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Polygenic determinants of severe hypertriglyceridemia

Jian Wang¹, Matthew R. Ban¹, Guang Yong Zou², Henian Cao¹, Tim Lin¹,
Brooke A. Kennedy¹, Sonia Anand³, Salim Yusuf³, Murray W. Huff¹, Rebecca L. Pollex¹
and Robert A. Hegele^{1,*}

1) Vascular Biology Research Group and 2) Clinical Trials Group,
Robarts Research Institute and Schulich School of Medicine and Dentistry,
University of Western Ontario, London, Ontario, Canada N6A 5K8; and
3) Population Health Research Institute, McMaster University,
Hamilton Health Sciences, Hamilton, Ontario, Canada L8L 2X2

Correspondence:

* Robert A. Hegele, MD FRCPC FACP

Blackburn Cardiovascular Genetics Laboratory, Robarts Research Institute
#406-100 Perth Drive, Box 5015, London, Ontario, Canada N6A 5K8
tel: 519-663-3461; fax: 519-663-3037; email: hegele@robarts.ca

ABSTRACT

Recent genome-wide association (GWA) studies have identified new genetic determinants of complex quantitative traits, including plasma triglyceride (TG). We hypothesized that common variants associated with mild TG variation identified in GWA studies would also be associated with severe hypertriglyceridemia (HTG). We studied 132 patients of European ancestry with severe HTG (fasting plasma TG >10 mmol/L), who had no mutations found by re-sequencing of candidate genes, and 351 matched normolipidemic controls. We determined genotypes for: *GALNT2* rs4846914, *TBL2/MLXIPL* rs17145738, *TRIB1* rs17321515, *ANGPTL3* rs12130333, *GCKR* rs780094, *APOA5* rs3135506 (S19W), *APOA5* dbSNP rs662799 (-1131T>C), *APOE* (isoforms) and *LPL* rs328 (S447X). We found that: 1) genotypes, including those of *APOA5* S19W, *APOA5* -1131C>T, *APOE*, *GCKR*, *TRIB1* and *TBL2/MLXIPL*, were significantly associated with severe HTG; 2) odds ratios for these genetic variables were significant in both univariate and multivariate regression analyses, irrespective of the presence or absence of diabetes or obesity; and 3) a significant fraction – about one-quarter - of the explained variation in disease status was associated with these genotypes. Therefore, common SNPs that are associated with mild TG variation in GWA studies of normolipidemic subjects are also associated with severe HTG. Our findings are consistent with the emerging model of a complex genetic trait. At the extremes of a quantitative trait, such as severe HTG, are found the cumulative contributions of both multiple rare alleles with large genetic effects and common alleles with small effects.

INTRODUCTION

Plasma lipoproteins are archetypal complex traits whose inter-individual variation is determined by both common and rare genetic variants (1). Recent genome-wide association studies (GWASs) have identified new genetic determinants of several complex quantitative traits, including plasma lipoproteins (2-7). These studies evaluated large samples of normolipidemic (i.e. nondyslipidemic) individuals and showed that multiple genetic determinants – single nucleotide polymorphisms (SNPs) - had replicable modest associations with plasma concentrations of total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and triglyceride (TG) (2, 3, 6, 7). For instance, numerous common genomic variants, including several within well-established candidate genes contributed cumulatively to ~12% of plasma LDL cholesterol variation in essentially normolipidemic samples (2), which was consistent with earlier findings in genetic isolates (8). In addition, associations were observed with many genes that had no previously known biochemical connection with lipoproteins (2, 3, 6, 7). The potential diagnostic or prognostic utility of lipoprotein-associated markers identified in GWASs as predictive of individual risk of cardiovascular disease or dyslipoproteinemia is unsettled, in part because the individual markers hold only a modest influence on lipoprotein traits (1, 4, 5). Furthermore, the association of these newly discovered common markers with severe dyslipidemia is unknown.

The genetic determinants of severe hypertriglyceridemia (HTG; MIM 144650), also called Fredrickson or World Health Organization hyperlipoproteinemia (HLP) type 5, are incompletely defined. Plasma TG >10 mmol/L is found in 1:600 North Americans (9). Candidate gene resequencing showed that ~10% of patients with plasma TG >10

mmol/L together with fasting chylomicronemia had heterozygous loss-of-function missense mutations, primarily in the *LPL* gene encoding lipoprotein lipase, compared with only 0.2% of controls (carrier odds ratio [OR] 52, 95% confidence interval [CI] 8.6 to 319) (9). Furthermore, the common *APOA5* S19W missense variant was associated with severe HTG (carrier OR 5.5 95% CI 3.3 to 9.1) (9). We hypothesized that common variants recently associated with relatively normal plasma TG identified in GWASs (3, 7) would also be associated with severe HTG. We evaluated polygenic determinants of severe HTG using multivariate linear and logistic regression analysis. We found significant contributions to severe HTG of common variants in several genes that included *APOA5*, *APOE*, *TRIB1*, *TBL2/MLXIPL*, *GCKR* and *GALNT2*, underscoring this trait's complex polygenic nature and indicating that genetic determinants of modest TG variation also underlie a related, but rarer and more extreme disease phenotype.

RESULTS

Clinical and biochemical features of study subjects

Baseline attributes of the study sample are shown in Table 1. After excluding 16 patients with heterozygous loss-of-function mutation in *LPL*, *APOC2* or *APOA5* (9), 132 patients or cases with severe HTG remained for analysis. These were each matched with up to 4 normolipidemic controls based on age within 5 years and sex. By definition, severe HTG patients had markedly higher plasma TG and total cholesterol and significantly lower HDL cholesterol (Table 1). Plasma TG concentration in severe HTG patients ranged from 10.1 to 180 mmol/L. In addition, 37/132 severe HTG patients

(28.0%) had been hospitalized on ≥ 1 occasion with pancreatitis and 90/132 (68.2%) had at least one first degree relative treated for dyslipidemia.

Differences in distribution of DNA variants between severe hypertriglyceridemia cases and controls

Genotype counts and frequencies in severe HTG patients and controls are shown in Table 2. Minor allele frequencies (MAFs) for each genotype in severe HTG cases and controls are shown in Table 3. Frequencies of each genotype did not deviate from Hardy-Weinberg equilibrium. The significance of the differences in genotype frequencies between severe HTG cases and controls are shown in Table 2: in univariate chi-square analysis, genotype frequencies of each evaluated marker had a significantly different distribution in HTG cases compared with controls (range of P-values 0.024 to 1.5×10^{-12}). The significance of the differences in MAFs between severe HTG cases and controls are shown in Table 3: the MAF of each marker studied was significantly different between groups.

Genetic risk of severe hypertriglyceridemia: univariate odds ratios

Univariate ORs for severe HTG were determined for two clinical variables – namely diabetes and marked obesity (defined as BMI $>33 \text{ kg/m}^2$) and for the HTG-risk genotype for each genomic variant. Both dominant and recessive models for each genotype were evaluated and the model that provided the strongest and most significant OR was chosen to serve as the nominal genotype variable for subsequent multivariate analyses. There was no significant linkage disequilibrium between the two *APOA5*

variants ($P=0.23$), so these were treated as independent variables for the purpose of subsequent analyses. For *APOE*, presence or absence of the common E3/3 genotype was evaluated.

Univariate ORs and 95% CIs are shown in Table 4 for the most significantly associated genetic model for each genotype: only the *ANGPTL3* and *LPL* genotypes were not significant for either dominant or recessive model. However, both *APOA5* variants, *APOE* non-E3/3 genotype, *GCKR* TT recessive genotype; *TRIB1* AA recessive genotype and *TBL2/MLXIPL* CC recessive genotype each had significant ORs for severe HTG.

Univariate ORs for severe HTG were also determined for combinations of genetic variables. Since both *APOA5* variants were very strongly associated with HTG, the presence of either served as the primary genetic predictor: the OR was 6.93 (95% CI 4.44 to 10.8). Adding any one or two of the other genetic variables did not substantially change this OR. However, adding 3, 4 or 5 additional genetic markers to the presence of either *APOA5* marker sequentially increased the OR from 7.58 to 8.92 to 25.0, so that when an individual had 7 genetic risk markers (i.e. both *APOA5* risk markers plus any other five), the resulting OR for severe HTG was very high indeed.

Polygenic determinants of severe hypertriglyceridemia: multivariate regression analysis

The multivariate ORs for severe HTG were calculated using the Wald statistic in multivariate logistic regression analysis with stepwise addition of variables and $P<0.05$ for each step (Table 5). The first model, which included two clinical variables in addition to nine genetic variables, found that diabetes, obesity, two *APOA5* markers, *APOE* non-

E3 genotype and *GCKR*, *TRIB1* and *TBL2/MLXIPL* genotypes were significantly associated with severe HTG. The C-statistic, which corresponds to the area under the receiver-operator curve for a diagnostic test, was 0.869 for this particular combination of clinical and genetic markers (Table 5). Hosmer and Lomeshow goodness of fit test showed that the models explained the observed data ($\chi_8^2 = 10.2$; $P=0.25$ and $\chi_8^2 = 7.47$; $P=0.38$). The second model assessed only genetic variables: the same genotypes from the first model remained significantly associated in the second model with one additional significantly associated genotype – namely *GALNT2*, assuming a recessive effect for the G allele. The C-statistic was 0.800 for this combination of genetic markers (Table 5).

The proportion of contribution of specific variables to severe HTG was calculated using partial r^2 -values in multivariate linear regression analysis with stepwise addition of variables and $P<0.05$ for each step (Table 5). The first model, which included two clinical variables in addition to nine genetic variables, found that diabetes, *APOA5* markers, obesity, *TBL2/MLXIPL* genotype, *APOE* genotype, *TRIB1* genotype and *GCKR* genotype were significantly associated with severe HTG. The model explained ~43% of total variation in case versus control status, and of the explained variation, the total contribution of the genetic variables was ~40% (range ~1 to 25%). The second model assessed only genetic variables: the same genotypes from the first model remained significantly associated in the second model with one additional significantly associated genotype – namely *GALNT2*. The model accounted for ~25% of total variation in case versus control status. Of explained variation, genetic markers accounted for ~1% each.

DISCUSSION

The principal novel findings in this study of newly identified genetic markers in patients with severe HTG were: 1) genotypes, including those of *APOA5* S19W, *APOA5* -1131C>T, *APOE*, *GCKR* rs780094, *TRIB1* rs17321515, *GALNT2* rs4846914 and *TBL2/MLXIPL* rs17145738, were significantly associated with severe HTG; 2) ORs for these genetic variables were significant in both univariate and multivariate regression analyses, irrespective of the presence or absence of diabetes or obesity; and 3) a significant fraction – about one-quarter - of the attributable variation in disease status was associated with these genotypes. The findings further indicate that several genotypes that were found by GWA studies to be associated with moderate variation in plasma TG in samples without severe dyslipidemia are also associated with severe HTG. This confirms the complex, polygenic nature of severe HTG and also replicates the importance of loci identified in GWA as being more generally important in TG metabolism, especially in the pathogenesis of severe HTG with chylomicronemia and increased pancreatitis risk.

The current findings extend our previous results, which showed that a relatively small proportion (~10%) of severe HTG subjects were carriers of rare, heterozygous loss-of-function mutations in candidate lipoprotein metabolism genes (9). In the current study, in which subjects with rare loss-of-function mutations were excluded, we found that common SNP alleles, including those in both known genes, such as *APOA5*, *LPL* and *APOE*, and in genes recently implicated as positional candidates, such as *TRIB1*, *GCKR*, *TBL2/MLXIPL*, *GALNT2* and *ANGPTL3*, are found in a substantial proportion – almost two-thirds – of individuals with severe HTG. Thus, the genetic component of this complex metabolic trait is comprised of both rare and common variants.

We selected *TBL2/MLXIPL* rs17145738; *TRIB1* rs17321515; *GALNT2* rs4846914; *ANGPTL3* rs12130333 and *GCKR* rs780094 because they were found by GWASs to be associated with modest variation in TG in large normolipidemic population samples. In each case, the allele that was associated with severe HTG in our study was also associated in the GWASs with higher plasma TG concentration: *GALNT2* rs4846914 G, *TBL2/MLXIPL* rs17145738 C, *TRIB1* rs17321515 A, *ANGPTL3* rs12130333 C, and *GCKR* rs780094 T. Our study indicates that these common – and so far mechanistically undefined - markers and loci are strongly and cumulatively associated with severely disturbed TG metabolism. This further suggests that rare loss-of-function variants in these genes, or in proximal genes for which the SNPs are markers, might be determinants of severe HTG. Resequencing of genes marked by these SNPs appears thus to be indicated. But while the findings clearly link these genotypes with severe HTG, other factors must be important both in severe HTG patients with and without the genotypes evaluated here, since ~30% of severe HTG patients had neither a rare dysfunctional variant nor an at-risk SNP genotype.

Thus, our findings are consistent with the emerging model but among individuals at the extremes of a complex genetic trait, such as severe HTG (HLP type 5), are found the cumulative contributions of both multiple rare alleles with large genetic effects and multiple common alleles with small effects. We do not suggest that the variants studied here are directly causative because severe HTG (HLP type 5) is a complex trait with no single simple genetic cause and additional factors, both genetic and non-genetic, are likely to be important determinants. However, the present study substantially increases the proportion of patients with severe HTG – now about two-thirds of patients - who have

a significantly associated underlying genetic predisposition. The findings further confirm that the genetic contribution to severe HTG is complex and suggest that other genes or non-genetic factors may still have an important role to play. Also, the results show that significant associations can be identified by studying a relatively small number of subjects with extreme values of a quantitative lipoprotein trait.

MATERIALS AND METHODS

Study subjects

We studied 148 patients of European geographic ancestry with severe HTG, defined as having fasting (>12 hour) plasma TG >10 mmol/L documented on 2 occasions, from a single tertiary referral lipid clinic (9). Patients underwent complete medical history and examination; basic clinical, biochemical, and demographic variables were collected. Normolipidemic adult controls were taken from the European subgroup of the Study of Health Assessment and Risk in Ethnic groups (SHARE), a survey of cardiovascular risk factors in Canadian subpopulations (10) together with healthy population-based controls from the same region of Canada. No control had ischemic heart disease and there was no use of medications among these healthy control subjects. All patients provided informed consent for DNA analysis.

DNA analysis

DNA was extracted as described (9). For SNP genotyping, we selected markers that were replicably associated with plasma TG in at least two studies (3, 7, 11) and that showed relatively strong association in each study (3, 7, 11). The selected genes and

dbSNP identification numbers were: *GALNT2* rs4846914, *TBL2/MLXIPL* rs17145738, *TRIB1* rs17321515, *ANGPTL3* rs12130333, *GCKR* rs780094, *APOA5* rs3135506 (S19W) and *LPL* rs328 (S447X) were genotyped using validated genotyping assays (TaqMan® SNP Genotyping Assays, Applied Biosystems, Foster City, CA). *APOA5* -1131T>C (dbSNP rs662799) was genotyped using a custom designed genotyping assay (TaqMan® SNP Custom Genotyping Assays, Applied Biosystems, Foster City, CA). The custom probe uses primers as follows: 5'- CCC TGC GAG TGG AGT TCA -3' and 5'- CTC TGA GCC CCA GGA ACT G. SNP genotyping was performed using an allelic discrimination assay using the 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA) and genotypes were read using automated software (SDS 2.3, Applied Biosystems, Foster City, CA). Reactions were run in 5 µL volumes using an amplification protocol of 95°C for 10 minutes, followed by 42 cycles of 95°C for 15 seconds, then 60°C for 1.5 minutes. An established method was used to genotype *APOE* isoforms (12). For SNP analysis, we excluded patients with a known sequence-proven loss-of-function mutation in *LPL*, *APOC2* or *APOA5*, encoding lipoprotein lipase, apo C-II and apo A-V, respectively (9). Blinded between-day replicated genotypes of a random 3% of samples showed >99.9% concordance across all markers.

Statistical analysis

The two-sample t-test was used to compare the difference between case and control groups for quantitative traits, while Pearson's chi-square test was used to compare discrete traits with exact P-values obtained whenever cell sizes <5. Deviations of genotype frequency from the Hardy-Weinberg assumption were assessed using a chi-

square test. Maximal likelihood linkage disequilibrium was estimated using PHASE v2.0 (13). To assess the relationship of SNPs with severe HTG, dominant and recessive models of minor allele genotypes were tested for each gene. A simple logistic regression model was used to assess univariate association between each SNP and severe HTG. A multiple logistic regression model with backward elimination procedure was adopted to assess the joint effects of genes and clinical variables such as presence of diabetes and marked obesity, i.e. body mass index (BMI) $>33 \text{ kg/m}^2$. For a genotype with frequency 0.20, the study sample afforded statistical power (alpha error level =0.05) to detect 1.4-, 1.6-, 1.8- and 2.0-fold increases in frequency of 59.1%, 85.7%, 96.9% and 99.9%, respectively. The adequacy of the final models was assessed using the Hosmer-Lemeshow goodness-of-fit test. Relative importance of genetic and clinical variables was quantified using the R-square computed with logistic regression raw residuals (14). Statistical significance was taken at nominal P-value <0.05 for all comparisons. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC), with the exception the exact tests which were performed using StatXact8 (Cytel Inc, Cambridge, MA).

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CONFLICT OF INTEREST STATEMENT

All of the authors declare no conflict of interests.

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Table 1. Clinical, biochemical and genetic attributes of study subjects

	Severe HTG cases	Controls	P-value
Number	132	351	
percent female	31.8%	40.7%	NS (0.091)
percent with diabetes	36.4%	1.1%	<0.0001
age (years)	50.8±13.1	47.3±14.9	NS (0.14)
body mass index (kg/m ²)	30.7±4.8	27.1±4.2	<0.0001
plasma cholesterol (mmol/L)			
- total	11.9±6.2	5.1±0.8	<0.0001
- high-density lipoprotein	0.8±0.34	1.3±0.34	<0.0001
plasma triglyceride (mmol/L)	31.2±26.5	1.2±0.41	<0.0001

Abbreviations: HTG, hypertriglyceridemia; NS, not significant

Table 2. Genotype counts and frequencies of candidate genes evaluated

		Severe HTG cases	Controls	P-value
<i>APOA5</i> S19W	S/S	88 (66.7%)	324 (92.8%)	1.5 X 10 ⁻¹²
	S/W	37 (28.0%)	21 (6.0%)	
	W/W	7 (5.3%)	4 (1.2%)	
<i>APOA5</i> -1131T>C	TT	88 (66.7%)	316 (90.0%)	1.0 X 10 ⁻¹⁰
	TC	36 (27.3%)	34 (9.7%)	
	CC	8 (6.1%)	1 (0.3%)	
<i>GCKR</i> rs780094	CC	30 (29.6%)	123 (35.0%)	8.24 X 10 ⁻⁶
	CT	63 (47.7%)	174 (49.6%)	
	TT	39 (22.7%)	54 (15.4%)	
<i>TRIB1</i> rs17321515	AA	56 (42.4%)	99 (28.2%)	4.5 X 10 ⁻⁶
	AG	62 (47.0%)	167 (47.6%)	
	GG	14 (10.6%)	85 (24.2%)	
<i>GALNT2</i> rs4846914	AA	38 (28.8%)	114 (32.5%)	5.3 X 10 ⁻⁵
	AG	60 (45.5%)	191 (54.4%)	
	GG	34 (25.8%)	46 (13.1%)	
<i>TBL2/MLXIPL</i> rs17145738	CC	115 (87.1%)	265 (75.5%)	7.2 X 10 ⁻⁴
	CT	16 (12.1%)	80 (22.8%)	
	TT	1 (0.8%)	6 (1.7%)	
<i>ANGPTL3</i> rs12130333	CC	93 (70.5%)	215 (61.3%)	7.1 X 10 ⁻⁴
	CT	38 (28.8%)	119 (33.8%)	
	TT	1 (0.8%)	17 (4.8%)	
<i>APOE</i> isotype	2/2	1 (0.8%)	0 (0.0%)	0.0002
	3/2	24 (18.2%)	33 (9.4%)	
	3/3	70 (53.0%)	247 (70.4%)	
	4/2	7 (5.3%)	3 (0.9%)	
	4/3	25 (18.9%)	62 (17.7%)	
	4/4	5 (3.8%)	6 (1.7%)	
<i>LPL</i> S447X	SS	123 (93.2%)	302 (87.3%)	0.024
	SX	9 (6.8%)	44 (12.7%)	

Abbreviations: *APOA5*, gene encoding apolipoprotein A-V; *GCKR*, gene encoding glucokinase receptor; *TRIB1*, gene encoding homologue of *Drosophila Tribbles 1*; *GALNT2*, gene encoding UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase; *TBL2/MLXIPL* locus containing genes encoding transducin-beta-like-2 and MLX interacting protein-like, also called carbohydrate response element binding protein (ChREBP); *ANGPTL3* gene encoding angiotensin-like 3; *APOE*, gene encoding apolipoprotein E; *LPL*, gene encoding lipoprotein lipase.

Table 3. Candidate gene minor allele frequencies

	Severe HTG cases (N=132)	Controls (N=351)	P-value
<i>APOA5</i> W19	0.193	0.042	<0.0001
<i>APOA5</i> -1131C	0.197	0.051	<0.0001
<i>GCKR</i> rs780094 T	0.534	0.402	<0.0001
<i>TRIB1</i> rs17321515 G	0.341	0.481	<0.0001
<i>GALNT2</i> rs4846914 G	0.485	0.403	0.022
<i>TBL2/MLXIPL</i> rs17145738 T	0.068	0.131	0.006
<i>ANGPTL3</i> rs12130333 T	0.152	0.218	0.024
<i>APOE</i> non-E3	0.284	0.161	<0.0001
<i>LPL</i> X447	0.034	0.064	NS (0.083)

Abbreviations: HTG, hypertriglyceridemia; NS, not significant and as for Table 2.

Table 4. Univariate odds ratios for severe hypertriglyceridemia

	Odds Ratio (95% CI)
Diabetes	49.6 (17.4, 141)
Obesity (BMI>33 kg/m ²)	6.04 (3.51, 10.4)
<i>APOA5</i> W19 dominant	6.52 (3.78, 11.2)
<i>APOA5</i> -1131C dominant	4.51 (2.73, 7.46)
<i>GALNT2</i> G recessive	2.30 (1.40, 3.79)
<i>GCKR</i> T recessive	2.31 (1.44, 3.70)
<i>TBL2/MLXIPL</i> C recessive	2.20 (1.25, 3.86)
<i>APOE</i> non-E3 allele	2.04 (1.35, 3.08)
<i>TRIB1</i> A recessive	1.88 (1.24, 2.84)
<i>LPL</i> S447 recessive	1.99 (0.94, 4.20)
<i>ANGPTL3</i> C recessive	1.51 (0.98, 2.32)
Male sex	1.47 (0.96, 2.25)
<i>APOA5</i> W19 dominant or -1311C dominant	6.93 (4.44, 10.8)
<i>APOA5</i> plus 1 additional	6.93 (4.44, 10.8)
<i>APOA5</i> plus 2 additional	6.79 (4.34, 10.6)
<i>APOA5</i> plus 3 additional	7.58 (4.79, 12.0)
<i>APOA5</i> plus 4 additional	8.92 (5.37, 14.8)
<i>APOA5</i> plus 5 additional	25.0 (9.53, 65.5)

Variables entered into model are defined as follows: *APOA5* W19 dominant had the test genotypes SW and WW and the reference genotype SS; *APOA5* -1131C dominant had the test genotypes CC and TC and the reference genotype TT; *GALNT2* G recessive had the test genotype GG and the reference genotypes AA and AG; *GCKR* T recessive had the test genotype AA and the reference genotypes GA and GG; *TBL2/MLXIPL* C recessive had the test genotype CC and the reference genotypes CT and TT; *APOE* non-E3 allele had the test genotypes 2/2, 4/2, 4/4 and the reference genotypes 3/2, 3/3 and 4/3; *TRIB1* A recessive had the test genotype AA and the reference genotypes AG and GG; *LPL* S447 recessive had the test genotype SS and the reference genotype SX (there were no XX individuals); *ANGPTL3* C recessive had the test genotype CC and the reference genotypes CT and TT. The last 6 rows show odds ratios for individuals with combinations of at-risk genotypes, starting with either *APOA5* genotype and then adding non-*APOA5* at-risk genotypes. BMI, body mass index.

Table 5. Multivariate odds ratios for severe hypertriglyceridemia

	Model 1: all variables	Model 2: genetic variables only
Type 2 diabetes	35.9 (11.7, 110)	
Obesity (BMI>33 kg/m ²)	2.63 (1.30, 5.55)	
<i>APOA5</i> W19 dominant	7.79 (3.98, 15.2)	7.36 (3.98, 13.6)
<i>APOA5</i> -1131C dominant	5.56 (2.93, 10.6)	5.57 (3.13, 9.90)
<i>APOE</i> non-E3 allele	2.01 (1.16, 3.52)	2.14 (1.31, 3.49)
<i>GCKR</i> T recessive	2.03 (1.08, 3.80)	2.11 (1.21, 3.67)
<i>TRIB1</i> A recessive	1.86 (1.07, 3.26)	2.02 (1.24, 3.30)
<i>TBL2/MLXIPL</i> C recessive	2.67 (1.27, 5.62)	2.81 (1.46, 5.24)
<i>GALNT2</i> G recessive	NS	2.10 (1.15, 3.81)
C- statistic	0.869	0.800

Variable names defined as the legend to Table 4; NS (not significant). The model used backward elimination and had a nominal P-value of 0.05 for each variable.

Table 6. Proportion of explained variation (PEV) severe hypertriglyceridemia

Model 1: All variables	Marginal	Partial
Diabetes	25.65%	14.06%
Obesity (BMI>33 kg/m ²)	10.27%	0.76%
<i>APOA5</i> W19 dominant	11.14%	6.54%
<i>APOA5</i> -1131C dominant	7.92%	4.34%
<i>APOE</i> non-E3 allele	2.43%	1.59%
<i>GCKR</i> T recessive	2.56%	0.81%
<i>TRIB1</i> A recessive	1.84%	1.21%
<i>TBL2/MLXIPL</i> C recessive	1.60%	1.11%
Model	43.87%	
Model 2: Genetic variables only	Marginal	Partial
<i>APOA5</i> W19 dominant	11.14%	8.17%
<i>APOA5</i> -1131C dominant	7.92%	6.17%
<i>APOE</i> non-E3 allele	2.43%	2.07%
<i>GCKR</i> T recessive	2.56%	0.83%
<i>TRIB1</i> A recessive	1.84%	1.72%
<i>TBL2/MLXIPL</i> C recessive	1.60%	1.78%
<i>GALNT2</i> G recessive	2.30%	1.60%
Model	25.93%	

Variable names defined as the legend to Table 4. The marginal percentages correspond to percent contribution without adjustment for other variables, while partial percentages reflect percent contribution when holding influences on other variables constant.