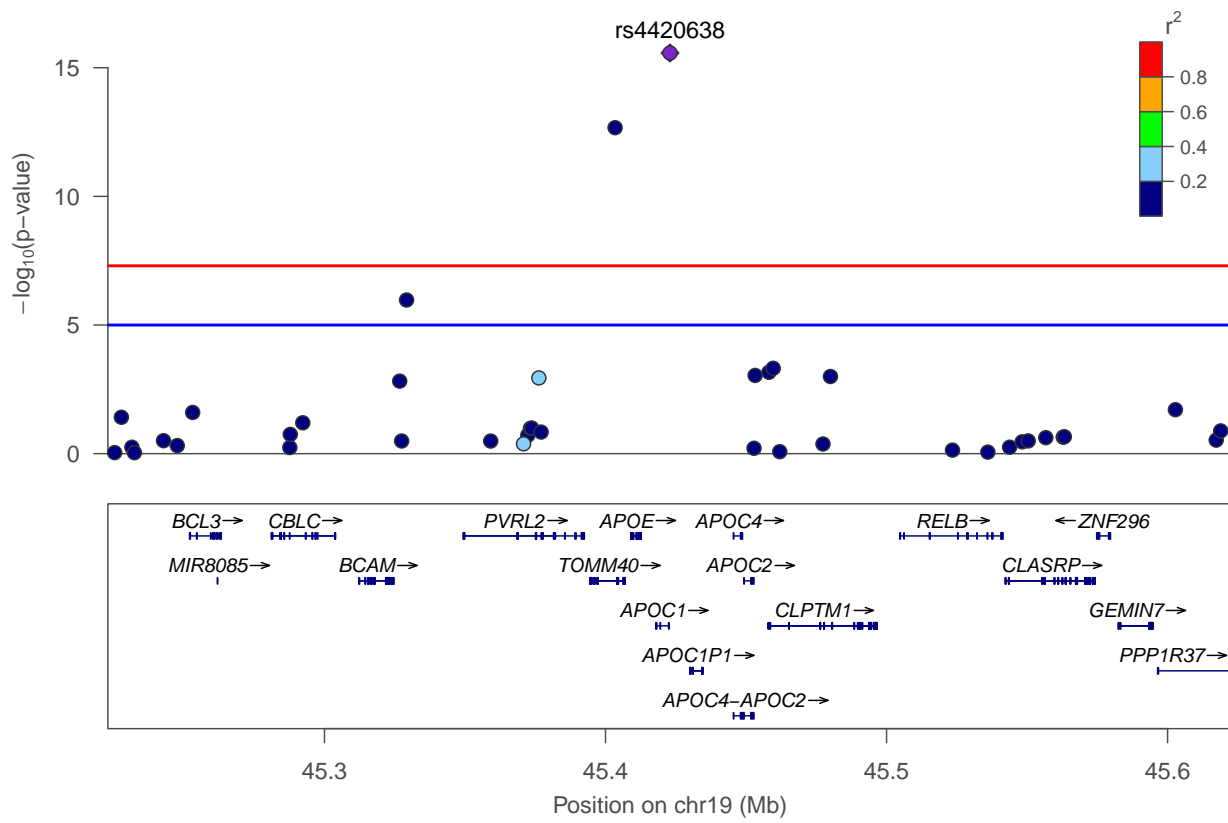


FIGURE S17. TC on chromosome 19 positions 45222946-45622946

6.2. HDL LocusZoom plots.

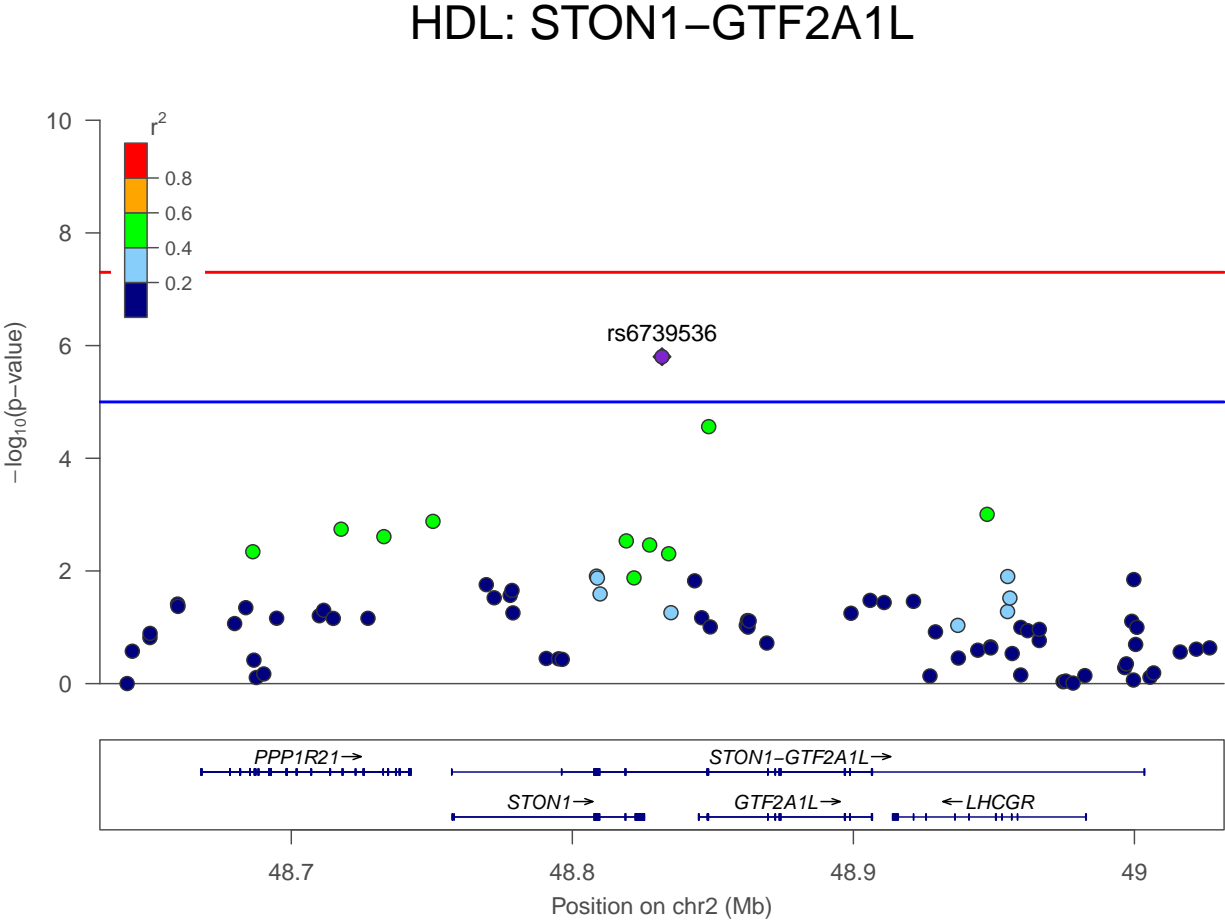


FIGURE S18. HDL on chromosome 2 positions 48631901-49031901

# HDL: MGAT1

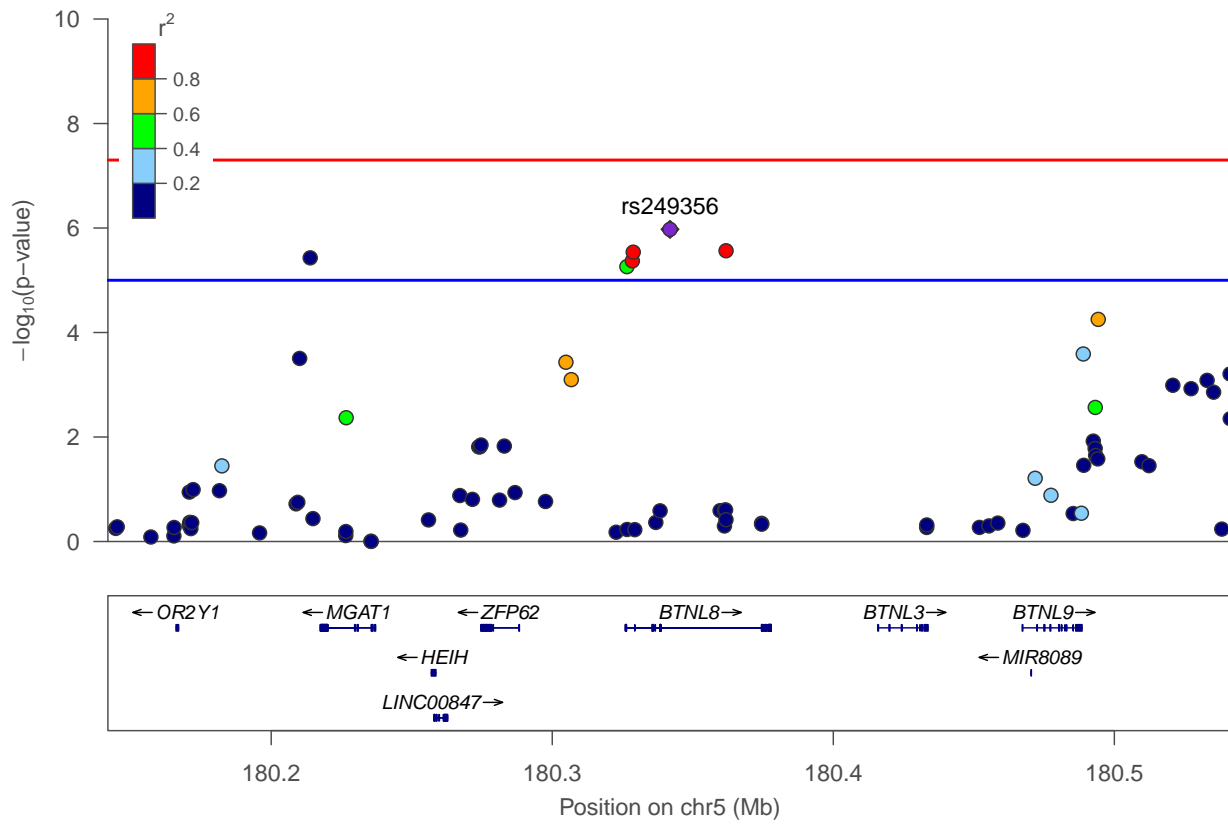


FIGURE S19. HDL on chromosome 5 positions 180141895-180541895

## HDL: AKAP7

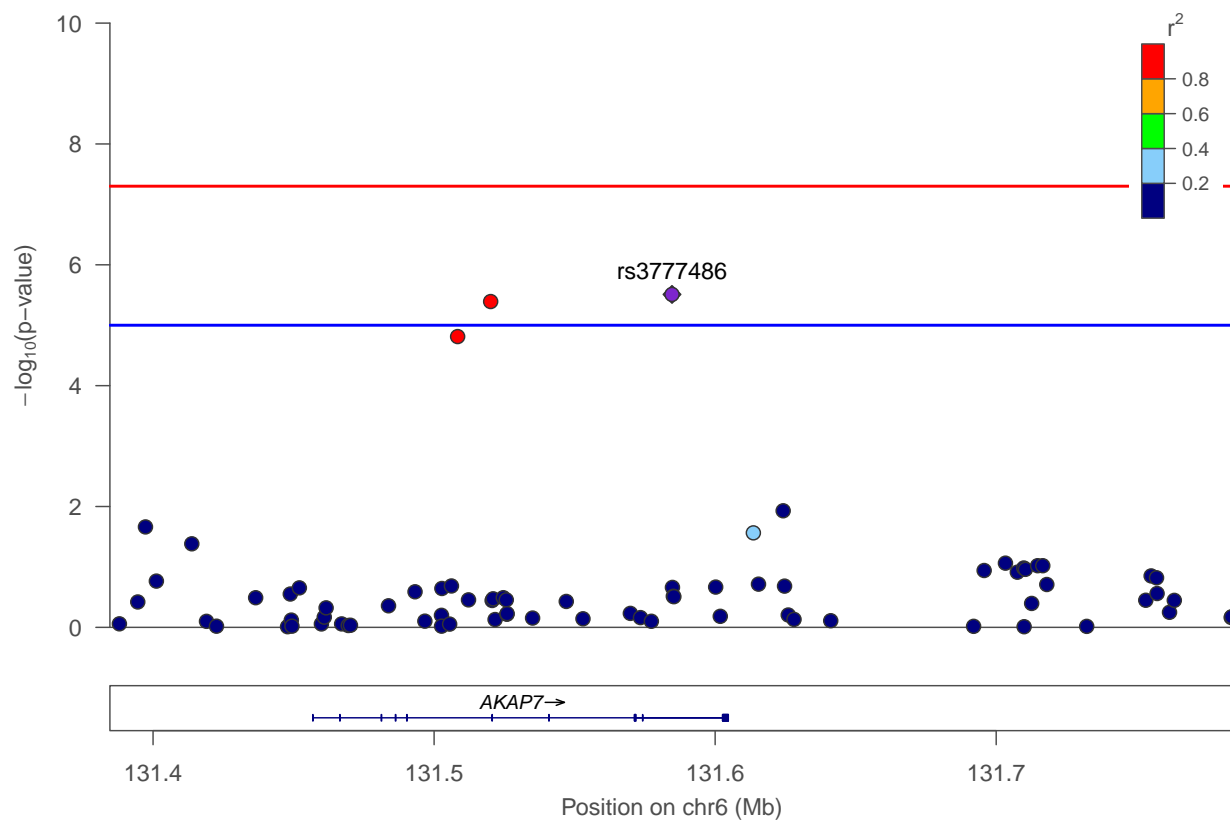


FIGURE S20. HDL on chromosome 6 positions 131384648-131784648



## HDL: CSMD1

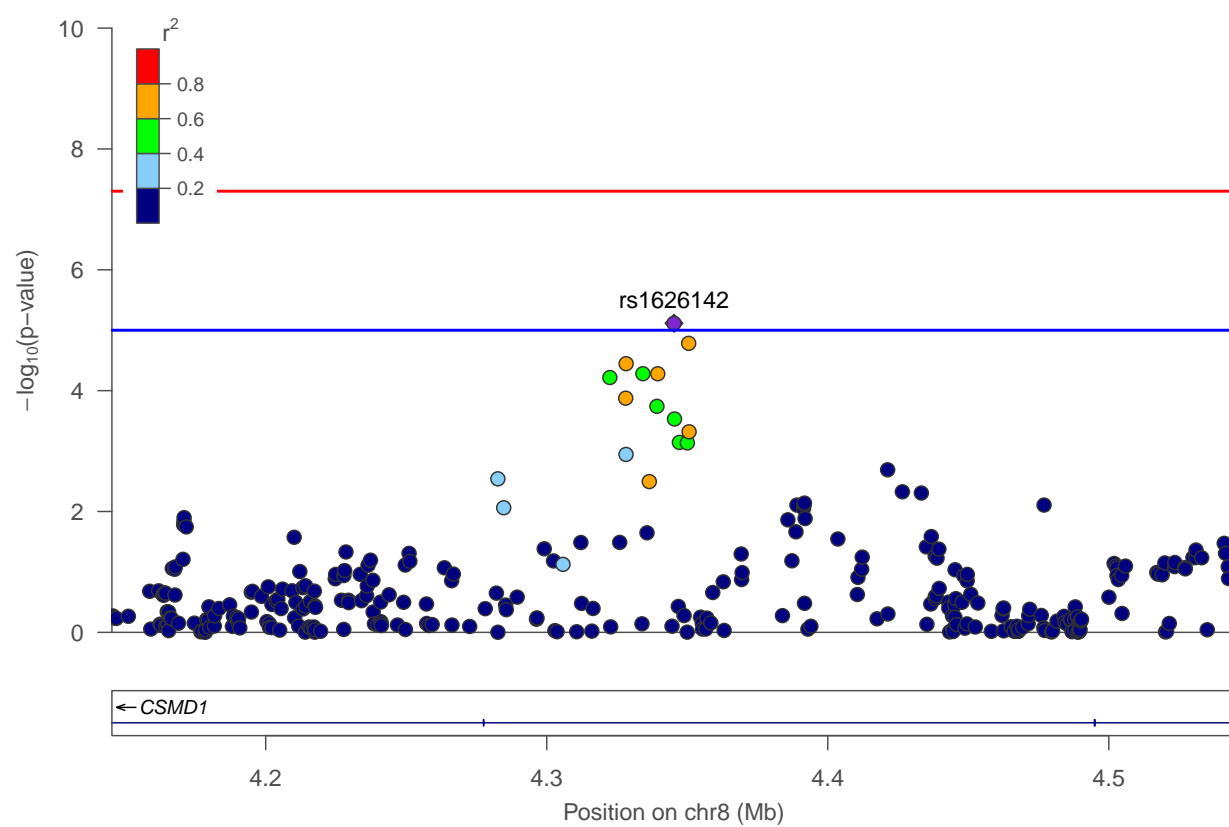


FIGURE S21. HDL on chromosome 8 positions 4145284-4545284

# HDL: RAB21

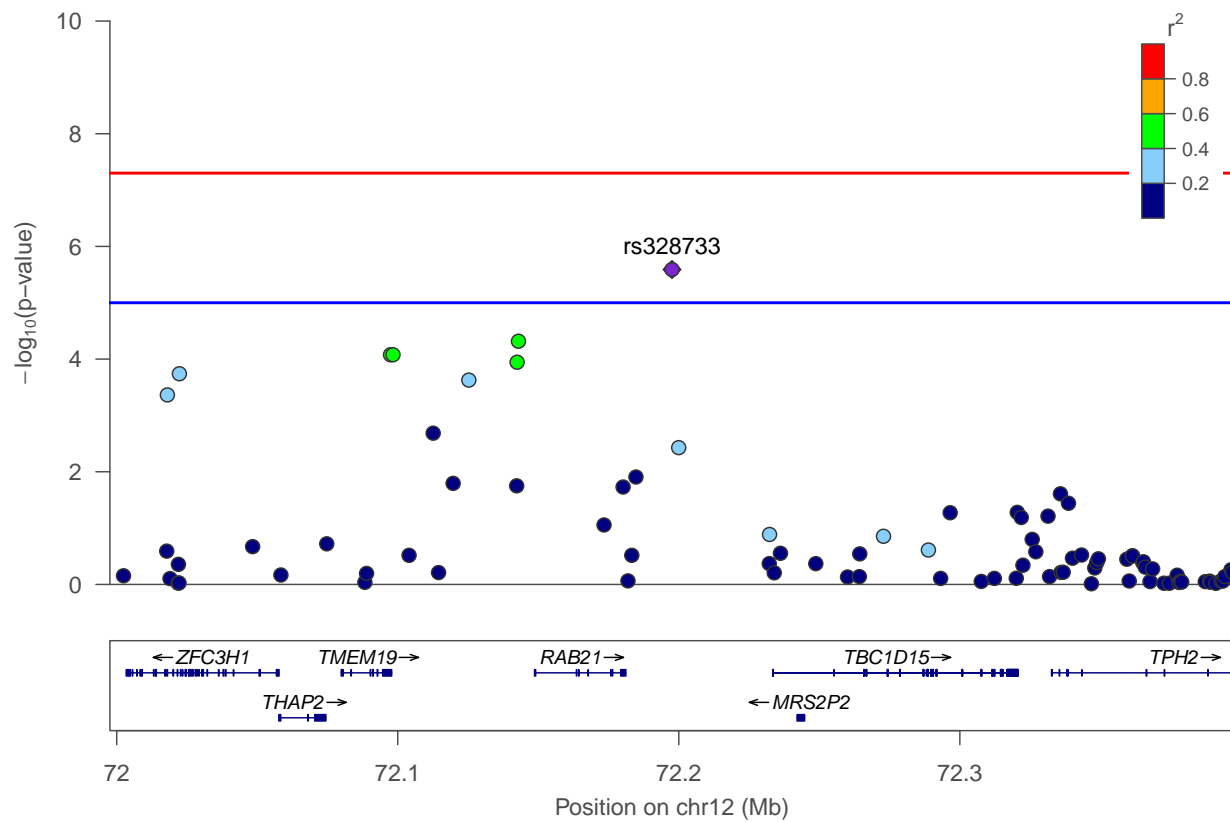


FIGURE S22. HDL on chromosome 12 positions 71997574-72397574

# HDL: ZNF10

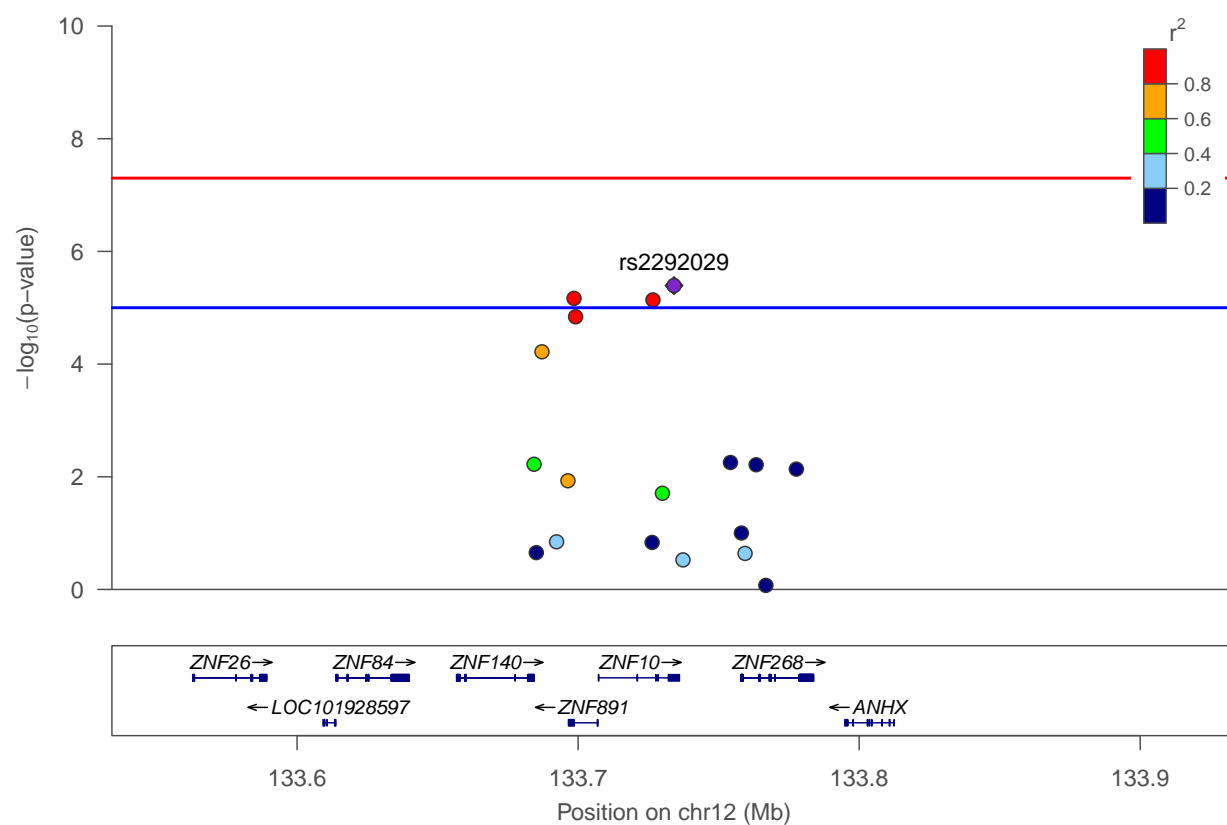


FIGURE S23. HDL on chromosome 12 positions 133534113-133934113

# HDL: HS6ST3

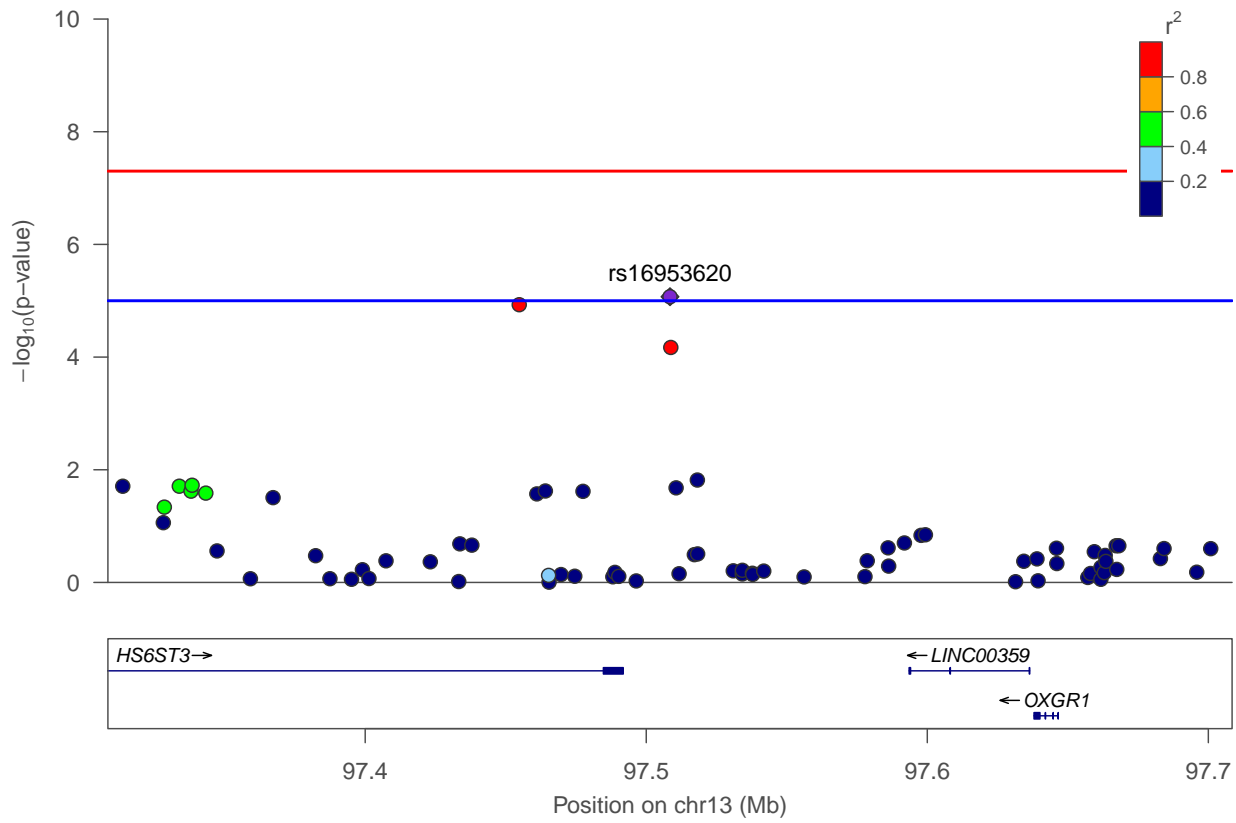


FIGURE S24. HDL on chromosome 13 positions 97308453-97708453

# HDL: LPC

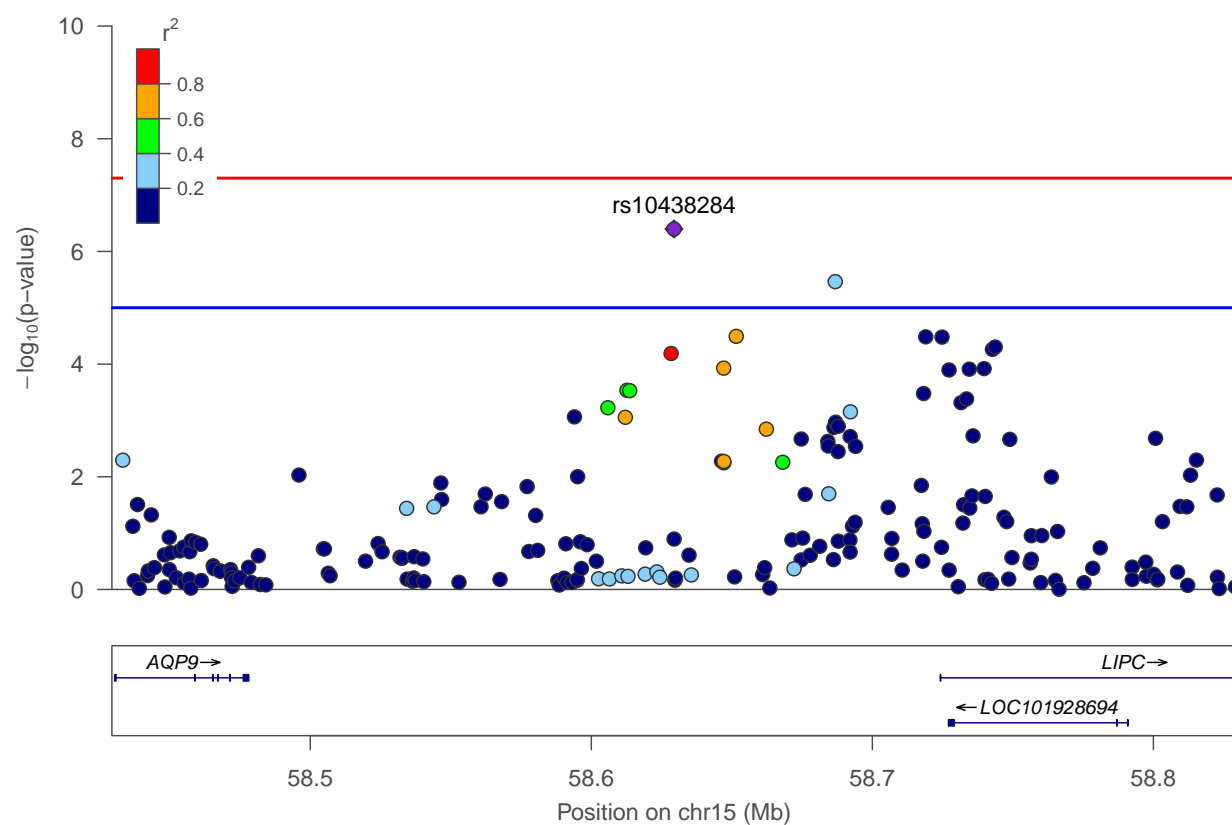


FIGURE S25. HDL on chromosome 15 positions 58429424-58829424

# HDL: CETP

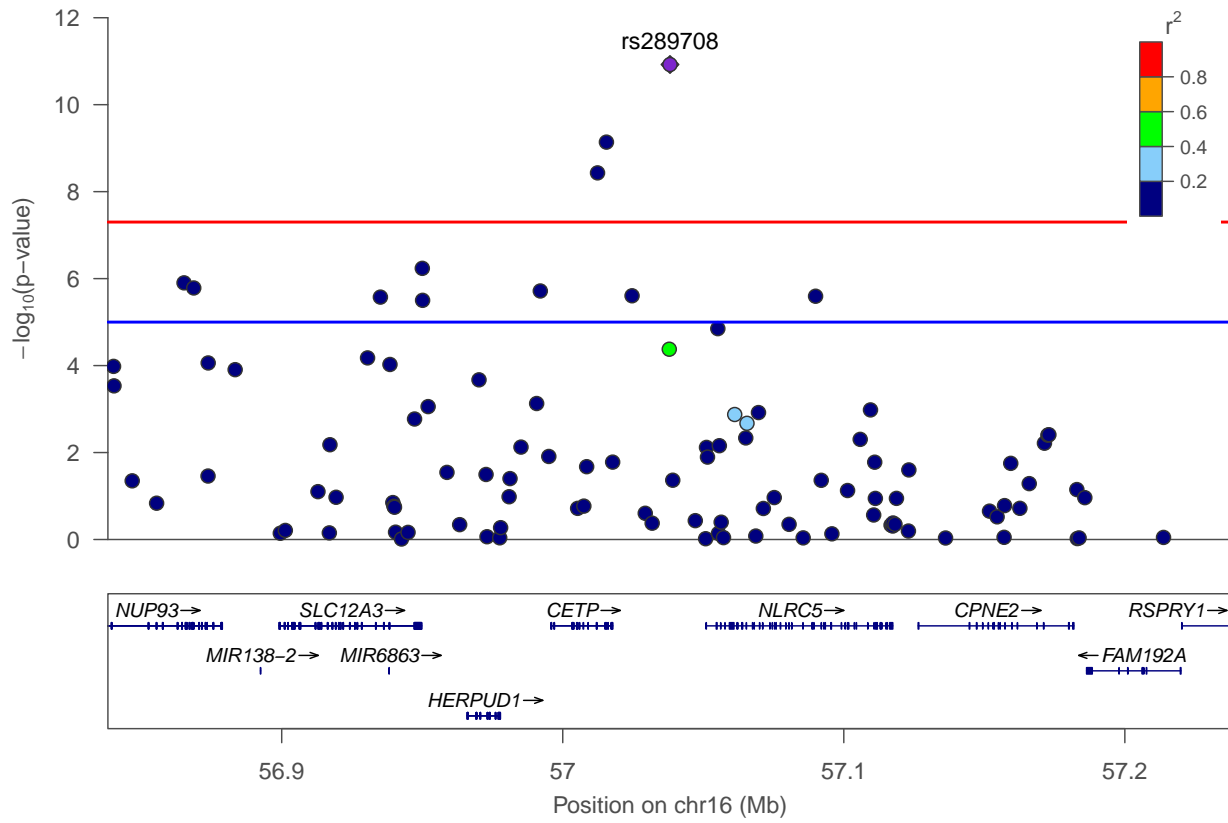


FIGURE S26. HDL on chromosome 16 positions 56838162-57238162

# HDL: LIPG

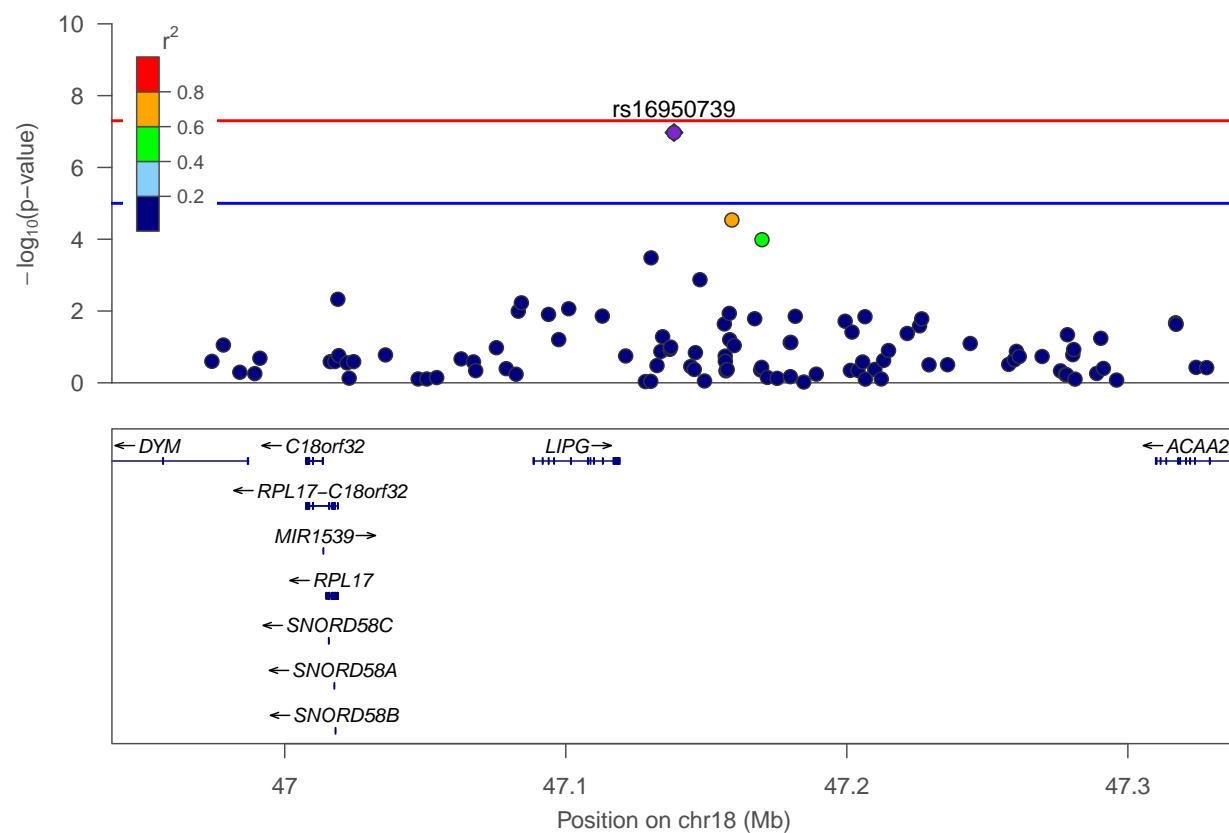


FIGURE S27. HDL on chromosome 18 positions 46938509-47338509

# HDL: APOE

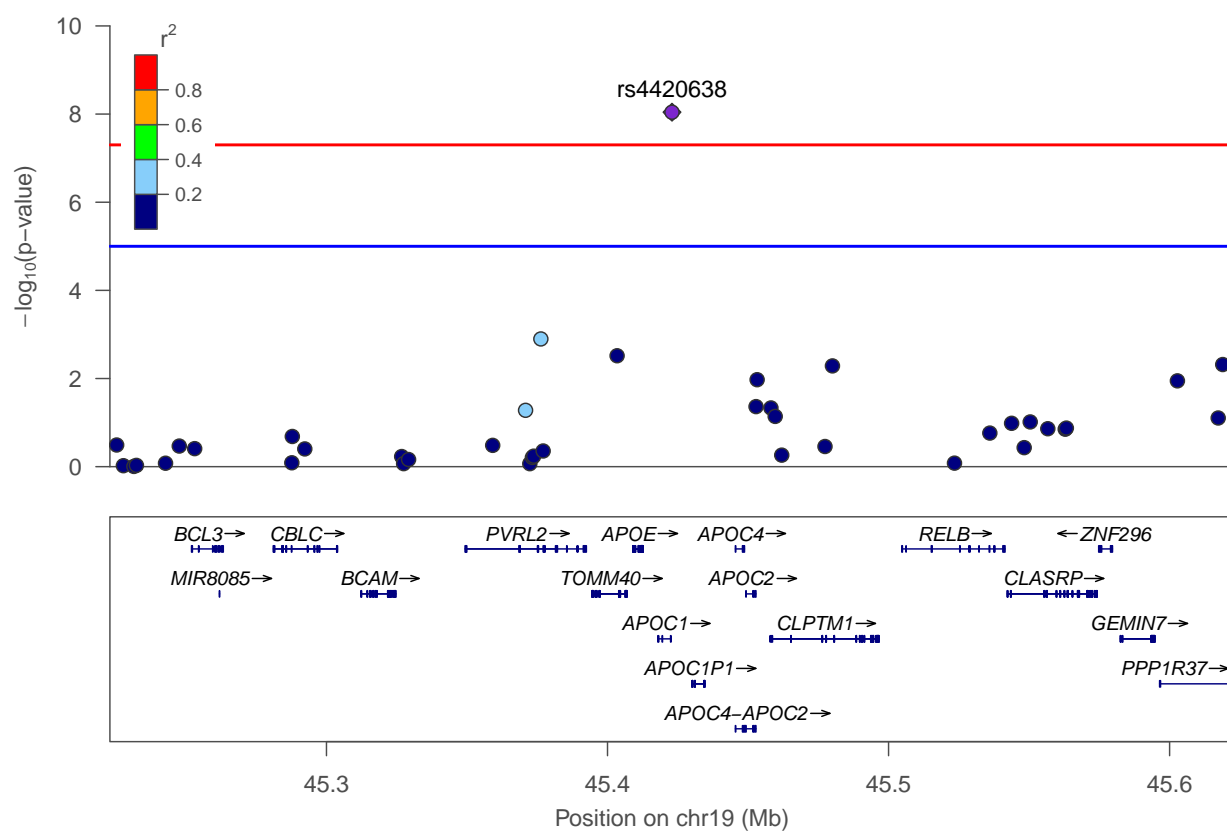


FIGURE S28. HDL on chromosome 19 positions 45222946-45622946



## HDL: CDH4

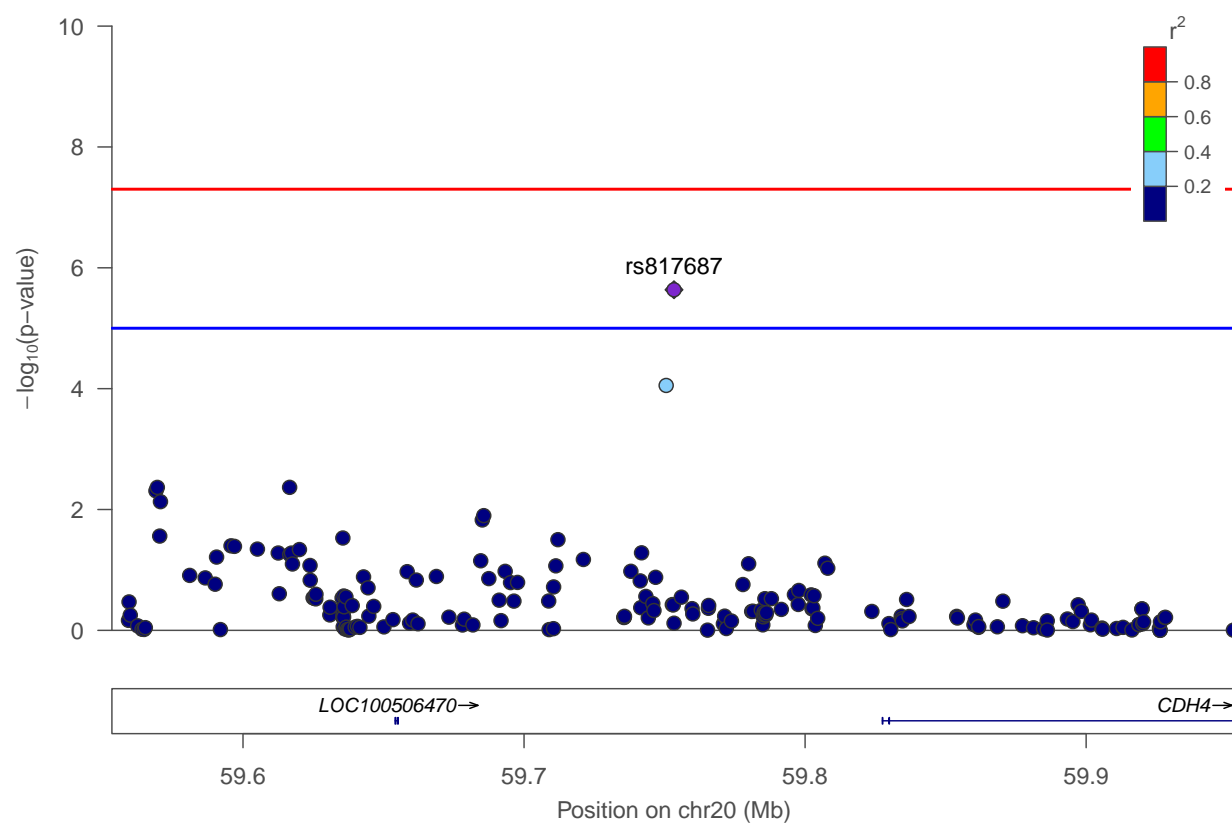


FIGURE S29. HDL on chromosome 20 positions 59553355-59953355

6.3. LDL LocusZoom plots.

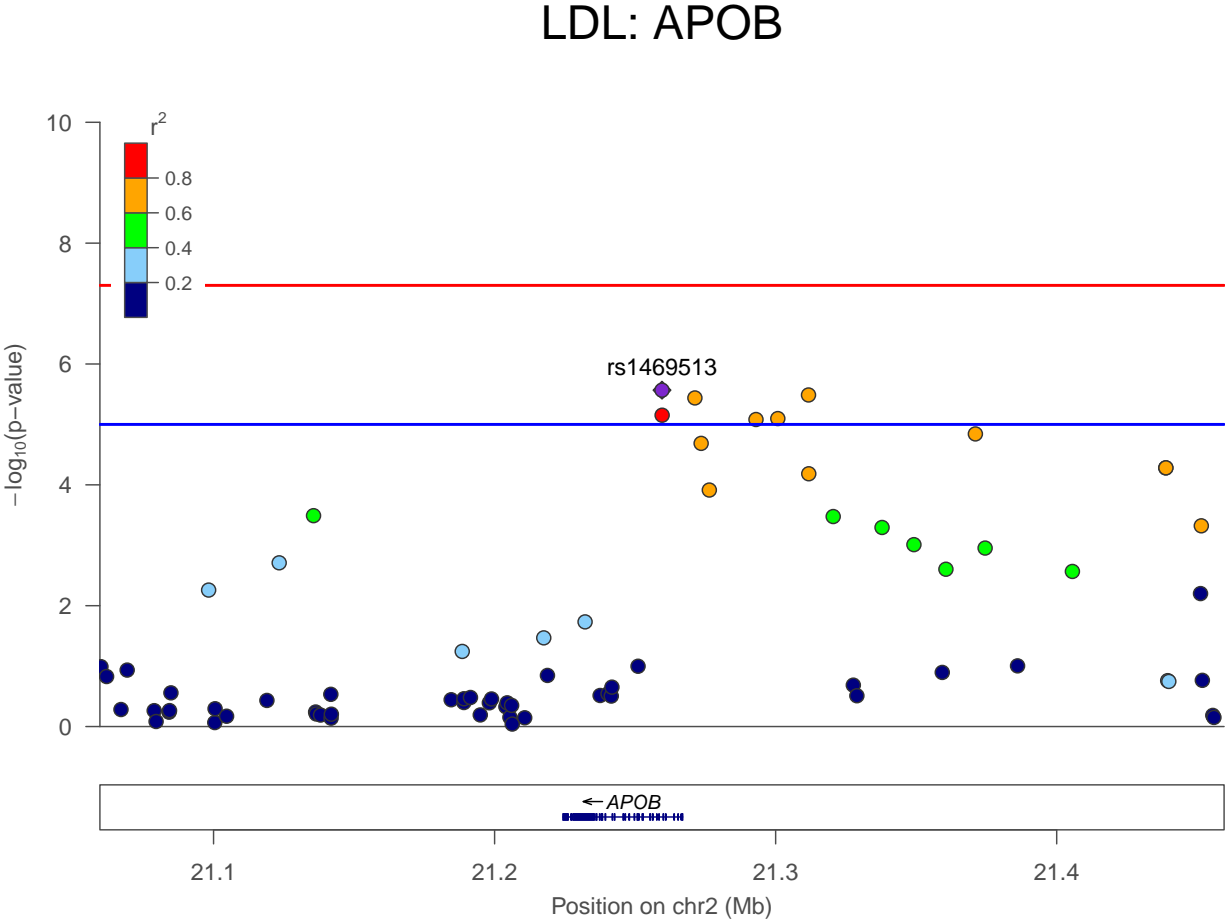


FIGURE S30. LDL on chromosome 2 positions 21059562-21459562

# LDL: KALRN

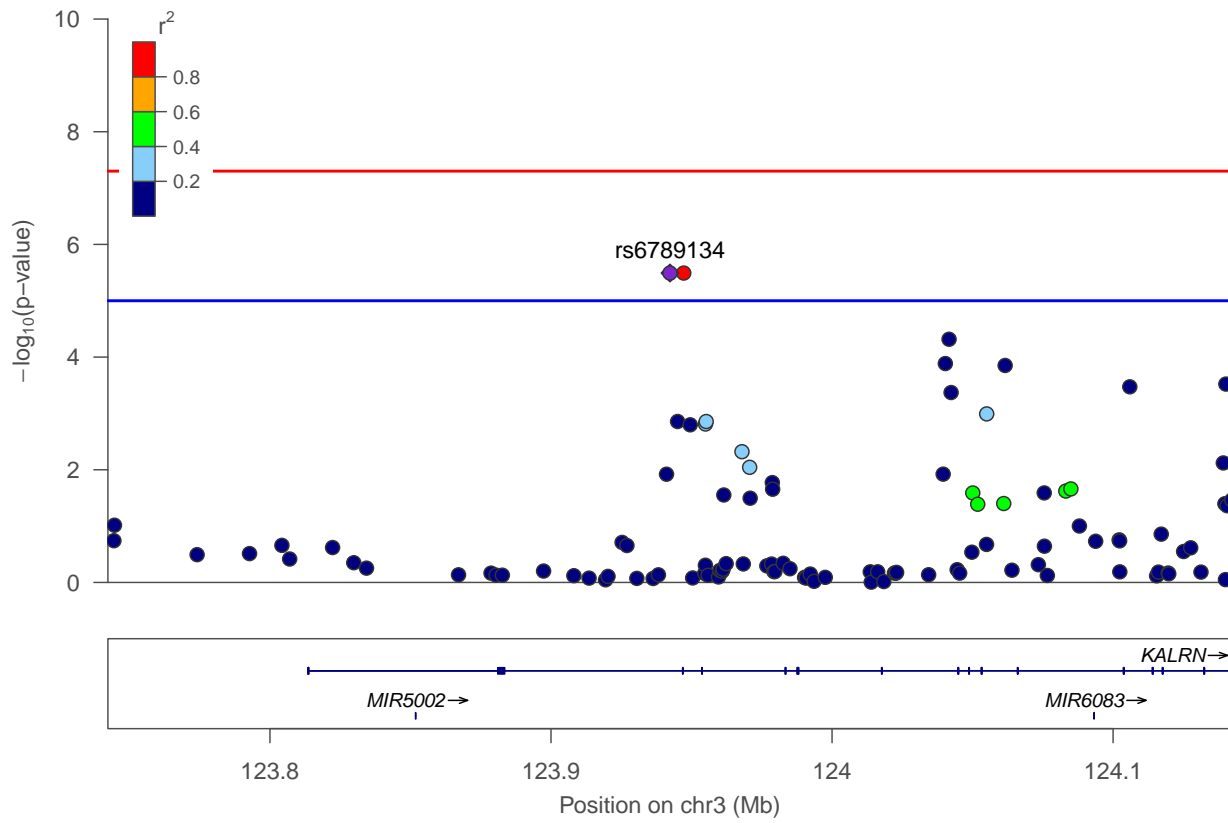


FIGURE S31. LDL on chromosome 3 positions 123742339-124142339

# LDL: ZHX2

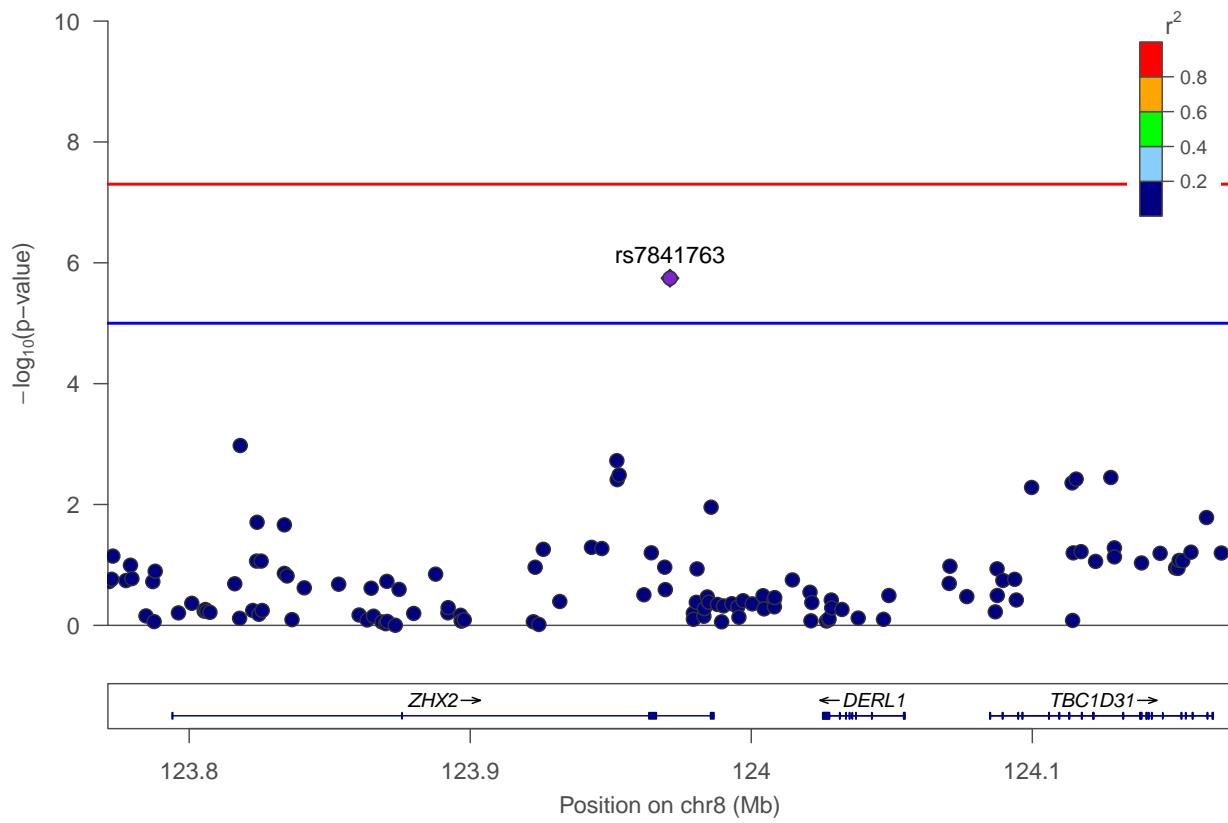


FIGURE S32. LDL on chromosome 8 positions 123771081-124171081

# LDL: SH2D4B

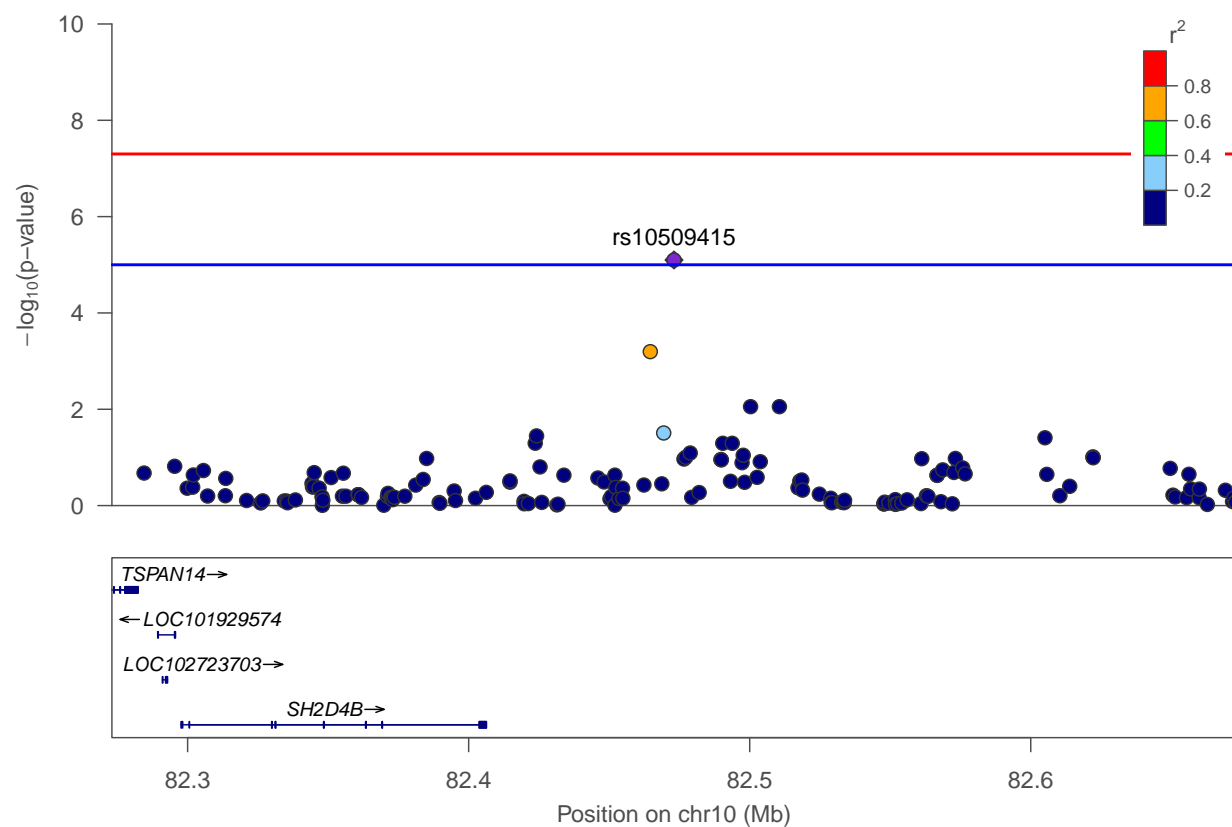


FIGURE S33. LDL on chromosome 10 positions 82273065-82673065

## LDL: ALG10

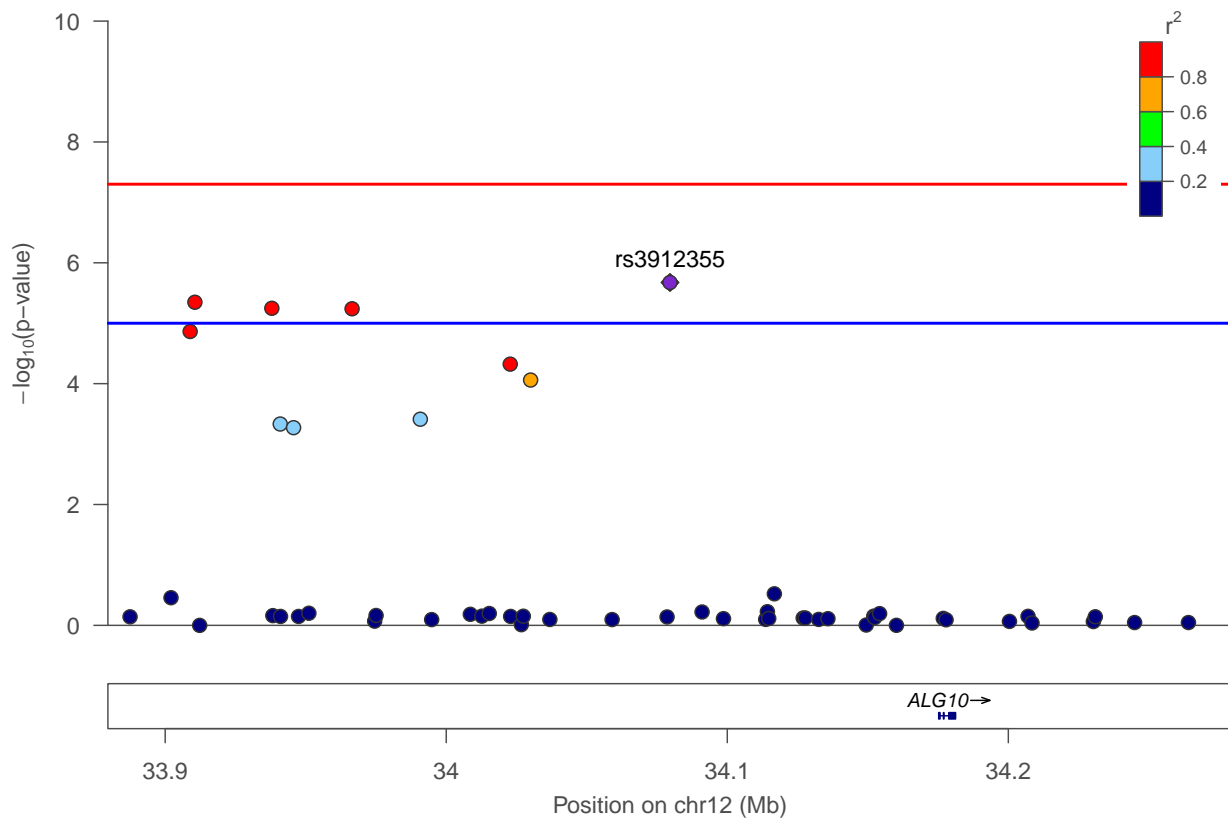


FIGURE S34. LDL on chromosome 12 positions 33879616-34279616

# LDL: ALG10B

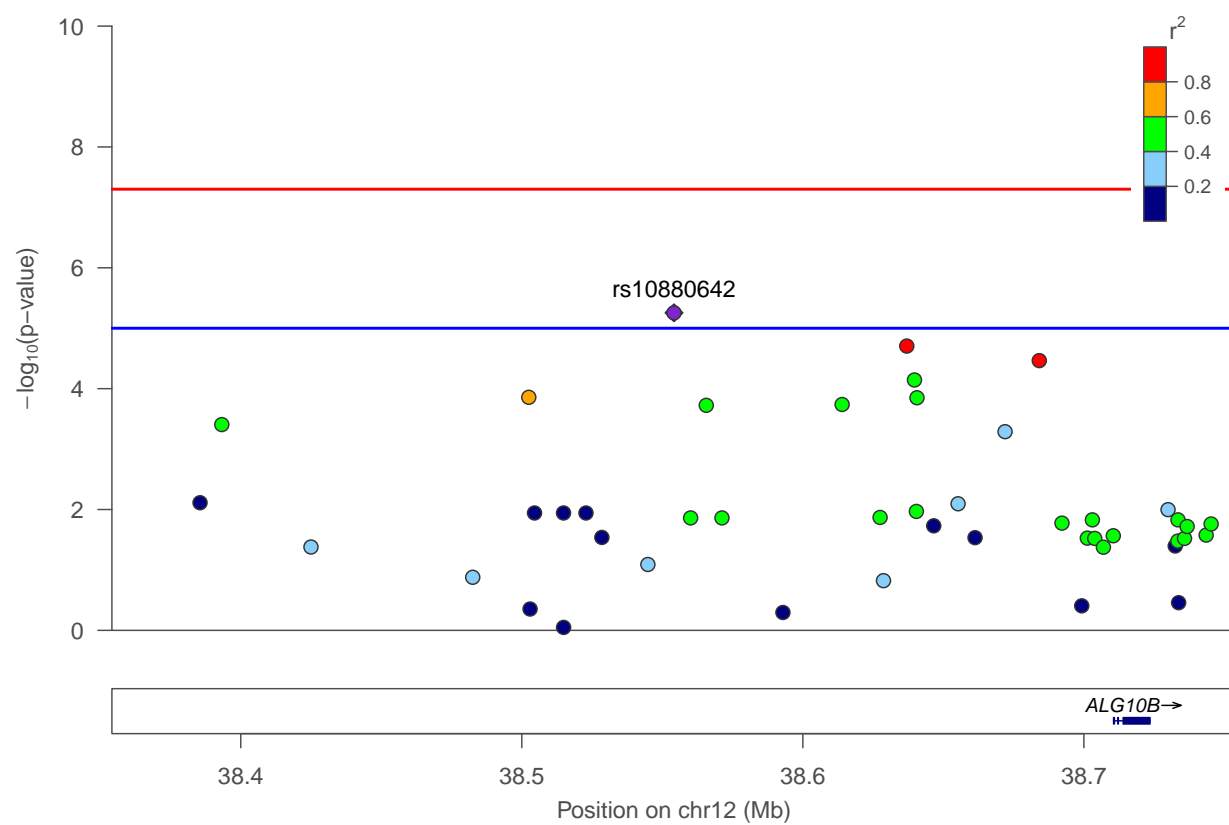


FIGURE S35. LDL on chromosome 12 positions 38354152-38754152

# LDL: CPNE8

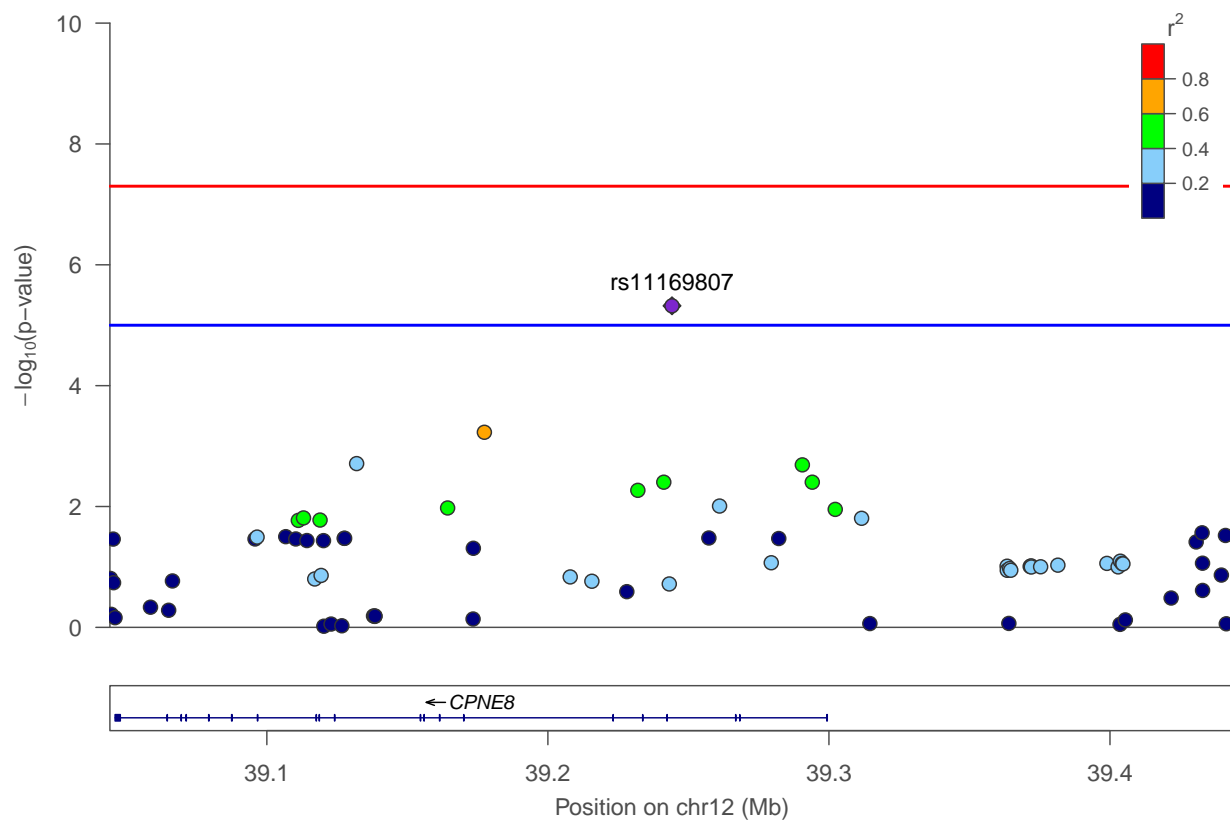


FIGURE S36. LDL on chromosome 12 positions 39044161-39444161



# LDL: LOC100507175

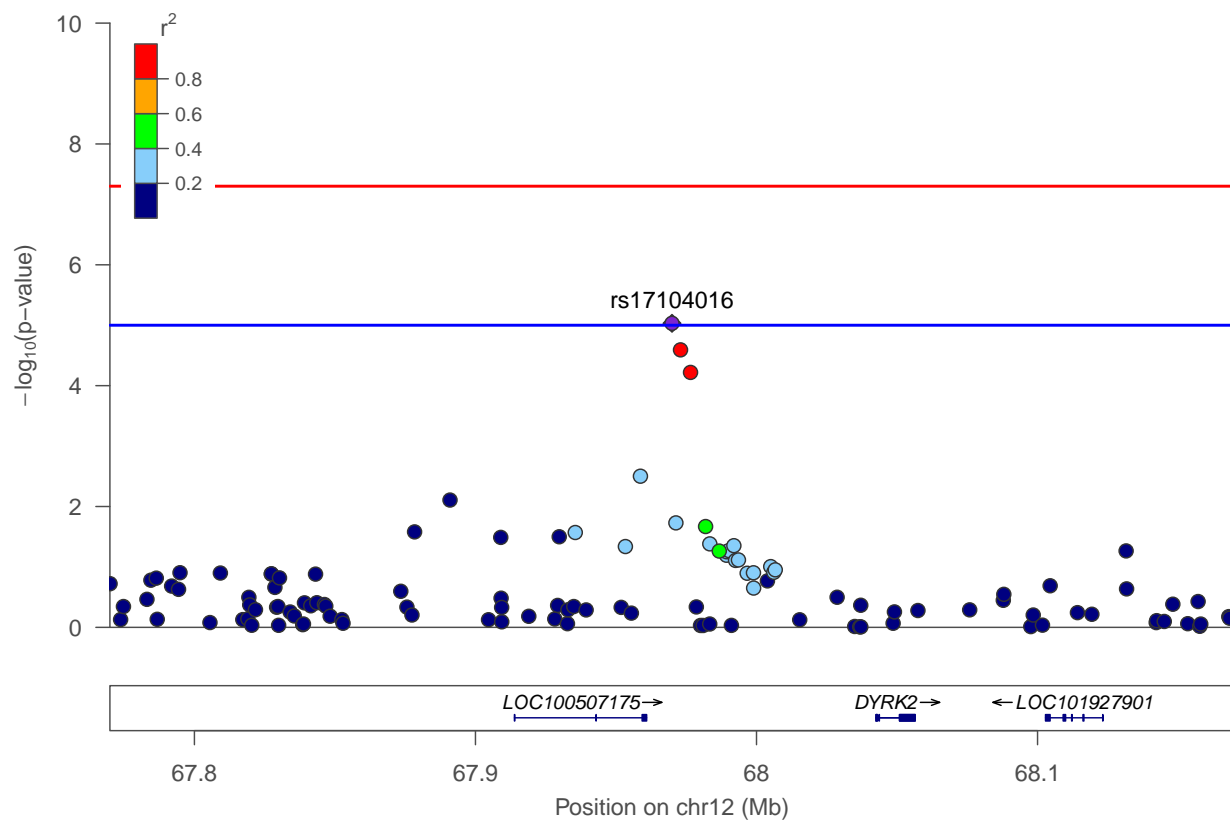


FIGURE S37. LDL on chromosome 12 positions 67769929-68169929

## LDL: LINC00922

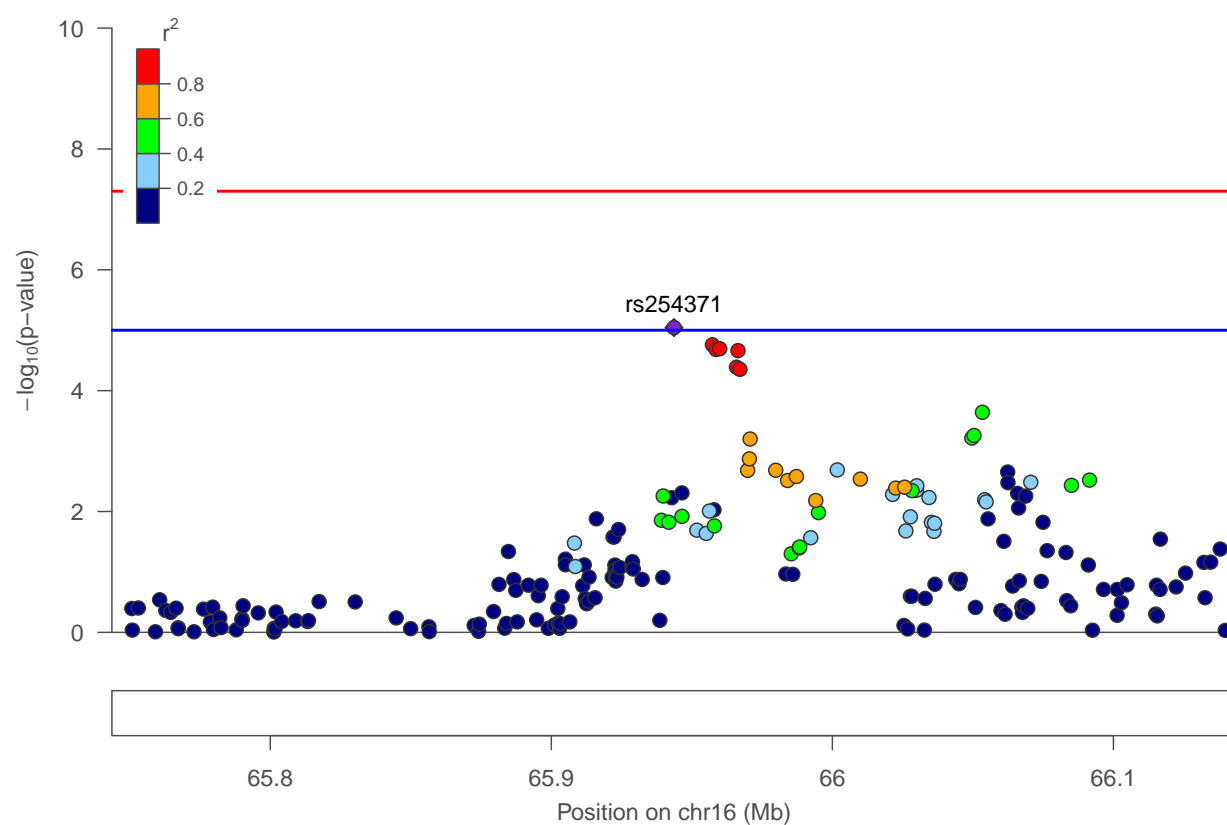


FIGURE S38. LDL on chromosome 16 positions 65743650-66143650

# LDL: ZNF283

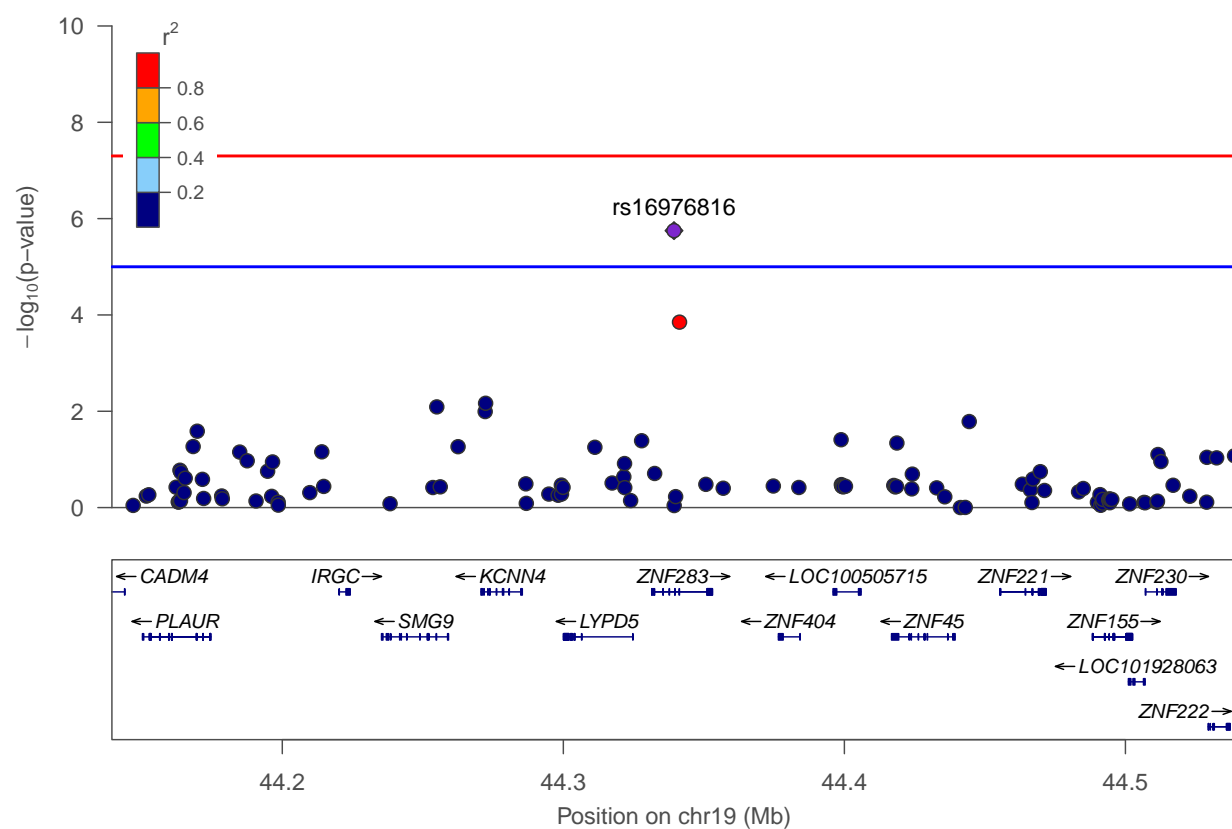


FIGURE S39. LDL on chromosome 19 positions 44139377-44539377

# LDL: APOE

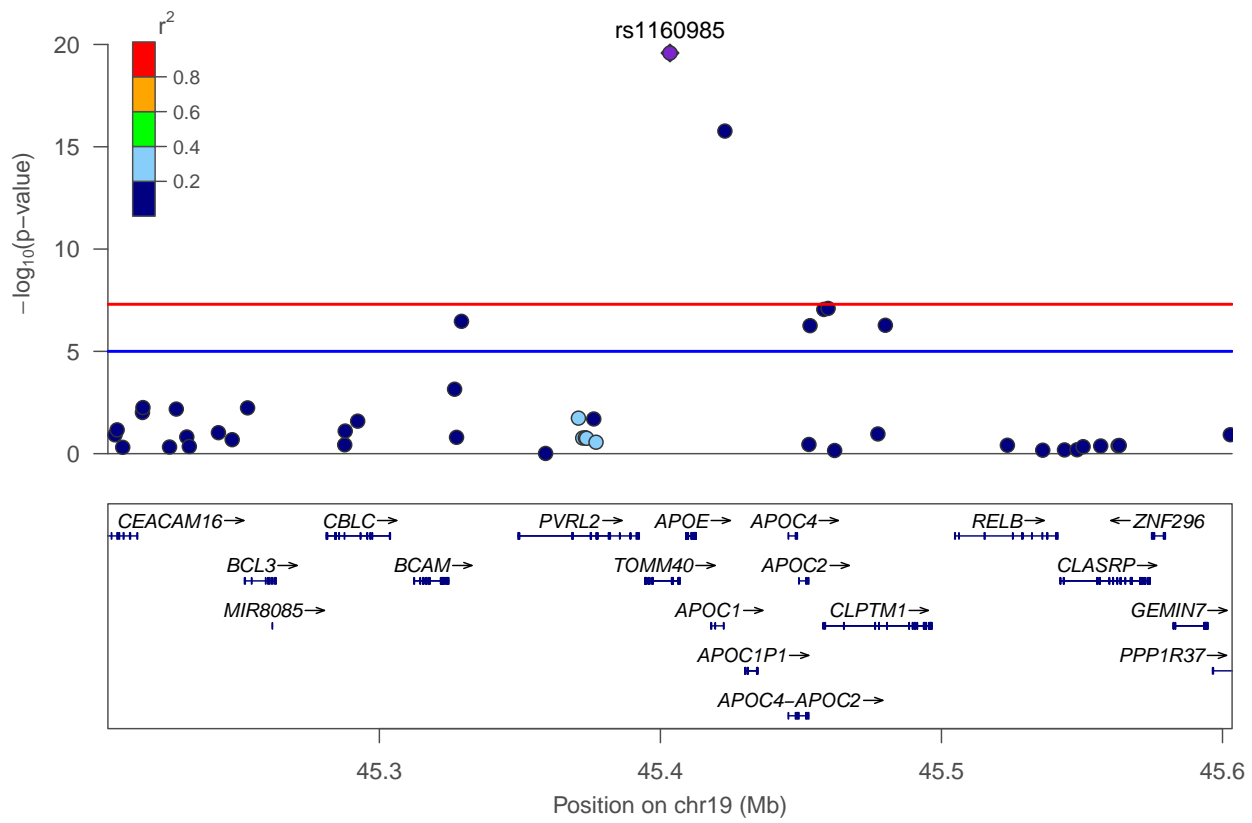


FIGURE S40. LDL on chromosome 19 positions 45203412-45603412

6.4. Triglycerides LocusZoom plots.

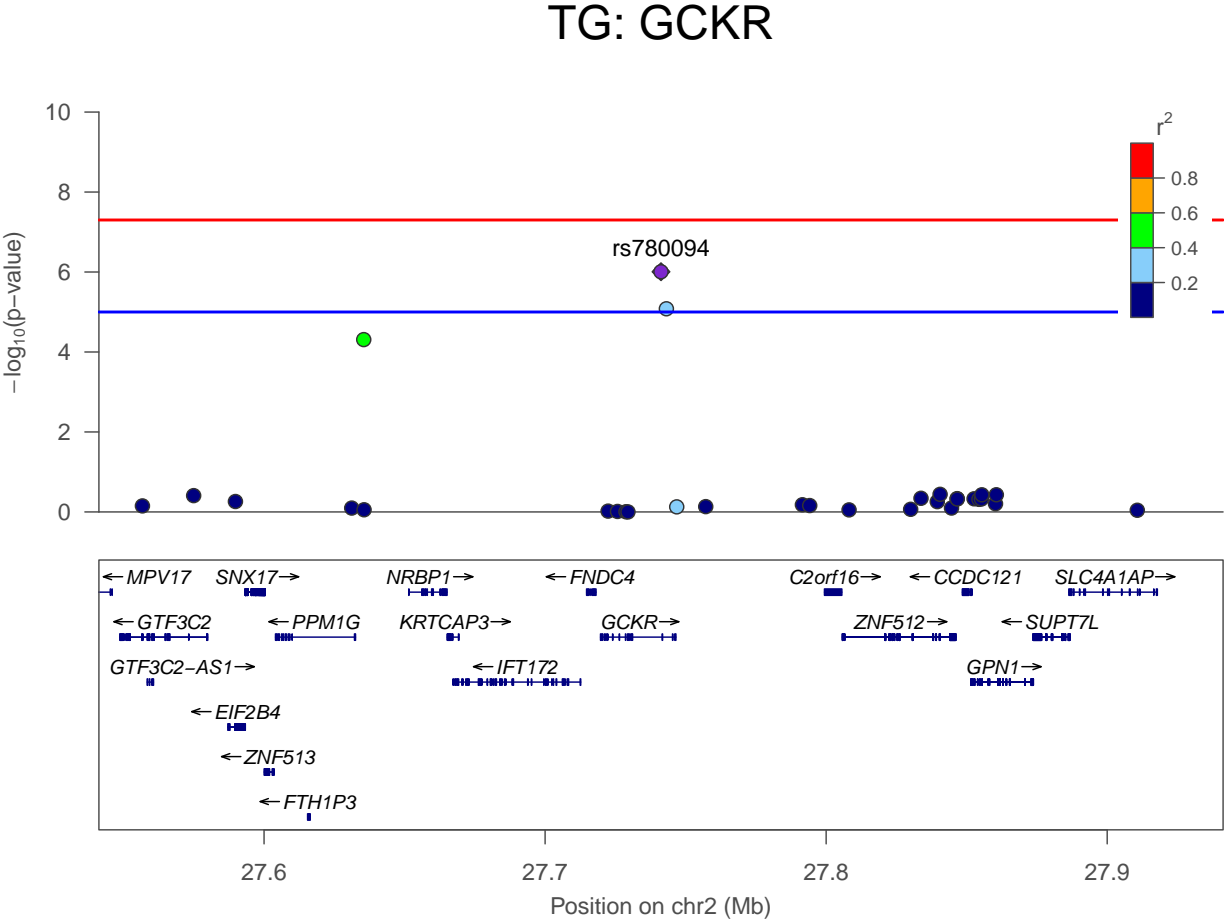


FIGURE S41. TG on chromosome 2 positions 27541237-27941237

# TG: CD200

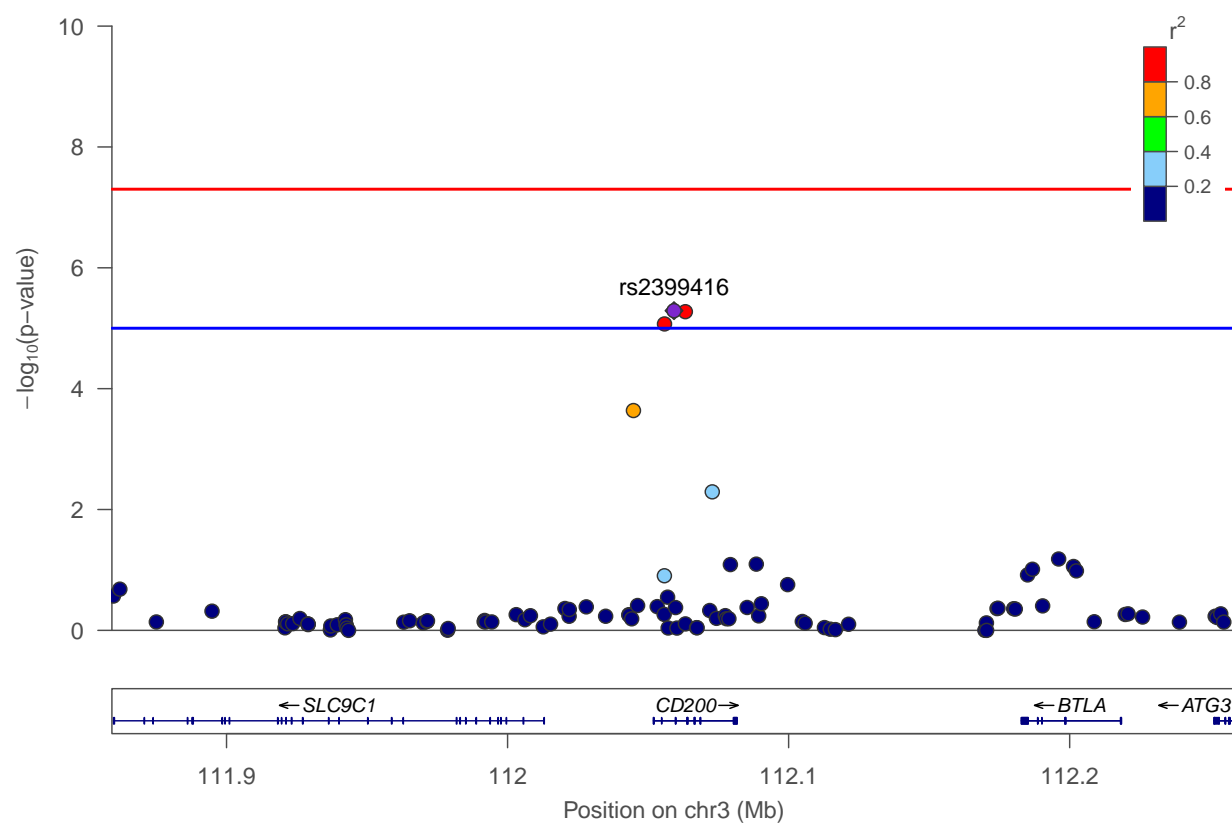


FIGURE S42. TG on chromosome 3 positions 111859213-112259213

# TG: SPIN1

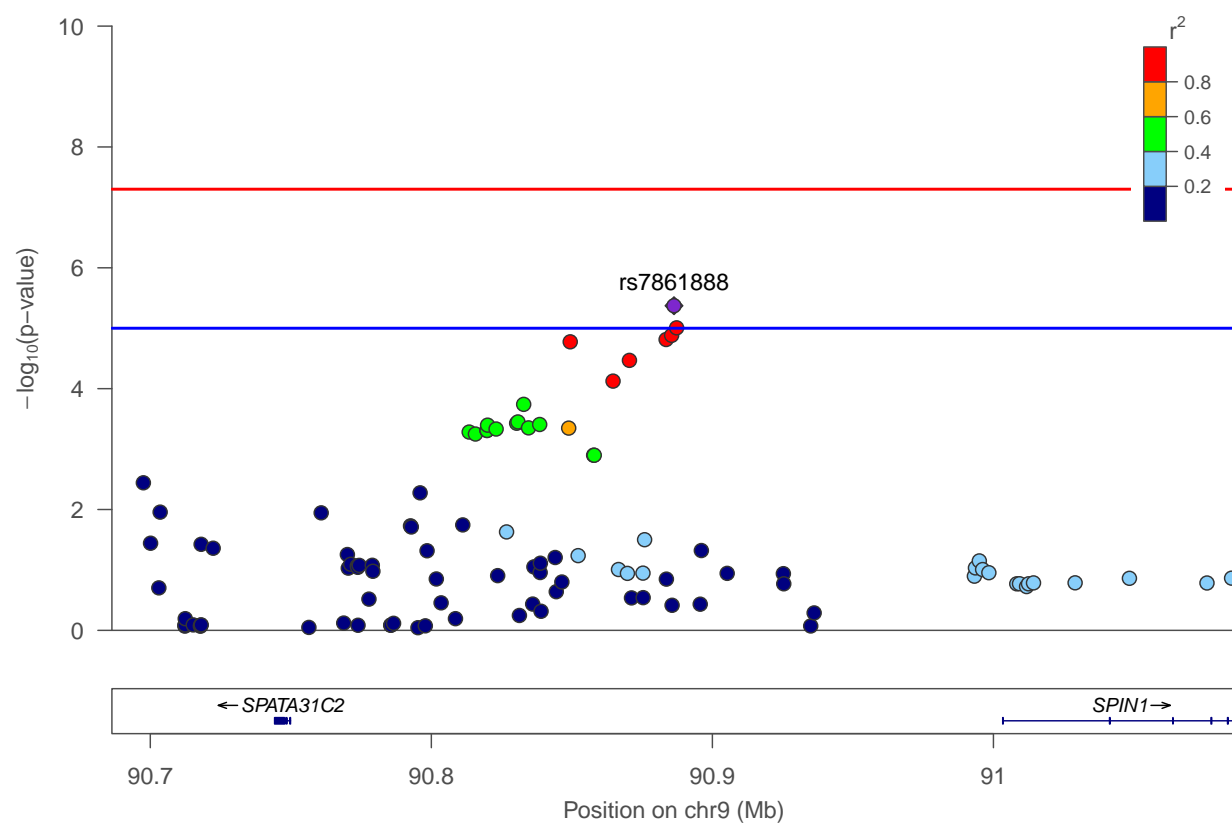


FIGURE S43. TG on chromosome 9 positions 90686340-91086340

# TG: APOA1

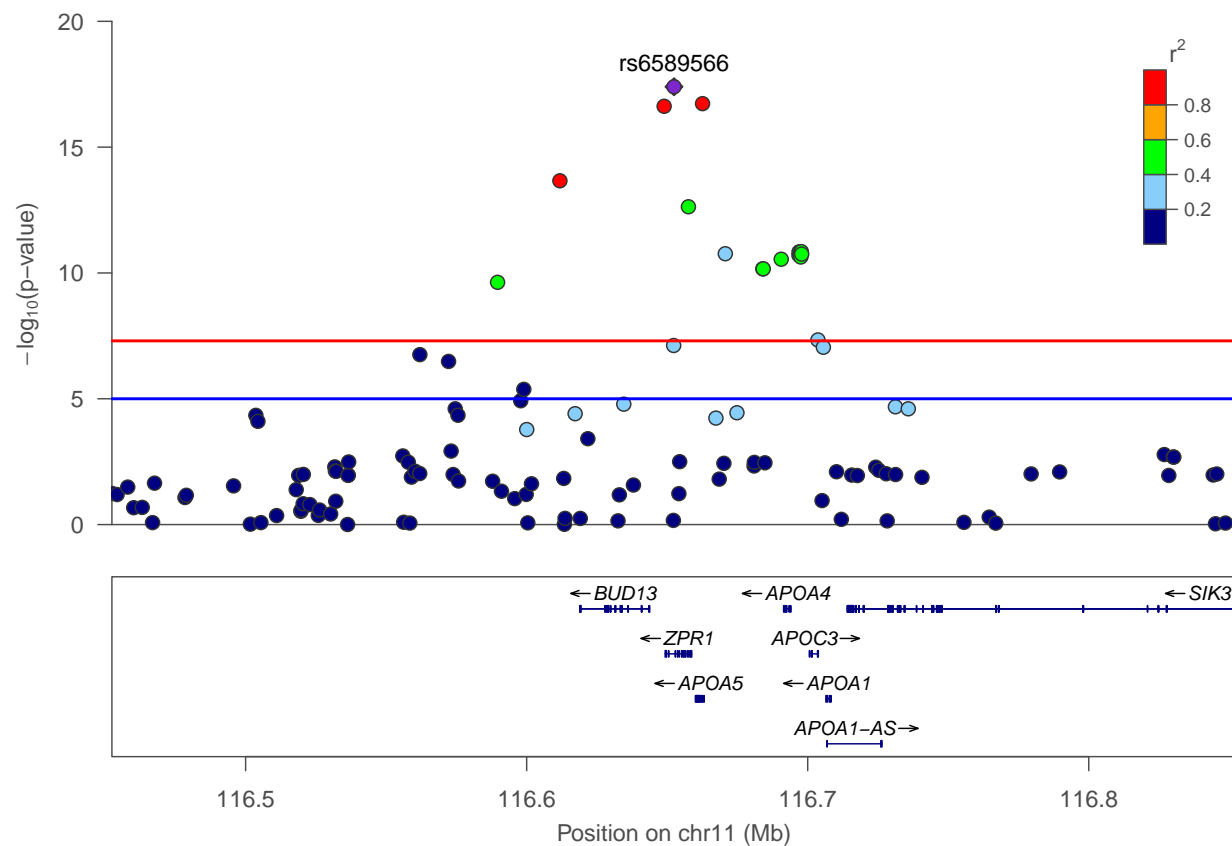


FIGURE S44. TG on chromosome 11 positions 116452423-116852423



# TG: KIRREL3

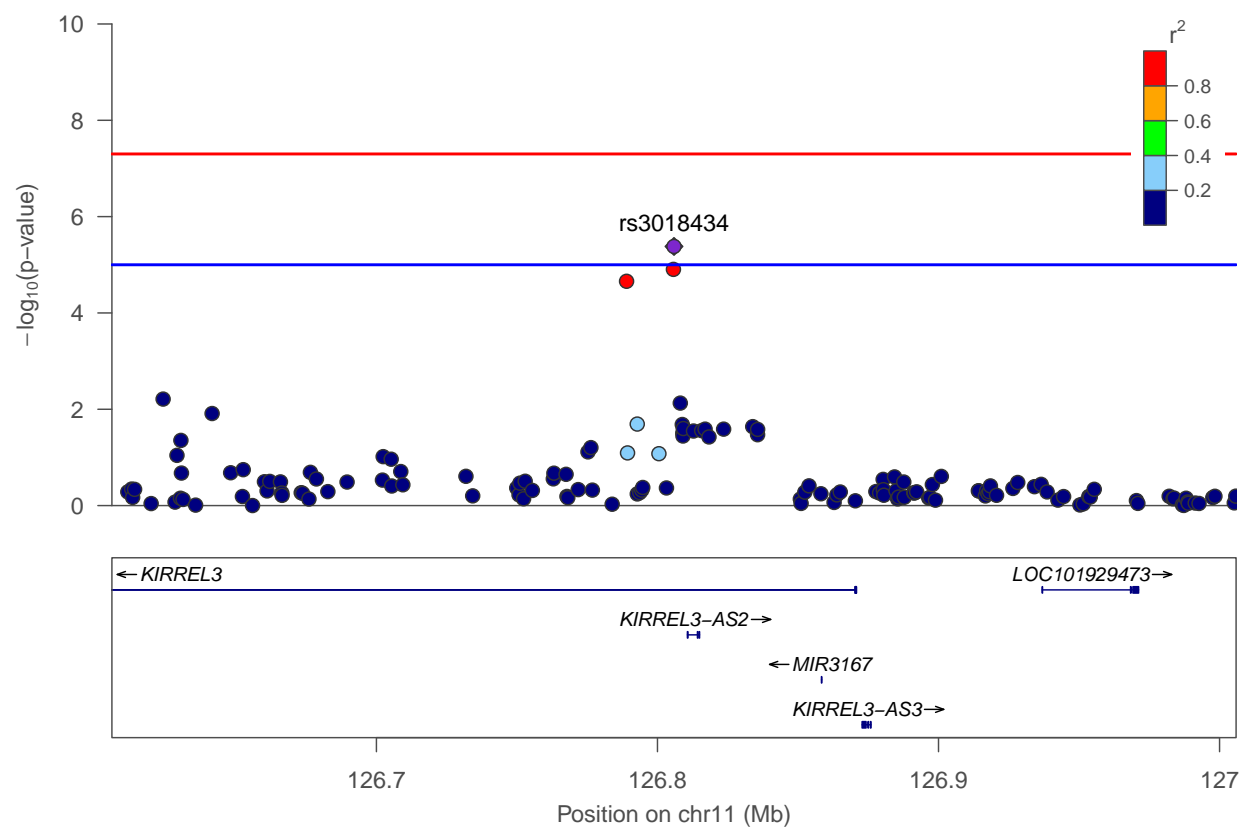


FIGURE S45. TG on chromosome 11 positions 126605881-127005881

# TG: APOE

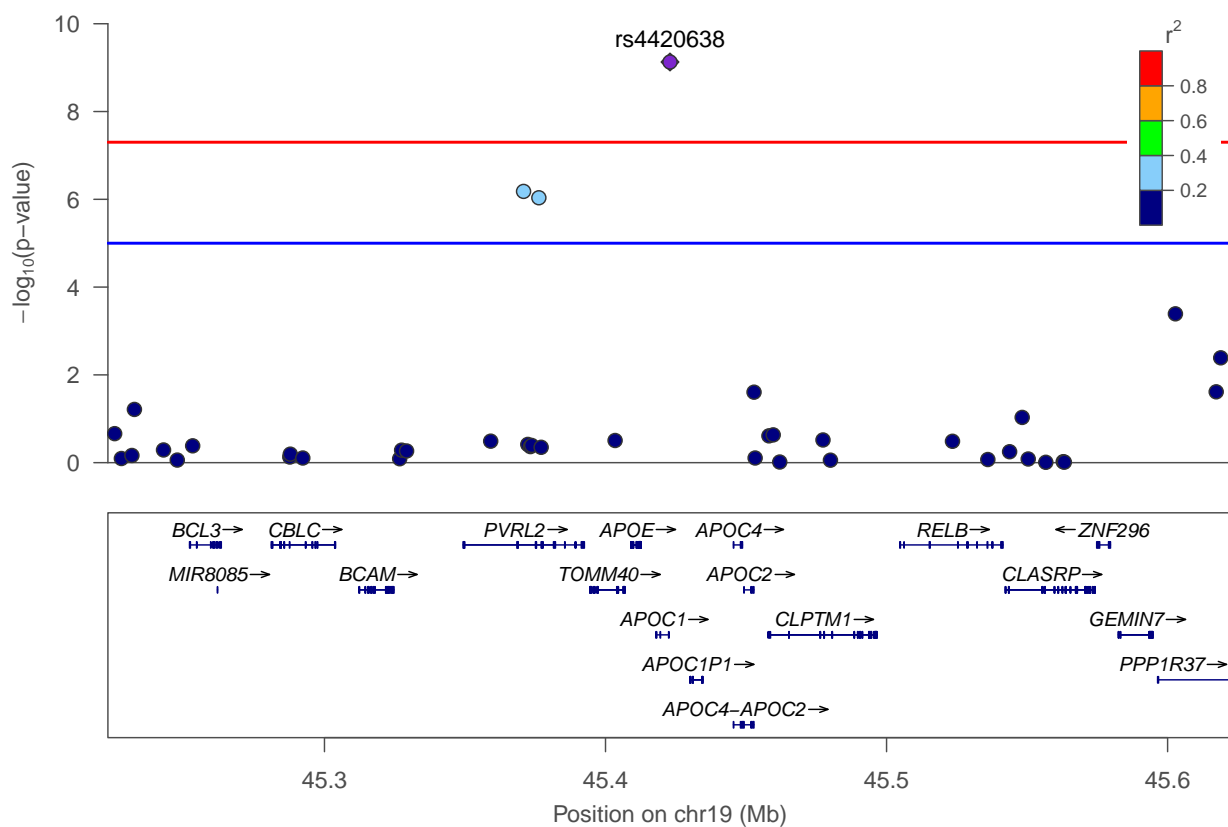


FIGURE S46. TG on chromosome 19 positions 45222946-45622946