SUPPLEMENTAL MATERIAL

Supplemental Methods

Phenotypic measurements

Individuals in the Pima study were community residents ≥ 15 years old; individuals in the FIND study were urban Amerindians (≥50% heritage by self-report) who were ≥18 years old. In both studies participants were included irrespective of health status. For the Pima study, we selected data from the time point from the last available examination prior to 2005 because the self-reported use of antilipidemic medication in this population was very limited (4.6% of subjects) during this time.[1] Use of antilipidemic medicines was also limited in the FIND participants (5.1% of subjects). Over 85% of those using antilipidemic medicines were taking statins; fibrate use was uncommon. Measurement methods of lipid levels were the same for both the Pima and FIND studies, and have been previously described.[2] Briefly, serum samples were collected 1–5 days before measurements. Total serum cholesterol was determined with a colorimetric method from 1965 to March 1992 and with an enzymatic method subsequently. Serum TG and HDL-C concentrations have been measured since 1993 by enzymatic methods. LDL-C was estimated with the Friedewald formula.[3] Hypertriglyceridemia was defined if TG was ≥1.69 mmol/L. In addition, measurements of 3 lipoprotein fractions (very low density lipoprotein cholesterol or VLDL-C, LDL-TG, and VLDL-TG) were available in a subset (n=206).[4]

In the Pima study, measurements of height and weight were performed by medically trained personnel to calculate body mass index (BMI). T2D was determined according to 1997 American Diabetes Association criteria based on results from an oral glucose tolerance test (or OGTT, i.e. fasting plasma glucose ≥7.0 mmol/l, 2-h plasma glucose concentration ≥11.1 mmol/l) or medical record reviews. In FIND participants, T2D was defined based on a previous medical

diagnosis, hemoglobin $A1_C$ ≥6.5% or fasting plasma glucose concentration ≥7.0 mmol/l (2010 American Diabetes Association criteria).

Genotypic data ascertainment

Genotype data used in the linkage analysis (to calculate IBD sharing in the autosomal genome and to assess local IBD) were produced with the Affymetrix 6.0 Human SNP Array (Affymetrix, Santa Clara, CA) using the BIRDSEED algorithm, as described previously.[5] SNPs were excluded under any of 4 conditions: (1) >15% of missing genotype calls, (2) genotype frequencies diverged from Hardy-Weinberg expectations (P <0.001), (3) concordance among 100 duplicate samples <97%, or (4) the minor allele frequency (MAF) <5%. Genotyping of SNPs in both replication sets was performed by BeadXpress system (Illumina, San Diego, CA), Taqman genotyping assays (Applied Biosystems, Carlsbad, CA), KASP based assays (LGC, Middlesex, UK), or a custom SNP Array designed to capture common variants in the Pima Indian population (Affymetrix, Santa Clara, CA), all according to manufacturers' protocols. Genotype quality control required a call rate >95%, no deviation from HWE (P<0.001) and a discrepancy rate of <2.5% for blind duplicates (>100 for each sample set). Genotypes of all carriers of *APOC3* A43T were verified by direct sequencing.

Statistical analyses

Estimation of the percentage of alleles shared identical-by-descent matrix. The execution of variance components linkage analysis of quantitative traits requires information on the alleles shared identical-by-descent (IBD) between 2 individuals. Traditionally, IBD was estimated between pairs of individuals in a pedigree based on self-reported relationships. In recent years, several new methods have been developed to estimate IBD more accurately using high-density genetic data, and these methods are applicable even in pairs of individuals without known relationships.[6-9] We used the program Beagle[10] and genetic maps from the Hapmap project

(http://hapmap.ncbi.nlm.nih.gov/, based on Phase II and Build 37 data) to carry out IBD estimation at each of ~400,000 SNPs in our dataset. The program Beagle takes the LD among variants into account for the IBD estimates. By using high-density genetic data (e.g. SNP data used for GWAS), probabilities for phased haplotypes are calculated and used as the basis to estimate IBD at any given locus. The average relatedness for any given pair was calculated as the genome-wide average of local IBD. As our Pima samples had the characteristics of a founder population, the recommended default setting for the scale parameter[11] was not optimal; thus we set the scale parameter at 10, which we determined by simulation to produce more accurate estimates for a sample of this size derived from a founder population. Beagle calculates the probability that a pair of individuals share ≥1 allele IBD at each SNP (*i.e.*, ignoring bilineal sharing); this value was converted to proportion IBD sharing by multiplying by ½. For known full sibling pairs (who are the major pair type with bilineal sharing), the multiplication was by ⅔ instead of ½, as given that they share ≥ 1 allele, they will on average share 1 allele ⅔ of the time and 2 alleles ⅓ of the time (*i.e.,* the expected proportion of alleles shared IBD conditional on sharing ≥1 allele =0.5*⅔ + 1.0*⅓ = ⅔).

Genome-wide linkage analysis of 4 lipid traits. Linkage analysis was conducted using the principles of the variance-components method developed by Amos.[12] Details of our approach have been described in detail previously.[13-15] Briefly, a linear mixed model is fitted to estimate fixed effects, representing the intercept and covariate effects, and three components of variance: an additive "monogenic" component (σ^2_M) that estimates effects of a locus in the region of interest, a "polygenic" component (σ^2_G) that incorporates overall relatedness, and an "environmental" component (σ^2_E) that incorporates effects unique to the individual. Thus, the variance-covariance matrix for the trait (Ω) among all individuals in the sample is modeled as:

$$\Omega = \Pi\sigma^2_M + \Phi\sigma^2_G + I\sigma^2_E,$$

where Π is a matrix of the IBD estimates between pairs of individuals at the location of interest, Φ is a matrix of the genome-wide average IBD, and I is an identity matrix. The null hypothesis of no linkage was assessed by comparing the full model to one in which the additive monogenic effect was constrained to 0, and the models were compared using a likelihood ratio test.[16] The logarithm of the odds score (LOD) for linkage was calculated by dividing the likelihood ratio test by $2\times\log_e(10)$.

As the variance component analysis can be sensitive to departures from a normal distribution of the trait, all 4 lipid traits were normalized by inverse Gaussian transformation for the linkage analysis. The same analysis of the trait using its natural logarithm transformation did not substantially alter results. The model was fit with the "PROC MIXED" function of SAS (SAS Institute, Cary, NC). To estimate the power of this approach in the present sample, we conducted simulations in which trait data were generated under the assumption that a randomly selected SNP was a functional variant with a specified effect on the trait variance.

Fine-mapping study –association analysis conditional on linkage effects. We used the GWAS data from the Affymetrix 6.0 array and the WGS data of 296 Pima subjects as the reference panel to impute genotypes of all variants (both SNPs and insertion-deletion variants) not available from the Affymetrix 6.0 array. Imputation was performed with MINIMAC.[17] All directly genotyped variants and imputed variants (either nsSNP, with minor allele frequency (MAF) ≥1% or any other variant with MAF ≥5%) with imputation r^2 >0.3 were analyzed for association. A total of 3,450 and 7,377 variants were analyzed for fine-mapping of the genome-wide significant TG and the HDL-C linkage locus, respectively. All analyses were conducted using SAS.

Replication association analyses of TG. The association between genotypes and TG was determined with linear regression modeling (additive model), where homozygotes for the major allele, heterozygotes, and homozygotes for the minor allele were coded to a numeric variable

for genotype (0, 1, and 2). To avoid the reduction in sample size resulting from missing data at multiple loci, we inferred missing genotypic data. To accomplish this, we calculated the probability of each of the 3 possible genotypes for each individual with missing data from the genotypes in the individual's relatives using MLINK,[18] and used these probabilities to construct the genotypic score. For the Pima sample, the model was fitted using a mixed model procedure to account for sibship. For the FIND sample, a linear regression model was used. To account further for cryptic relatedness in FIND (where family data are less extensive), the genomic control procedure was used, based on 42 randomly-selected SNPs.[19] Finally, meta-analysis for the Pima and FIND sample was conducted by the inverse variance method[20] to evaluate the association effects based on the largest sample. TG values were transformed by their natural logarithms (ln) to reduce skewness. We also included tag SNPs (r^2>0.8) of variants found to have significant associations with TG in the fine-mapping study in the replication study. The tag SNPs and haploblocks (default definition) were identified using Haploview.[21]

Correction for multiple testing in association analyses. We corrected for multiple comparisons accounting for linkage disequilibrium among SNPs by calculating the effective number of independent comparisons as suggested by Moskvina and Schmidt.[22] This method estimates the effective number of independent tests based on the pairwise correlation matrix between markers (i.e. the maximum absolute pairwise correlation between a given marker and all other markers in a defined window) and the desired overall type I error rate. By this method, for example, the 3,450 variants tested in the fine-mapping study of TG represented 718 effectively "independent" tests. In the replication study using the Pima sample, 11 variants tested were equivalent to 7.6 "independent" tests. Observed p values were corrected with a Bonferroni correction using this factor accordingly. All presented p values for the fine-mapping and replication studies are corrected p values.

Haplotype construction and analyses. Haplotype frequencies for pairs of variants were calculated in all Pima and FIND subjects with the Estimating Haplotypes (EH) program.[23, 24] D′ was calculated as a measure of allelic association, and r^2 as a measure of concordance. Association between traits and individual haplotypes were examined with a modification of the zero-recombinant haplotyping procedure.[25]

Estimates of population admixture. In the genome-wide and fine-mapping linkage studies, this estimate was calculated as the first principal component (PC1) in the principal component analysis of GWAS SNPs. For all samples used in the replication studies, as there were no SNP array data available, we typed 45 ancestry informative markers (AIMs) recommended by Tian et al.[26] The proportion of Amerindian heritage (% AI heritage) was estimated using a maximum likelihood method proposed by Hanis et al.[27] The correlation between PC1 and % AI heritage was high (r=0.87). In other words, the population admixture estimate for each subject used in the linkage studies was done based on GWAS SNP data, and that used in the replication studies was obtained based on 45 AIMs.

Covariates. Covariates used in all models included age, sex, T2D status at the time of the lipid measurement, and population admixture estimates. Participants taking antilipidemic medicines were included in the analyses presented (without adjustment), but linkage and association analyses were repeated excluding those taking antilipidemic medicines with similar results.

TABLE AND FIGURE LEGENDS

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Figure S2. Genome-wide linkage study results for 4 serum lipid traits

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Figure S6. rs964184 vs. *APOA5* 3-SNP haplotypes and frequencies

Table S1. Characteristics of 3 sets of study samples

Pima Indian subjects (n = 1,024) used for genome-wide linkage analysis

characteristics	Men (n = 458, 44.7%)	Women (n = 566, 55.3%)
Age (years)	41.1 ± 13.6	42.9 ± 13.8
BMI (kg/m^2)	34.0 ± 8.2	36.9 ± 9.1
% T2D	37.6%	52.5%
Total cholesterol (mmol/L)	4.76 ± 0.99	4.69 ± 1.10
HDL cholesterol (mmol/L)	1.20 ± 0.41	1.26 ± 0.37
LDL cholesterol (mmol/L)	2.79 ± 0.81	2.63 ± 0.80
Triglycerides (mmol/L)	1.76 ± 1.48	1.70 ± 1.21

Replication Set 1 - 5,491 additional Pima Indians (Pima sample)

characteristics	Men (n = 2,295, 41.8%)	Women (n = 3,196, 58.2%)
Age	34.8 ± 14.5	36.9 ± 15.4
BMI	33.3 ± 8.0	35.5 ± 8.8
% T2D	31.6%	39.1%
% Amerindian heritage	0.88 ± 0.16	0.90 ± 0.14
Total cholesterol (mmol/L)	4.69 ± 1.02	4.51 ± 0.98
HDL cholesterol (mmol/L)	1.16 ± 0.37	1.23 ± 0.35
LDL cholesterol (mmol/L)	2.79 ± 0.84	2.58 ± 0.77
Triglycerides (mmol/L)	1.67 ± 1.47	1.51 ± 1.09
Hypertriglyceridemia*	34.7%	30.6%

Replication Set 2 - 3,189 southwestern Native Americans (FIND sample)

characteristics	Men (n = 1,576, 49.4%)	Women (n = 1,613, 50.6%)
Age	36.5 ± 12.4	36.7 ± 13.3
BMI	30.1 ± 6.5	32.8 ± 7.8
% T2D	24.2%	31.6%
% Amerindian heritage	0.80 ± 0.16	0.81 ± 0.16
Total cholesterol (mmol/L)	4.73 ± 1.07	4.50 ± 1.09
HDL cholesterol (mmol/L)	1.30 ± 0.45	1.25 ± 0.37
LDL cholesterol (mmol/L)	2.68 ± 0.80	2.49 ± 0.75
Triglycerides (mmol/L)	1.69 ± 1.31	1.61 ± 1.79
Hypertriglyceridemia*	36.0%	32.1%

* Hypertriglyceridemia was defined as having a serum triglyceride levels ≥ 1.69 mmol/L.

Table S2. Maximum LOD from genome wide linkage studies of 4 serum lipid traits*

Trait	Total heritability	n	Chromosome	LOD	p	variance explained
Total cholesterol	48%	1,023	15q	2.75	1.8×10^{-4}	7.7%
Triglycerides	36%	1,007	11q	9.23	3.5×10^{-11}	10.6%
HDL-cholesterol	37%	1,024	1p	3.77	1.5×10^{-5}	7.5%
LDL-cholesterol	51%	970	15q	2.12	8.9×10^{-4}	6.8%

* The distributions of all 4 traits were normalized for the linkage analyses.

Table S3. Results for 4 rounds of fine-mapping studies of 11 variants in 4,668 Pima Indians (Pima sample)

rs number	Position*	Gene	Variant type	Reason for testing	p† from Round 1 analysis	p† from Round 2 analysis	p† from Round 3 analysis	p† from Round 4 analysis
rs2075295	116628401	*BUD13*	Intronic	Tag SNP for rs2072560	2.5×10^{-8}	8.8×10^{-6}	0.091	1.00
rs3825041	116631707	*BUD13*	Intronic	Tag SNP for rs2072560	1.4×10^{-16}	1.4×10^{-13}	0.004	1.00
rs964184	116648917	*ZPR1*	Near 3' UTR	GWAS SNP	5.4×10^{-30}	2.1×10^{-22}‡	covariate	covariate
rs2072560	116661826	*APOA5*	Intronic	The 2nd strongest SNP from find-mapping study	2.9×10^{-8}	9.5×10^{-7}	0.100	1.00
rs3135506	116662407	*APOA5*	Missense SNP, S19W	GWAS SNP	4.6×10^{-6}	4.1×10^{-4}	0.041	1.00
rs651821	116662579	*APOA5*	5' UTR	Tag SNP for rs2072560 and a GWAS SNP	1.2×10^{-17}	1.5×10^{-14}	0.0012‡	covariate
rs662799	116663707	*APOA5*	Promoter	GWAS SNP	1.9×10^{-17}	6.6×10^{-14}	0.027	1.00
rs147210663	116701560	*APOC3*	Missense SNP, A43T	The strongest SNP from find-mapping study	7.4×10^{-48}‡	covariate	covariate	covariate
rs12225230	116728630	*SIK3*	Missense SNP, P917R	GWAS SNP	3.1×10^{-6}	4.4×10^{-4}	0.63	1.00
rs11357208	116784304	*SIK3*	Indel, Intronic	The 3rd strongest SNP from find-mapping study	1.2×10^{-6}	1.8×10^{-4}	0.79	1.00
rs139961185	116807343	*SIK3*	Intronic	GWAS SNP	2.6×10^{-9}	1.1×10^{-7}	1.00	1.00

* Build 37 position on chromosome 11.

† Corrected for multiple testing.

‡ The SNP with the strongest p value in a given round of analysis.

Table S4. The associations between rs147210663, rs964184, 3 *APOA5* SNPs and triglycerides-related traits combining Pima and FIND samples

A. Results for quantitative traits

Trait	SNP	n	β*±s.e	variance explained	p
Ln(triglycerides)	rs147210663	7,297	-0.922 ± 0.059	3.53%	9.7×10^{-55}
	rs964184	7,057	0.208 ± 0.017	2.26%	8.6×10^{-33}
	APOA5 SNPs†	6,487	0.142 ± 0.012	2.41%	1.2×10^{-31}
Total cholesterol	rs147210663	8,413	-0.265 ± 0.058	0.23%	4.7×10^{-6}
	rs964184	8,153	0.101 ± 0.017	0.47%	4.5×10^{-9}
	APOA5 SNPs	7,500	0.065 ± 0.012	0.45%	6.7×10^{-8}
HDL cholesterol	rs147210663	8,414	0.437 ± 0.059	0.67%	9.2×10^{-14}
	rs964184	8,154	-0.085 ± 0.018	0.28%	1.6×10^{-6}
	APOA5 SNPs	7,501	-0.045 ± 0.012	0.18%	3.7×10^{-4}
LDL cholesterol	rs147210663	7,822	-0.089 ± 0.055	0.01%	0.101
	rs964184	7,734	0.052 ± 0 .021	0.15%	0.013
	APOA5 SNPs	7,089	0.030 ± 0.011	0.13%	0.006
VLDL-C‡	rs147210663	206	-1.11 ± 0.240	10.2%	3.9×10^{-6}
	rs964184	206	0.29 ± 0.095	1.67%	0.0022
	APOA5 SNPs	191	0.21 ± 0.069	3.46%	0.0019
VLDL–triglycerides	rs147210663	206	-1.26 ± 0.231	14.5%	5.6×10^{-8}
	rs964184	206	0.42 ± 0.092	7.17%	3.8×10^{-6}
	APOA5 SNPs	191	0.34 ± 0.067	9.57%	5.0×10^{-7}
LDL–triglycerides	rs147210663	206	-0.019 ± 0.0051	7.20%	0.00017
	rs964184	206	0.0071 ± 0.0019	6.04%	3.8×10^{-6}
	APOA5 SNPs	191	0.0060 ± 0.0014	8.43%	1.6×10^{-5}

B. Results for a qualitative trait

Trait	SNP	n	OR§ (95% CI)	p
Hypertriglyceridemia¶	rs147210663	8,039	0.14 (0.09, 0.22)	4.5×10^{-18}
	rs964184	7,945	1.53 (1.42, 1.65)	5.0×10^{-31}
	APOA5 SNPs	7,281	1.32 (1.25, 1.39)	2.0×10^{-27}

* Based on an additive genetic model, for the effect of the minor allele, in SD unit.

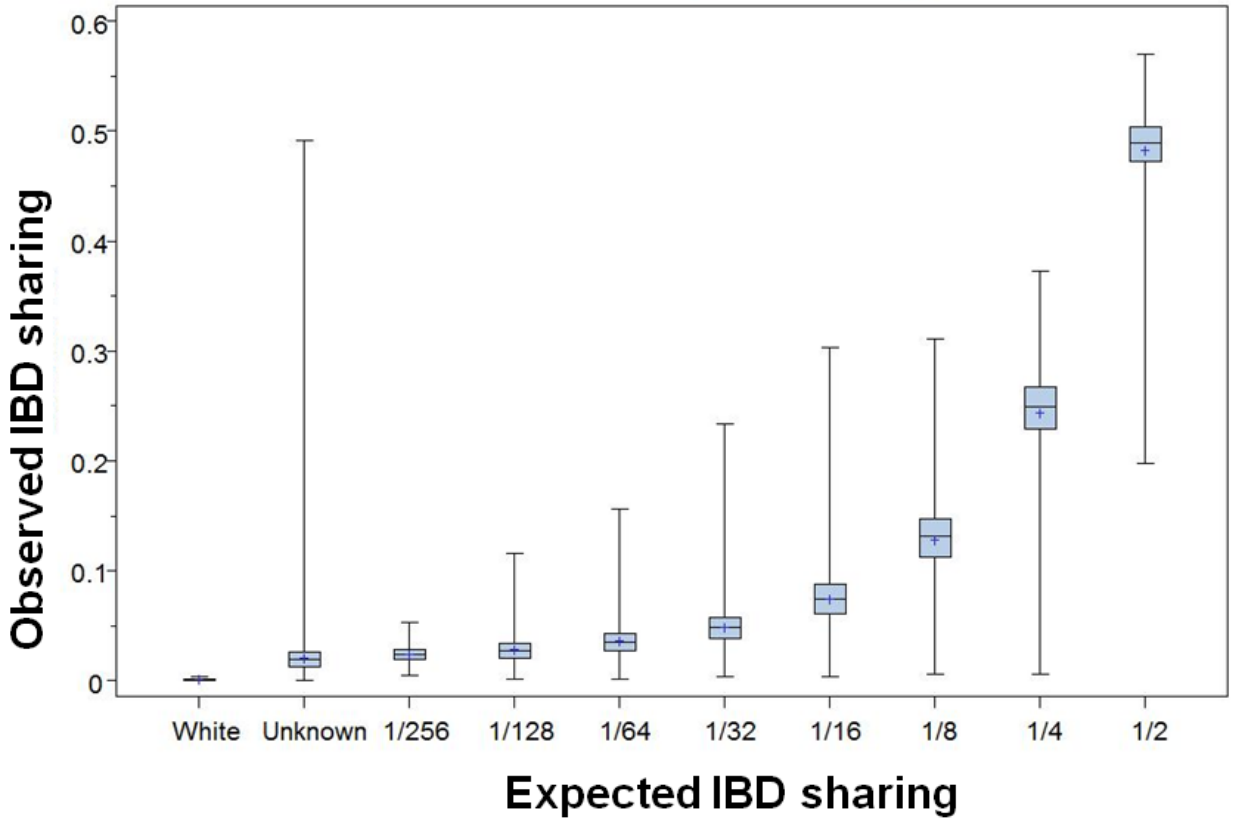
† Effects expressed per copy of any minor allele of these 3 functional SNPs in *APOA5*: rs2266788, rs3135506, rs662799.

‡ Very low density lipoprotein cholesterol.

§ OR = odds ratio.

¶ Hypertriglyceridemia defined as having serum triglyceride levels ≥ 1.69 mmol/L.

Figure S1. Empirically estimated IBD sharing by expected IBD sharing in the sample used for linkage analysis of serum lipids



IBD sharing refers to the percentage of allele shared identical by decent. N = 1,024 subjects, or 523,776 pairs; 9,664 pairs (1.8%) with known relationship. 98.2% pairs had no known relationship. Data are shown as a box plot, with the error bars representing the range, the thicker bars representing the 25th and 75th centiles, the horizontal bar representing the median and the + sign representing the mean. IBD sharing estimates for whites (19 individuals) were calculated with ibdscale = 1 (which was determined to give comparable estimates in 19 Pimas to those obtained in the larger set of 1,024 Pimas).

Figure S2. Genome-wide linkage study results for 4 serum lipid traits

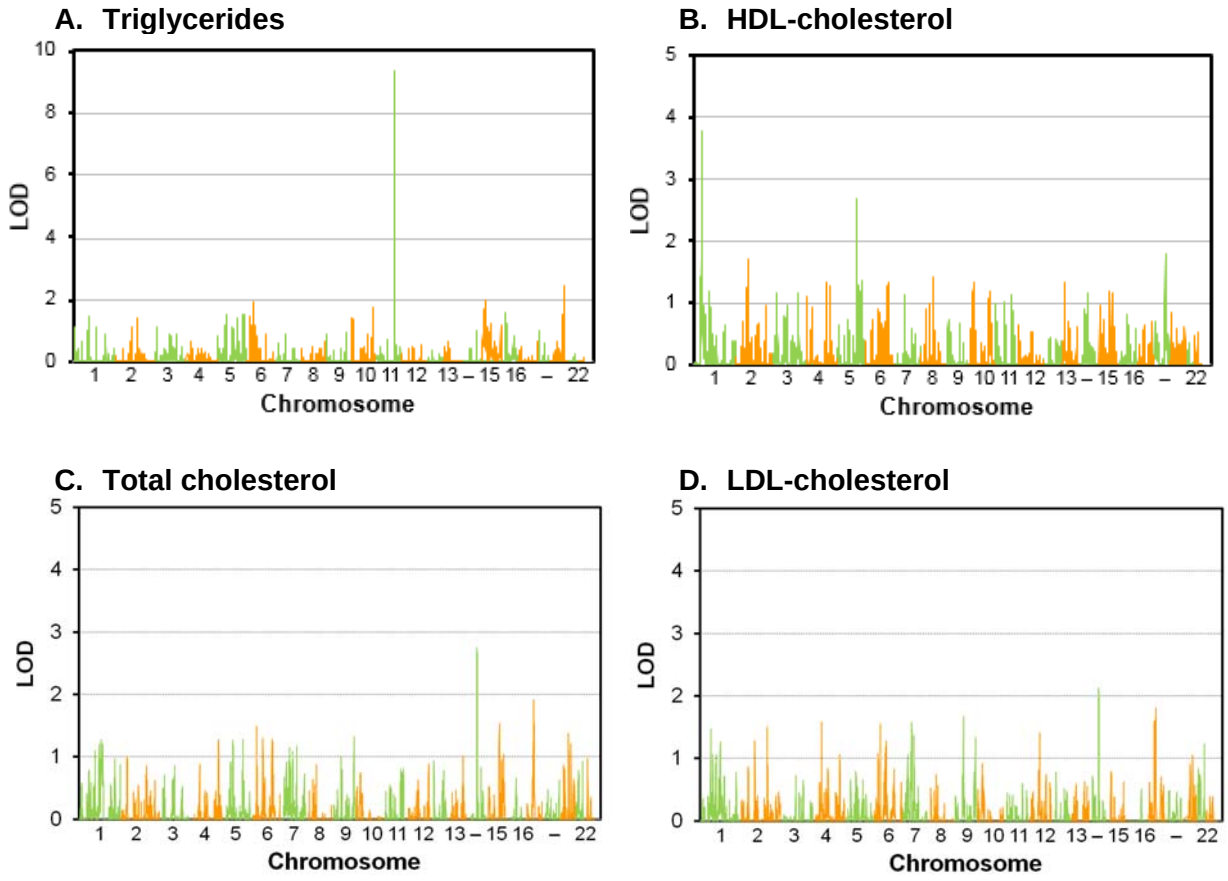
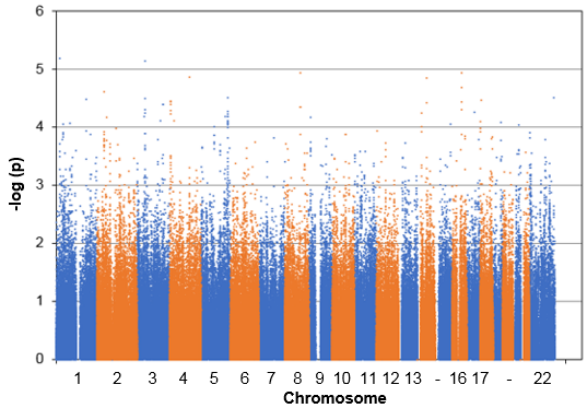
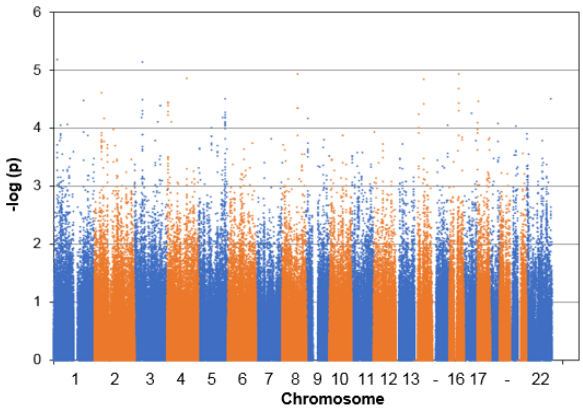


Figure S3. Genome-wide association study results for four serum lipid traits using the Affymetrix 6.0 array

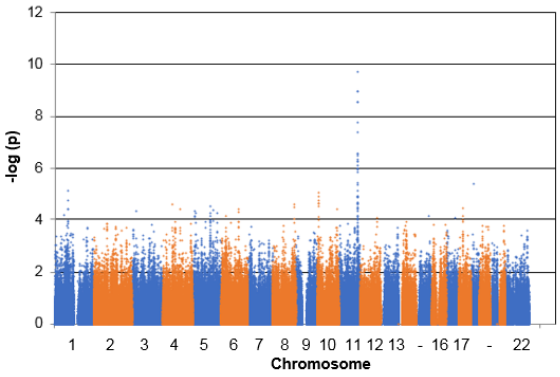
A. Total cholesterol



B. HDL cholesterol



C. Triglycerides



D. LDL cholesterol

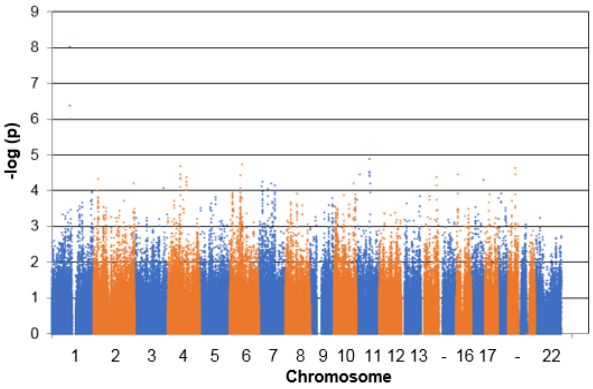


Figure S4. Linkage disequilibrium pattern (r^2) between 6 SNPs in 4,636 Pima samples

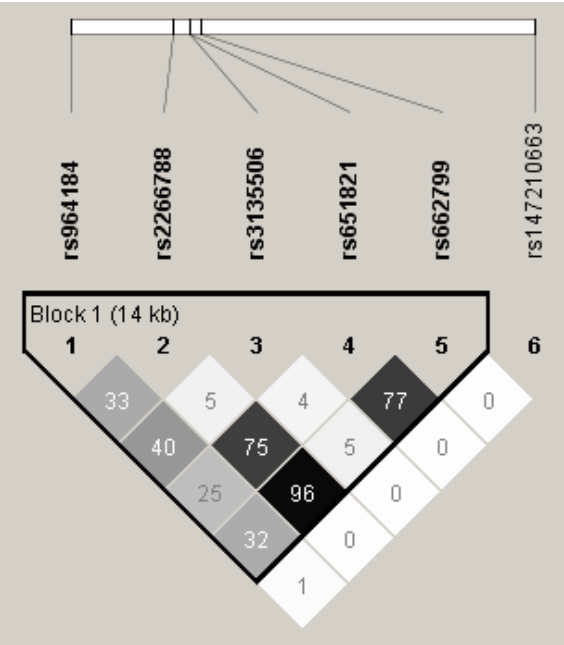
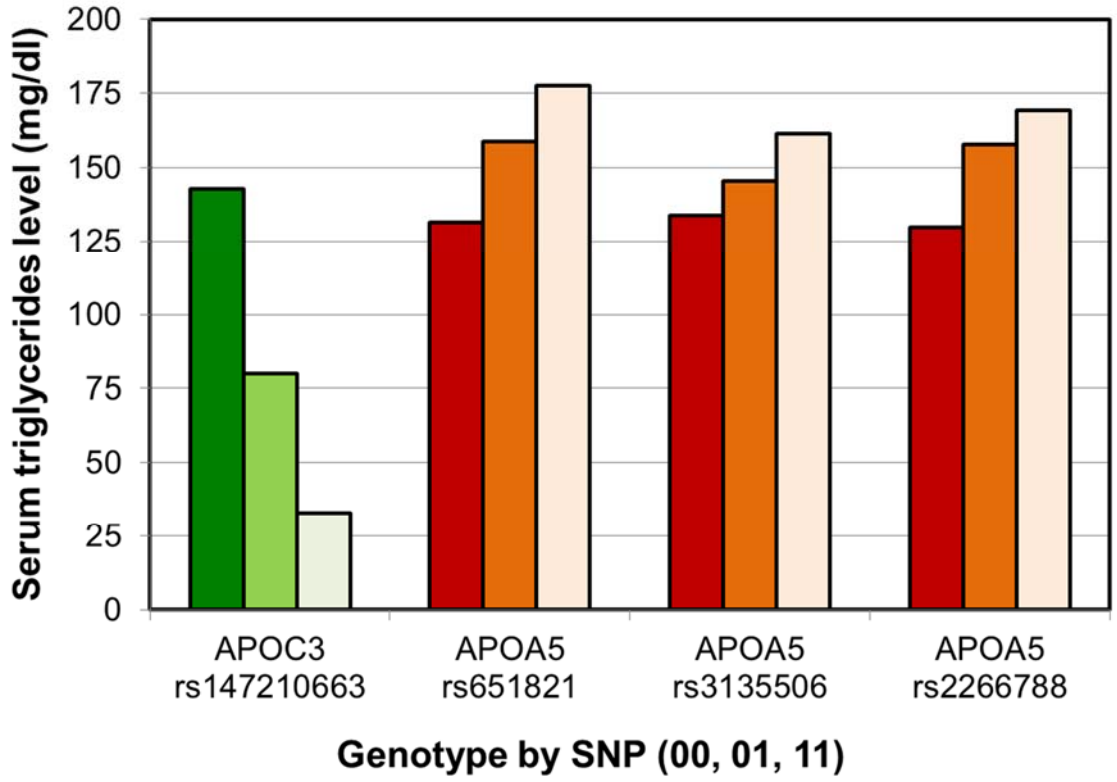


Figure S5. Raw levels of serum triglycerides by genotypes of 4 SNPs in Pima Indians



Bars of a dark color represent mean levels of plasma triglycerides among homozygotes of the major allele (genotype 00); bars of an intermediate color represent mean levels of serum triglycerides among heterozygotes of the major allele (genotype 01); and bars of a light color represent mean levels of serum triglycerides among homozygotes of the minor allele (genotype 11).

Figure S6. rs964184 vs. *APOA5* 3-SNP haplotypes and frequencies

rs964184	rs2266788	rs3135506	rs651821	rs6622799	Frequency
G	T	S	T	A	60.6%
C	T	W	T	A	20.8%
C	C	S	C	G	14.0%
C	C	S	T	G	3.3%

These results were calculated in the Pima sample (n = 4,636).

Supplemental References

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