SUPPLEMENTAL INFORMATION:

Mutation skew in genes identified by genome-wide association study of hypertriglyceridemia

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Supplemental Methods

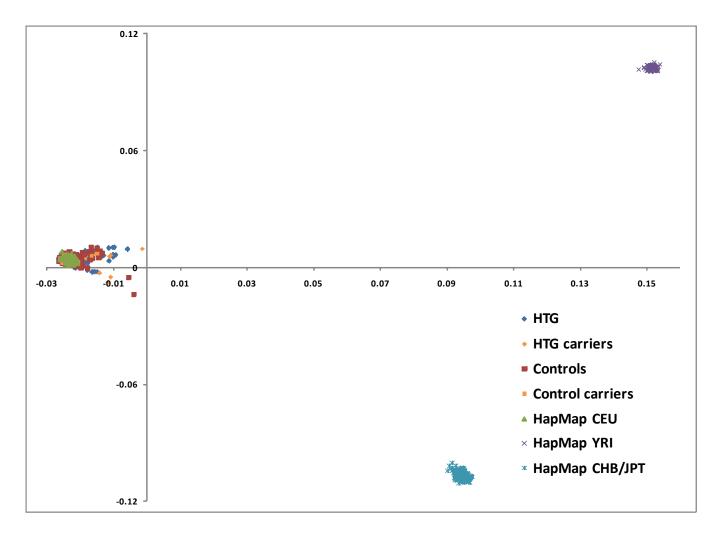
Study Subjects. This study was approved by the ethics boards at all institutions. All subjects provided informed consent for blood sampling, DNA analysis, and collection of clinical, biochemical and other demographic data. All subjects in this study were unrelated and of self-declared European ancestry. The GWAS included 463 HTG patients and 1197 low TG controls: HTG patients were predominantly obtained from a single tertiary referral lipid clinic (92% of patients) in London, Ontario, Canada, or from a tertiary referral lipid clinic in Amsterdam, Netherlands, and low TG controls were subjects with familial hypercholesterolemia (4% of controls) obtained from a single tertiary referral lipid clinic in London, Ontario, Canada, or normal healthy controls obtained from population-based studies including the Study of Health Assessment and Risk in Ethnic Groups¹ (18%) or the Myocardial Infarction Genetics Consortium² (78%). Subjects with familial hypercholesterolemia were included as negative controls only in the GWAS to counterbalance the increased cholesterol phenotype that is observed in patients with HTG. The resequencing cohort included 438 HTG patients and 327 low TG controls: HTG patients were obtained only from the lipid clinic in London, Ontario, Canada, and low TG controls included only normal healthy subjects from the Study of Health Assessment and Risk in Ethnic Groups.

Sequencing and Mutation Accumulation

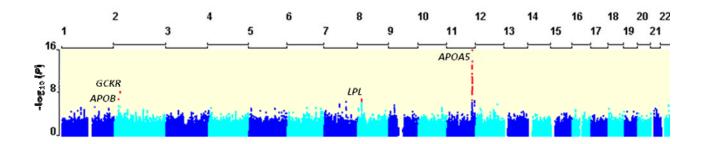
All subjects in the resequencing cohort were sequenced fully across the translated coding sequence of *APOA5*, *GCKR*, *LPL*, and exons 26 and 29 of *APOB* (67.8%). Subjects missing sequencing data in any one gene were removed prior to analysis. Rare variants were defined as having minor allele frequencies <1% in controls. Our intention was to identify rare missense and nonsense variants potentially

responsible for HTG disease causation, accordingly we excluded intronic variants, untranslated region variants, and synonymous variants from mutation accumulation analyses. Exclusive variants were defined as rare variants found exclusively in HTG patients or controls (not both), deliberately excluding variants previously reported without demonstrated functional compromise. Mutation accumulation analyses compared either the number of observed rare alleles versus reference alleles, or the number of rare variant carriers versus non-carriers, in HTG patients and controls. Carriers were defined as having ≥ 1 rare variant. Association between mutation accumulation and HTG phenotype was tested using a two-tailed Fisher's exact test, with nominal significance defined as P < 0.05.

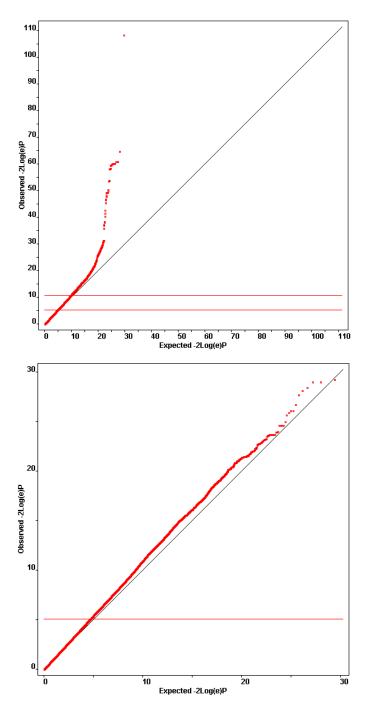
Explained Variation. Subjects included in this analysis were common to both GWAS and re-sequencing cohorts. Explained variation was calculated from the residuals of a multivariate logistic regression model, using discrete case-control status as the dependent variable. Independent variables included clinical covariates age, sex, body mass index and diabetes status as either continuous or discrete variables, common variants as continuous variables of HTG risk associated alleles at each of the 7 HTG-associated loci, and rare variants as a continuous variable including the number of rare variants carried by each subject. The calculation of explained variation was generated using a published SAS v9.2 macro written for this purpose³. In logistic regression, the proportion of explained variation [as measured by the coefficient of determination (R²) in linear regression] does not exist in an interpretable straightforward manner. The macro used here produces a metric comparable to R² calculated from the residuals of the logistic regression model³.



Supplemental Figure 1. Subjects in the resequencing cohort have confirmed European ancestry. Identity-by-state and multidimensional scaling was performed on resequencing subjects with wholegenome SNP data to ensure they were of European ancestry, and that rare variants identified by resequencing cannot be attributed to differences in ancestry.



Supplemental Figure 2. Manhattan plot of regression *P***-values.** SNPs were independently tested for association with HTG using multivariate logistic regression entering sex, body mass index, diabetes status and 10 principal components of ancestry as covariates. A threshold of $P < 5 \times 10^{-7}$ was considered genome-wide significant. Red data points represent SNPs surpassing genome-wide significance, as visualized using WGAViewer⁴. Genome-wide associated loci are labeled. *APOA5* reached a maximum association statistic of 5.4 X 10⁻²⁴, however the y-axis scale is truncated for better visualization of other results.



Supplemental Figure 3. Quantile-quantile plot of regression *P*-values. Deviation of *P*-values from the null is caused predominantly by significant associations with hypertriglyceridemia (A), which is eliminated when these loci are removed from analysis (B). Both plots show some residual inflation of association test statistics as visualized using WGAViewer⁴. Genomic control inflation factor was calculated as $\lambda = 1.07$ in PLINK⁵.

APOAS p.N665 New 1 0 Possibly Possibly p.0305X Reduced LPL activation by "23% ⁴ p.0305X New 1 0 Truncation p.0335X New 1 0 Truncation p.0332V/5336X New 1 0 Truncation GCKR		Mutation	New/Known	HTG	Controls	Damaging?*	Published Dysfunction
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		p.R1662H	Known	2	0	Benign	

Supplemental Table 1. Annotation of rare variants found in GWAS-identified genes.

p.K1703T	New	0	1	Possibly	
p.D1827N	New	0	1	Possibly	
p.V2019I	Known	0	1	Possibly	
p.A2172T	New	1	0	Benign	
p. del2186D	New	3	4	Deletion	
p.R2192C	New	1	0	Probably	
p.S2217N	New	1	0	Benign	
p.L2239M	New	1	0	Benign	
p.V2286I	Known	2	1	Benign	
p.M2331I	New	1	0	Possibly	
p.S2402T	Known	1	0	Benign	
p.A2429D	Known	1	0	Benign	
p.V2512I	Known	2	3	Benign	
p.E2539К	Known	5	0	Benign	
, p.E2539D	New	1	0	Benign	
p.R2685C	New	0	1	Possibly	
p.P2794L	Known	6	2	Probably	
p.12850Y	New	1	0	Possibly	
p.K2958E	New	1	0	Benign	
p.T3020R	Known	1	0	Benign	
p.P3216S	New	1	0	Benign	
p.S3252G	Known	4	0	Possibly	
p.M3253V	New	1	1	Possibly	
p.S3267P	Known	3	0	Possibly	
p.Q3405E	Known	5	3	Benign	
p.Y3435C	Known	1	0	Probably	
p.D3472N	New	1	0	Benign	
p.R3500W	Known	1	0	Probably	Causative of familial defective
p.11330011	Kilowii	-	Ū	Trobubly	apolipoprotein B-100 ¹³
p.T3540M	New	0	1	Benign	aponpop. c.c 2 200
p.V3718I	New	1	1	Benign	
p.13741T	New	1	0	Possibly	
p.D3768N	New	0	1	Possibly	
p.S3774T	New	3	3	Benign	
p. T3799M	Known	1	1	Possibly	
p.V3804F	New	0	1	Benign	
p.V4101M	Known	3	3	Benign	
p.\$4206T	Known	1	0	Benign	
p.V4238A	New	8	3	Benign	
p.14287V	Known	6	4	Benign	
p.M4293V	New	1	0	Benign	
p.V4367A	Known	1	0	Benign	
p.\$4403T	Known	1	0	Benign	
p.14455V	New	0	1	Benign	
p.T4457M	Known	6	0	Possibly	
p.F4486lfs4488X	New	1	0	Truncation	
p:144001134400X					deleterious nature of non synonymou

*Polyphen (<u>http://genetics.bwh.harvard.edu/pph/</u>) was used only to predict the deleterious nature of non-synonymous variants, other mutation types are indicated.

Supplemental References

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