Fig. S1 Main effect filter analysis - underlying linkage disequilibrium (LD) structure of SNPs within pairwise interactions (P-value < 0.05) associated with LDL cholesterol level. LD diagram was generated using Haploview

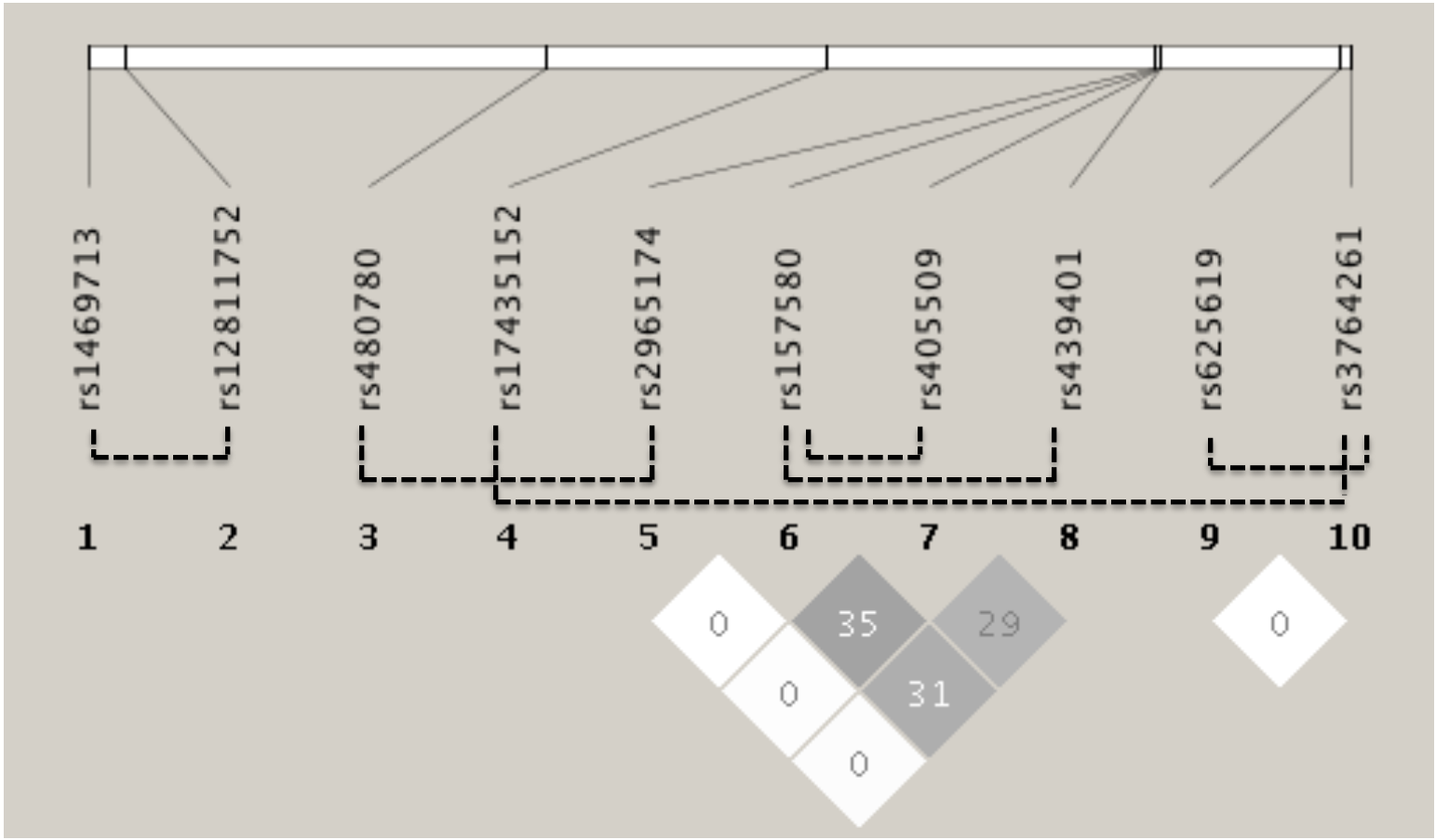

Fig. S2 Main effect filter analysis - underlying linkage disequilibrium (LD) structure of SNPs within pairwise interactions (P-value < 0.05) associated with total cholesterol level. LD diagram was generated using Haploview

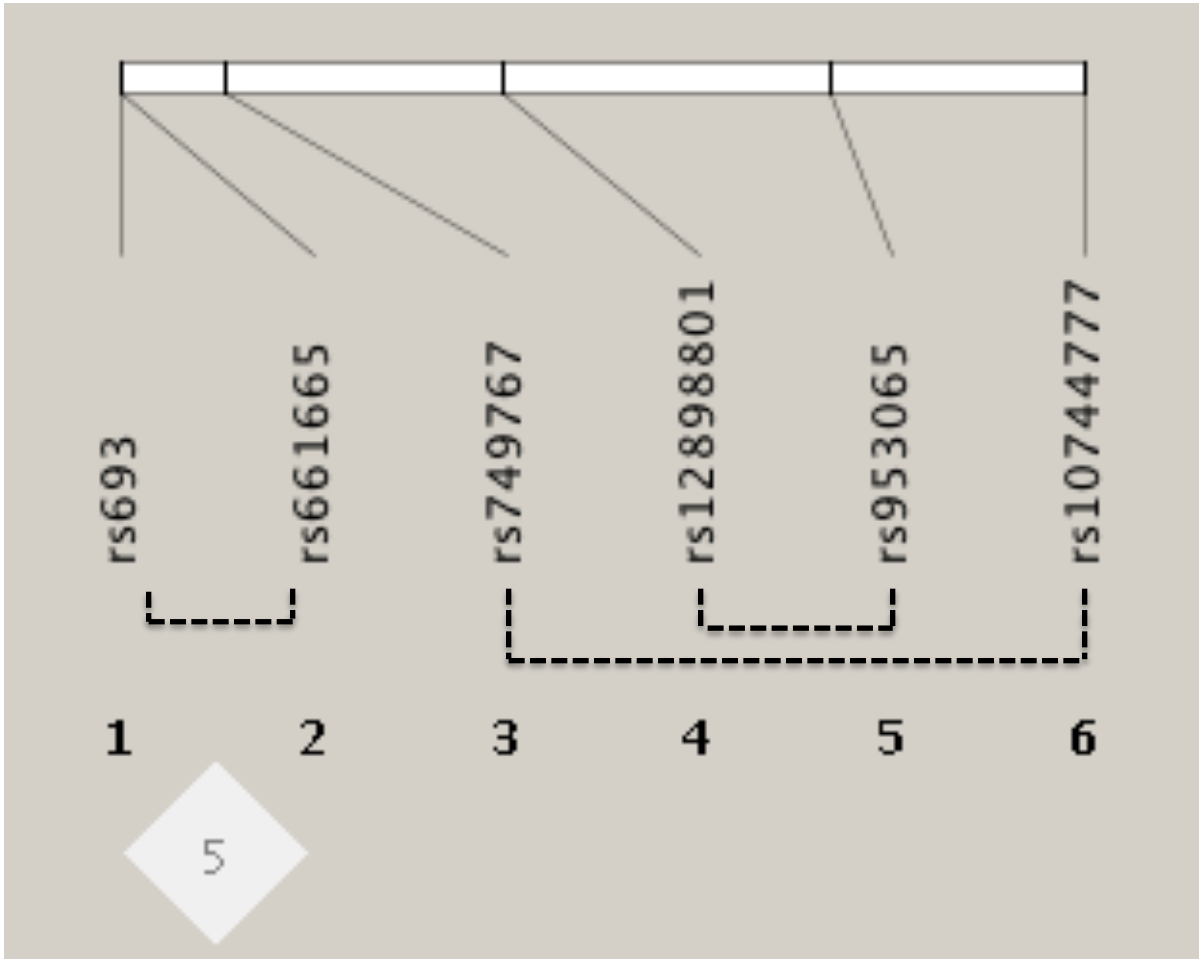

Fig. S3 Main effect filter analysis - underlying linkage disequilibrium (LD) structure of SNPs within pairwise interactions (P-value < 0.05) associated with triglyceride level. LD diagram was generated using Haploview

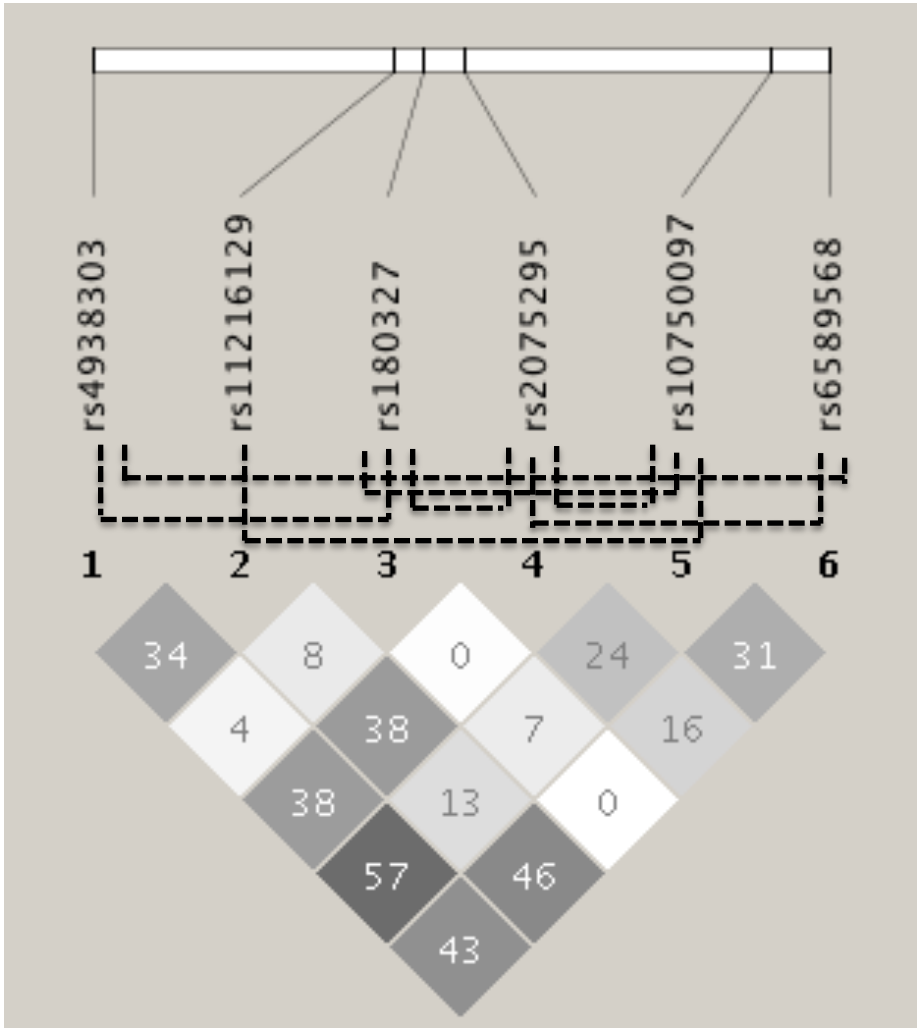

Fig. S4 Biofilter analysis - underlying linkage disequilibrium (LD) structure of SNPs within pairwise interactions (P-value < 0.05) associated with HDL cholesterol level. LD diagram showing r2 values was generated using Haploview

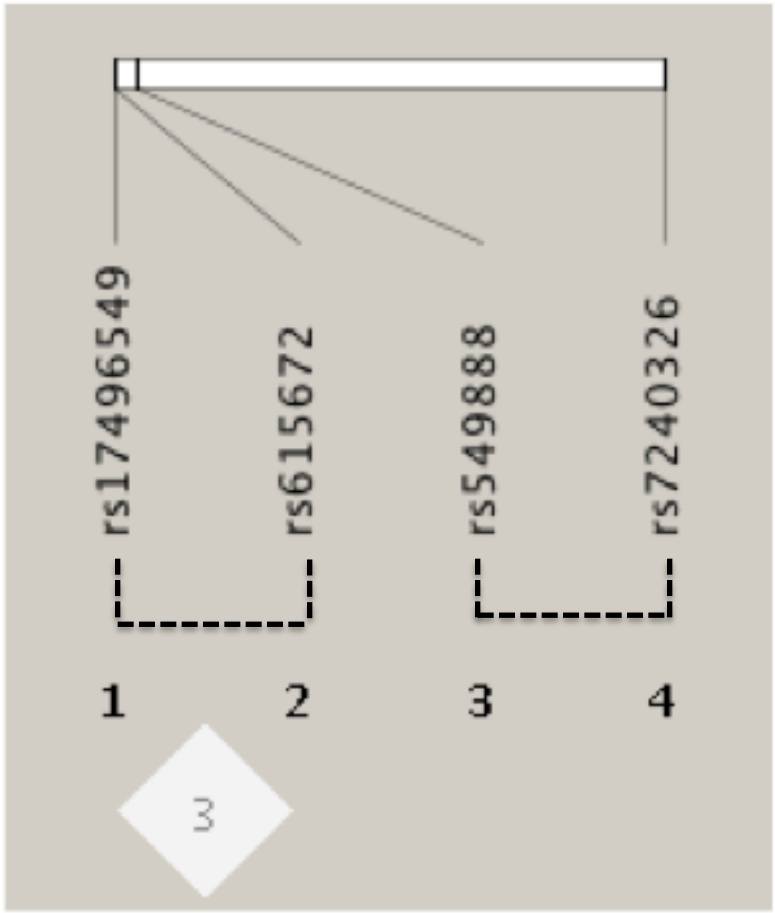

Fig. S5 Biofilter analysis - underlying linkage disequilibrium (LD) structure of SNPs within pairwise interactions (P-value < 0.05) associated with LDL cholesterol level. LD diagram showing r2 values was generated using Haploview

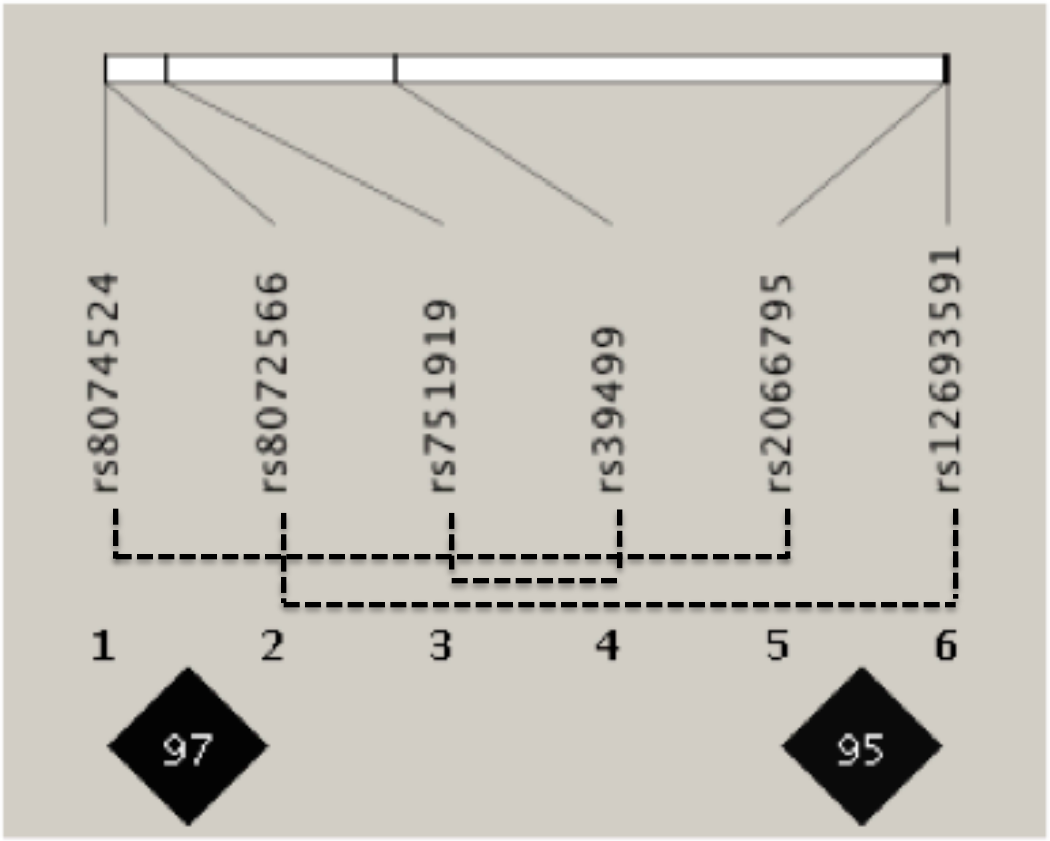

Fig. S6 Biofilter analysis - underlying linkage disequilibrium (LD) structure of SNPs within pairwise interactions (P-value < 0.05) associated with total cholesterol level. LD diagram showing r2 values was generated using Haploview

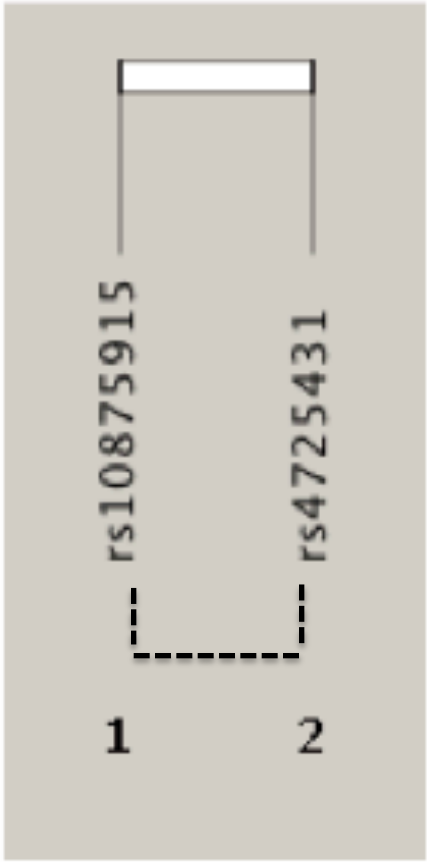

Fig. S7 Biofilter analysis - underlying linkage disequilibrium (LD) structure of SNPs within pairwise interactions (P-value < 0.05) associated with triglyceride level. LD diagram showing r2 values was generated using Haploview

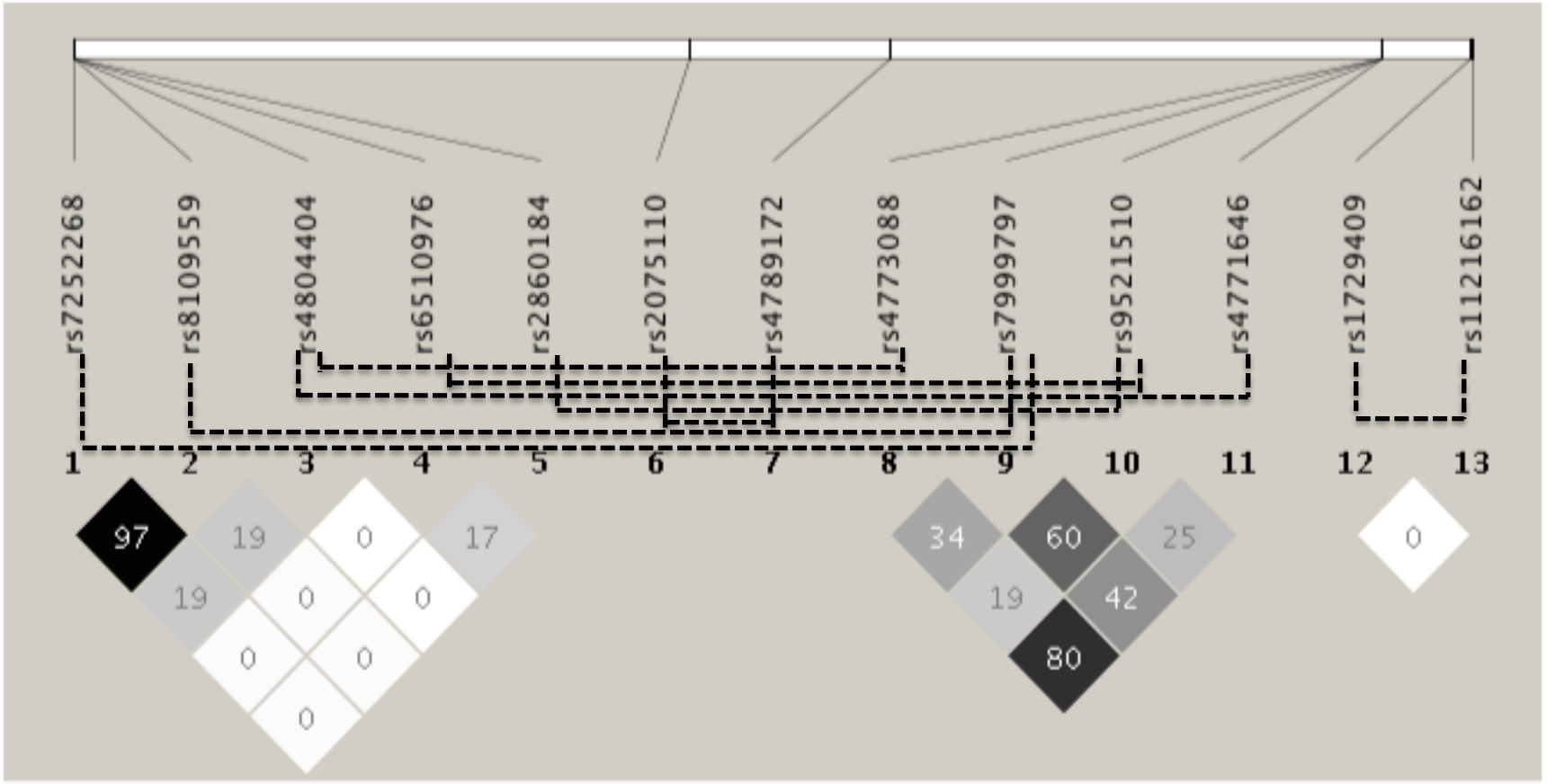

Table S1 Known biological roles of genes identified within SNP-SNP interactions associated with each lipid trait. Gene information found using GeneCards database (www.genecards.org, Accessed March 28, 2015)

Gene	Biological Role
Main effect filter: HDL-C	
CETP	Involved in the transfer of cholesteryl ester from HDL to other lipoproteins.
PDE4B	Belongs to the cyclic phosphodiesterase faily. Hydrolyzes cAMP, which is a key regulator of various physiological processes.
NFKB1	Encodes for the DNA binding subunit of the NFKB complex. NFKB activates multiple immune response genes.
COX6B2	Encodes for subunit 6B2 of cytochrome C oxidase, an enzyme that is a part of mitochondrial respiration.
LPL	Mutations in LPL can cause type 1 hyperlipoproteinemia and other lipoprotein metabolism disorders.
PSRC1	Involved in microtubule dynamics and mitotuc spindle organization.
DAG1	It is a part of the dystrophin-glycoprotein complex which provides a linkage between the cytoskeleton and extracellular matrix.
STAB1	Encodes for a transmembrane scavenger receptor protein that endocytoses low density lipoprotein.
MBL2	Encodes for mannose-binding lectin that is a part of the innate immune system.
FANCB	Associated with the recessive disorder Fanconi Anemia.
IDS	Mutations in this gene cause a lysosomal storage disease called Hunter syndrome.
Main effect filter: LDL-C	

TOMM40	Encodes for a membrane protein required for transport into the mitochondria. Has been associated with increased risk of Alzheimer's disease and shown to affect LDL-C levels.
C7orf10	Mutations in this gene are associated with glutaric aciduria type III.
PDE3A	Encodes for a cGMP inhibited phosphodiesterase, involved in platelet aggregation, cardiac contracility, hormone secretion, etc.
KL	Encodes for a transmembrane protein which has decreased expression in patients with chronic kidney disease
APOE	Encodes for apolipoprotein E which binds the LDL receptor and is involved in lipoprotein formation, sterol transport and cholesterol homeostasis.
CETP	Involved in the transfer of cholesteryl ester from HDL to other lipoproteins.
GATAD2A	Encodes for a zinc finger domain containing protein that acts as a transcriptional repressor.
BCL3	A candidate proto-oncogene, that is associated with the regulation of transcriptional activation of NFκB target genes.
PCSK9	Encodes for an enzyme that is an attractive drug target for hypercholesterolemia.
Main effect filter: TC	
APOB	Mutations within this gene can cause an inherited form of hypercholesterolemia.
LIPC	Encodes for hepatic lipase which is involved in lipoprotein metabolism.
ALDH2	Encodes for aldehyde dehydrogenase that is involved in alchohol metabolism. Has been found to interact with genes involved in maintaining mitochondrial cholesterol levels. A polymorphism within this gene has been shown to be associated with HDL-C.
ACAN	Forms a part of the extracellular matrix in cartilagenous tissues.
BCKDK	Involved in the inactivation of a key enzyme of the valine, leucine and isoleucine catabolic pathways.

Main effect filter: TG	
BUD13	Originally discovered as a splicing factor in yeast, that is involved in nuclear pre-mRNA retention.
GALNT2	Encodes for a member of the GalNAc-transferase family, that catalyzes the initial reaction in O-linked oligosaccharide biosynthesis.
FADS3	Member of the fatty acid desaturase gene family. Encodes for enzymes that regulate the unsaturation of fatty acids.
APOA5	Encodes for an apolipoprotein that maintains plasma triglyceride levels.
LIPA	Encodes for a cholesterol ester hydrolase involved in the hydrolysis of triglycerides within lysosomes.
KIAA0999	Encodes for a serine-threonine protein kinase that is a part of the SIK family.
ZNF259	Encodes for a zinc finger protein. Variants on this gene have been found to be associated with total choelsterol and triglycerides in the past.
Biofilter: HDL-C	
HLA-DRA	Encodes for a member of the HLA-DR class of molecules that are a part of the major histocompatibility complex.
GGNBP1	Pseudogene of unknown function.
HLA-DRB1	Encodes for a member of the HLA-DR class of molecules that are a part of the major histocompatibility complex.
BCL2	A proto-oncogene that suppresses apoptosis. Altering cholesterol levels in the plasma membrane have been shown to affect *BCL2* gene expression.
Biofilter: LDL-C	
RIPK2	Encodes for a serine-threonine kinase that is a part of the receptor interacting protein family.

STAT1	Encodes for a transcription factor that belongs to the signal transducer and transcription activator family. It is also involved in the IL-6 signaling pathways involved in inflammation, immune regulation and oncogenesis. Oxidized LDL has been shown to activate *STAT1*.
CYLD	Encodes for a cytoplasmic protein involved in ubiquitination.
STAT3	Encodes for a transcription factor that belongs to the signal transducer and transcription activator family. It is also involved in the IL-6 signaling pathways involved in inflammation, immune regulation and oncogenesis. Oxidized LDL has been shown to activate *STAT1*.
Biofilter: TC	
PRKAG2	*PRKAG2* encodes for the regulatory γ2 subunit of an AMP-activated protein kinase.
MLL2	Encodes for a mixed-lineage leukemia histone methylase.
Biofilter: TG	
IRS2	Encodes for the insulin receptor substrate 2 molecule that mediates the effects of insulin.
EGFR	Encodes for the epidermal growth factor receptor. Cholesterol levels in the plasma membrane have been shown to regulate *EGFR* activity.
APOA5	Encodes for an apolipoprotein that maintains plasma triglyceride levels.
INSR	Encodes for the insulin receptor molecule.
GRB2	Encodes for the growth factor receptor binding protein.
KIAA0999	Encodes for a serine-threonine protein kinase that is a part of the SIK family

Table S2 Information for cohorts providing individual level data

Cohort No.	Cohort Name	Geographic Location	No. of Samples
1	ARIC	Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN	9588
2	CARDIA	Birmingham, AL; Minneapolis, MN; Chicago, IL; and Oakland, CA	1443
4	CHS	Sacramento, CA; Hagerstown, MD; Winston-Salem, NC; and Pittsburgh, PA	3952
5	FHS	Framingham, MA	7556
6	MESA	New York, NY; Baltimore, MD; Chicago, IL; Los Angeles, CA; Twin Cities, MN; and Winston-Salem, NC	2298
		Total Samples	**24837**

Table S3 Information of eMERGE cohorts providing individual level data for replication analyses

Site Name	Geographic Location	No. in Sample
	HDL-C	
Group Health Cooperative	Seattle, WA	1861
Vanderbilt University	Nashville, TN	552
Marshfield Clinic	Stevens Point, WI	2100
Mayo Clinic	Rochester, MN	1447
Northwestern University	Evanston, IL	624
	Total Sample Size	**6584**
	LDL-C	
Group Health Cooperative	Seattle, WA	959
Vanderbilt University	Nashville, TN	578
Marshfield Clinic	Stevens Point, WI	1929
Mayo Clinic	Rochester, MN	1477
Northwestern University	Evanston, IL	553
	Total Sample Size	**5496**

TC		
Group Health Cooperative	Seattle, WA	1886
Vanderbilt University	Nashville, TN	583
Marshfield Clinic	Stevens Point, WI	2832
Mayo Clinic	Rochester, MN	1489
Northwestern University	Evanston, IL	632
	Total Sample Size	**7422**
TG		
Group Health Cooperative	Seattle, WA	1127
Vanderbilt University	Nashville, TN	586
Marshfield Clinic	Stevens Point, WI	2184
Mayo Clinic	Rochester, MN	1495
Northwestern University	Evanston, IL	625
	Total Sample Size	**6017**

Table S4 Number of original (non-proxy) and LD-expanded (proxy) SNP-SNP models tested for replication in eMERGE dataset. Numbers are shown for each lipid trait after using both filtering methods

	No. of original SNP-SNP models tested	No. of LD-expanded models tested
Main effect filter: HDL-C	4	114
Main effect filter: LDL-C	2	23
Main effect filter: TC	0	24
Main effect filter: TG	2	15
Biofilter: HDL-C	0	3
Biofilter: LDL-C	0	305
Biofilter: TC	0	8
Biofilter: TG	8	56

Table S5 Number of LD-expanded (proxy) SNP-SNP models generated for each original discovered SNP-SNP model. Also shown are the number of SNP-SNP models tested for replication in eMERGE dataset per signal. Numbers are shown for each lipid trait after using both main effect and Biofilter filtering methods

Original discovered model	No. of additional LD expanded models generated	No. of LD-expanded models tested for replication in eMERGE
Main effect filter: HDL-C		
rs4783961,rs1800775	9	7
rs12720918,rs158477	1	0
rs4783961,rs1864163	0	1
rs12720918,rs4783961	2	0
rs1864163,rs4784744	4	3
rs12708967,rs820299	1	0
rs12447924,rs9939224	39	0
rs4783961,rs158477	0	0
rs1864163,rs158477	0	0
rs1864163,rs820299	0	0
rs4783961,rs9939224	7	1
rs1800775,rs820299	9	0
rs12744291,rs1010554	97	4
rs230541,rs4935047	159	80
rs12976922,rs2952101	7	0
rs9644636,rs7013777	25	15

rs9939224,rs4784744	39	3
rs599839,rs2952101	8	0
rs12708967,rs158477	1	0
rs3870336,rs6641322	1	0
Main effect filter: LDL-C		
rs157580,rs439401	0	1
rs17435152,rs3764261	29	0
rs157580,rs405509	1	1
rs12811752,rs1469713	215	0
rs480780,rs2965174	35	21
rs625619,rs3764261	9	0
Main effect filter: TC		
rs693,rs661665	31	0
rs12898801,rs953065	4	0
rs10744777,rs749767	131	24
Main effect filter: TG		
rs2075295,rs6589568	0	0
rs4938303,rs180327	5	0
rs180327,rs2075295	1	2
rs180327,rs10750097	1	0
rs11216129,rs10750097	7	0
rs609526,rs12257915	20	0
rs2075295,rs10750097	0	0

rs4938303,rs6589568	2	0
rs174455,rs689243	63	11
rs180327,rs618923	3	2
Biofilter: HDL-C		
rs17496549,rs615672	51	0
rs549888,rs7240326	41	3
Biofilter: LDL-C		
rs39499,rs751919	1539	261
rs12693591,rs8072566	83	11
rs2066795,rs8074524	83	11
Biofilter: TC		
rs4725431,rs10875915	11	8
Biofilter: TG		
rs9521510,rs2860184	20	0
rs9521510,rs6510976	41	22
rs2075110,rs4789172	11	6
rs4773088,rs4804404	19	6
rs7999797,rs8109559	11	7
rs4771646,rs4804404	69	15
rs1729409,rs11216162	15	0
rs7999797,rs7252268	11	7

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each study site, and written informed consent was obtained from all participants. This cohort was genotyped as part of the National Heart Lung and Blood Institute's (NHLBI) Candidate Gene Association Resource (CARe) (Musunuru, K., Lettre, G., Young, T., Farlow, D.N., Pirruccello, J.P., Ejebe, K.G., Keating, B.J., Yang, Q., Chen, M.H., Lapchyk, N. et al. Candidate gene association resource (CARe): design, methods, and proof of concept. Circ. Cardiovasc. Genet, 3, 267-275.).