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Association of Rare and Common Variation in the Lipoprotein Lipase Gene With Coronary Artery Disease

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IMPORTANCE The activity of lipoprotein lipase (LPL) is the rate-determining step in clearing triglyceride-rich lipoproteins from the circulation. Mutations that damage the LPL gene (*LPL*) lead to lifelong deficiency in enzymatic activity and can provide insight into the relationship of LPL to human disease.

OBJECTIVE To determine whether rare and/or common variants in *LPL* are associated with early-onset coronary artery disease (CAD).

DESIGN, SETTING, AND PARTICIPANTS In a cross-sectional study, *LPL* was sequenced in 10 CAD case-control cohorts of the multinational Myocardial Infarction Genetics Consortium and a nested CAD case-control cohort of the Geisinger Health System DiscovEHR cohort between 2010 and 2015. Common variants were genotyped in up to 305 699 individuals of the Global Lipids Genetics Consortium and up to 120 600 individuals of the CARDIoGRAM Exome Consortium between 2012 and 2014. Study-specific estimates were pooled via meta-analysis.

EXPOSURES Rare damaging mutations in *LPL* included loss-of-function variants and missense variants annotated as pathogenic in a human genetics database or predicted to be damaging by computer prediction algorithms trained to identify mutations that impair protein function. Common variants in the *LPL* gene region included those independently associated with circulating triglyceride levels.

MAIN OUTCOMES AND MEASURES Circulating lipid levels and CAD.

RESULTS Among 46 891 individuals with *LPL* gene sequencing data available, the mean (SD) age was 50 (12.6) years and 51% were female. A total of 188 participants (0.40%; 95% CI, 0.35%-0.46%) carried a damaging mutation in *LPL*, including 105 of 32 646 control participants (0.32%) and 83 of 14 245 participants with early-onset CAD (0.58%). Compared with 46 703 noncarriers, the 188 heterozygous carriers of an *LPL* damaging mutation displayed higher plasma triglyceride levels (19.6 mg/dL; 95% CI, 4.6-34.6 mg/dL) and higher odds of CAD (odds ratio = 1.84; 95% CI, 1.35-2.51; $P < .001$). An analysis of 6 common *LPL* variants resulted in an odds ratio for CAD of 1.51 (95% CI, 1.39-1.64; $P = 1.1 \times 10^{-22}$) per 1-SD increase in triglycerides.

CONCLUSIONS AND RELEVANCE The presence of rare damaging mutations in *LPL* was significantly associated with higher triglyceride levels and presence of coronary artery disease. However, further research is needed to assess whether there are causal mechanisms by which heterozygous lipoprotein lipase deficiency could lead to coronary artery disease.

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Supplemental content

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The enzymatic activity of lipoprotein lipase (LPL) serves as the rate-determining step in the postprandial clearance of circulating triglyceride-rich lipoproteins.[1] Homozygous LPL deficiency, known as *familial chylomicronemia syndrome*, is associated with marked elevations in chylomicrons, severe hypertriglyceridemia, and recurrent pancreatitis.[2] However, an increased risk of coronary artery disease (CAD) in this condition has not been observed, potentially because the large circulating chylomicrons are unable to penetrate the arterial wall.[3,4] By contrast, in heterozygous LPL deficiency, the attenuated capacity for lipolysis leads to a buildup of circulating chylomicron remnants and intermediate-density lipoproteins that are rich in both triglycerides and cholesterol. A study of 9 such individuals suggested an increased risk of CAD,[5] but this association has not been confirmed.

In this study, the LPL gene (*LPL*; RefSeq NM_000237.2) was sequenced to test the hypothesis that rare damaging mutations leading to heterozygous LPL deficiency are associated with differences in circulating lipid levels as well as higher odds of early-onset CAD. In addition, to provide complementary evidence, independent common variants (allele frequency >1%) in the *LPL* gene region were also tested for association with CAD.

Key Points

Question Do heterozygous carriers of a damaging mutation in the gene encoding lipoprotein lipase have increased odds of coronary artery disease?

Findings In this cross-sectional study of coronary artery disease case-control studies, gene sequencing identified a damaging mutation in the lipoprotein lipase gene in 188 of 46 891 individuals (0.4%). These mutations were associated with an increase of 19.6 mg/dL in plasma triglycerides and an increased presence of coronary artery disease.

Meaning The presence of rare damaging mutations in the lipoprotein lipase gene was significantly associated with higher triglyceride levels and presence of coronary artery disease; however, further research is needed to assess whether this association is causal, including possible mechanisms by which heterozygous lipoprotein lipase deficiency could lead to coronary artery disease.

Methods

Study Populations

Gene sequencing of *LPL* was performed in participants of 10 previously described CAD case-control cohorts (eTable 1 in the Supplement). Studies included the Atherosclerosis, Thrombosis, and Vascular Biology Italian Study[6]; the Exome Sequencing Project Early-Onset Myocardial Infarction study[7]; a nested case-control of the Jackson Heart Study[8]; the South German Myocardial Infarction study[9]; the Ottawa Heart Study[10]; the Precocious Coronary Artery Disease study[11]; the Pakistan Risk of Myocardial Infarction Study[12]; the Registre Gironí del COR (Gerona Heart Registry) study[13]; the Leicester Myocardial Infarction study[14]; and the North German Myocardial Infarction study.[15] Clinical data were assessed in each study. The majority of CAD cases in this analysis (97.5%) were ascertained with onset at an early age (defined as ≤50 years in men and ≤60 years in women). Written informed consent was obtained from all participants of contributing studies, each of which received ethical approval from respective institutional review boards. Approval for this analysis was obtained from the institutional review board of Partners HealthCare.

Replication of the observed associations with regard to lipid levels and CAD was performed via analysis of the previously described DiscovEHR study.[16] DiscovEHR study participants were recruited as part of the MyCode Community Health Initiative of the Geisinger Health System and Regeneron Genetics Center. The present analysis was restricted to early-onset CAD cases and CAD-free controls (aged <55 years for men or <65 years for women for both cases and controls). Median values for serially measured laboratory and anthropometric traits were calculated for all individuals with 2 or more measurements in the electronic health record (EHR) following removal of likely spurious values that were more than 3 SDs from the intraindividual median value. Participants were considered to have CAD if they had a history of coronary revascularization in the EHR, or history of acute coronary syndrome, ischemic heart disease, or exertional angina (*International Classification of Diseases, Ninth Revision* codes 410*, 411*, 412*, 413*, and 414*) with angiographic evidence of obstructive coronary atherosclerosis (>50% stenosis in ≥1 major epicardial vessel from catheterization report). The CAD-free controls were defined as individuals without any case criteria or any single encounter or problem list diagnosis code indicating CAD.

Across all studies, the effect of lipid-lowering therapy in individuals reporting use at the time of lipid measurement was taken into account by dividing the measured total cholesterol and low-density lipoprotein cholesterol (LDL-C) by 0.8 and 0.7, respectively.[16-19] Because remnant cholesterol was not measured in study cohorts, values were estimated according to the following formula: remnant cholesterol = total cholesterol minus high-density lipoprotein cholesterol minus LDL-C.[20]

To extend the analysis to common variants in *LPL*, summary statistics of 2 large genome-wide association studies were analyzed. The effect of common *LPL* variants on circulating triglyceride levels was used as a proxy for influence on LPL activity. The relationship of common *LPL* variants with triglyceride levels was assessed in an analysis of up to 305 699 individuals from 73 cohorts of the Global Lipids Genetics Consortium genotyped using the Illumina HumanExome BeadChip between 2012 and 2014. These same variants were subsequently linked to CAD in up to 120 600 individuals also genotyped between 2012 and 2014 in the previously reported CARDIoGRAM Exome Consortium study.[15]

Gene Sequencing

Whole-exome sequencing of the Myocardial Infarction Genetics Consortium participants was performed between

2010 and 2015 at the Broad Institute as previously described.[7] In brief, sequence data of all participants were aligned to a human reference genome build GRCh37.p13 using the Burrows-Wheeler Aligner algorithm. Aligned nonduplicate reads were locally realigned and base qualities were recalibrated using Genome Analysis Toolkit software.[21] Variants were jointly called using Genome Analysis Toolkit HaplotypeCaller software. The sensitivity of the selected variant quality score recalibration threshold was 99.6% for single-nucleotide polymorphisms and 95% for insertion or deletion variants as empirically assessed using HapMap controls with known genotypes included in the genotyping call set. *LPL* sequence data from the Geisinger Health System DiscovEHR participants were extracted from exome sequences generated at the Regeneron Genetics Center between 2014 and 2015 as previously described.[16]

Damaging *LPL* Variant Ascertainment

The positions of genetic variants were based on the complementary DNA reference sequence for *LPL* (RefSeq NM_000237.2). Rare *LPL* variants (minor allele frequency <1%) were annotated with respect to the following 3 classes in a sequential fashion: (1) loss-of-function variants, ie, single base changes that introduce a stop codon leading to premature truncation of a protein (nonsense), insertions or deletions (indels) of DNA that disrupt the translated protein's amino acid sequence beyond the variant site (frameshift), or point mutations at sites of pre-messenger RNA splicing that alter the splicing process (splice-site); (2) variants annotated as pathogenic in ClinVar, a publicly available archive of genetic variations associated with clinical phenotypes[22]; and (3) missense variants predicted to be damaging or possibly damaging by *each* of 5 computer prediction algorithms (LRT score, MutationTaster, PolyPhen-2 HumDiv, PolyPhen-2 HumVar, and SIFT) as performed previously.[7,23] Software used to annotate observed variants included Variant Effect Predictor version 81 and its associated Loss-of-Function Transcript Effect Estimator (LOFTEE) plugin,[24,25] and the dbNSFP database version 3.0b1.[26]

Statistical Analysis

The association of rare damaging *LPL* mutations with lipid phenotypes in the Myocardial Infarction Genetics Consortium and the DiscovEHR studies was estimated using linear regression with adjustment for age, age squared, sex, study cohort, and the first 5 principal components of ancestry. Principal components of ancestry were based on observed genotypic differences across subpopulations (eg, race or ethnicity) in the overall study. Inclusion of principal components as covariates in linear regression analyses increases statistical power for true relationships and minimizes confounding by ancestry.[27] The association of *LPL* mutations with odds of CAD was determined via meta-analysis using Cochran-Mantel-Haenszel statistics for stratified 2-by-2 tables without continuity correction as implemented previously.[9,18,28]

Common variants (allele frequency >1%) at the *LPL* locus independently associated with circulating triglyceride levels were ascertained via analysis of the Global Lipids Genetics Consortium cohorts. The association of variants with inverse normal transformed residuals of natural log of triglyceride levels was determined in a model adjusted for age, age squared, sex, and up to 4 principal components of ancestry. For any given genetic locus, such as *LPL*, multiple variants may be associated with circulating triglyceride levels in an independent fashion. Sequential forward selection provides a statistical framework to identify such independent variants.[29,30] The relationship of all genetic variants in the *LPL* locus with triglyceride levels was first determined. This analysis was then repeated using regression conditional on the most strongly associated variant, continuing the process until the top result was no longer significant at a prespecified threshold of $P < 5 \times 10^{-8}$ (to represent genome-wide significance). To aid in interpretability, the beta coefficients derived from this analysis were converted into units of milligrams per deciliter using data from the National Health and Nutrition Examination Survey from 2005 through 2012, in which a similar transformation was used (substituting self-reported race for principal components of ancestry) to yield a conversion factor of 60.7-mg/dL change in triglyceride level per 1-unit change in inverse normal transformed values.

These same common *LPL* variants were linked to CAD using summary-level test statistics in the previously reported CARDIoGRAM Exome Consortium study.[15] The cumulative association of these variants with odds of CAD was determined, standardized per genetic 1-SD increase in triglyceride levels. Explicitly, if x is the association of each variant with the outcome of interest, and y the association of each variant with triglyceride levels, then the estimated association of a 1-SD increase in triglycerides mediated by *LPL* locus variants is calculated as a fixed-effects meta-analysis of x/y for all variants. This method is mathematically equivalent to a previously reported approach.[31]

Analyses were performed using R version 3.2.2 software (The R Foundation). All reported P values were 2-tailed, with $P < .05$ used as a threshold for statistical significance unless otherwise specified.

Results

Gene sequencing of *LPL* was performed in 22 533 participants of the Myocardial Infarction Genetics Consortium, including 12 395 controls and 10 138 cases with CAD (**Table 1**). A total of 123 loss-of-function or missense variants in *LPL* with minor allele frequency less than 1% were identified. Of these 123 variants, 52 were classified as damaging (**Table 2**). Eight of these 123 variants led to loss of function, including 5 premature stop (nonsense) codons, 2 splice acceptor or donor variants, and 1 frameshift mutation. Only about 25% of missense variants in any given gene have a strongly damaging effect on protein function[32]; additional annotation algorithms were thus needed for the 115 missense variants. Six were previously deemed pathogenic based on ClinVar annotation. In addition, 38 of the 109 remaining missense variants were predicted to be damaging

Table 1. Baseline Characteristics of the Myocardial Infarction Genetics Consortium and Early-Onset CAD DiscovEHR Study Participants

Characteristic	Myocardial Infarction Genetics Consortium		Geisinger Health System DiscovEHR Cohort[a]	
	Participants With CAD (n = 10 138)	CAD-Free Controls (n = 12 395)	Participants With CAD (n = 4107)	CAD-Free Controls (n = 20 251)
Age, median (IQR), y	45 (41-50)	60 (48-68)	52 (47-57)	46 (35-55)
Female, No. (%)[b]	1294 (28)	4276 (19)	2169 (53)	16 334 (81)
BMI, median (IQR)	26 (24-29)	27 (25-31)	32 (28-38)	31 (26-37)
Current smoker, No. (%)[b]	4322 (47)	2406 (21)	986 (24)	4110 (20)
Medical history, No. (%)[b]				
Type 2 diabetes	2190 (25)	1942 (19)	1520 (37)	2661 (13)
Hypertension	2918 (47)	3741 (42)	3373 (82)	6848 (34)
Lipid-lowering medication[c]	2739 (31)	473 (5)	2494 (61)	3711 (18)
Lipid phenotypes, median (IQR), mg/dL				
Total cholesterol[d]	216 (181-252)	197 (168-228)	209 (184-240)	198 (173-227)
LDL cholesterol[d]	138 (107-171)	120 (96-147)	124 (101-151)	117 (96-142)
HDL cholesterol	37 (31-45)	42 (33-53)	44 (37-53)	50 (42-61)
Triglycerides	166 (116-246)	133 (90-198)	154 (112-215)	120 (85-167)
Remnant cholesterol	33 (23-48)	28 (19-40)	33 (22-50)	24 (16-35)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply values by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

[a] Participants were considered to have early-onset CAD (ages <55 years for men, <65 years for women) if they had a history of coronary revascularization in the electronic health record, or history of acute coronary syndrome, ischemic heart disease, or exertional angina (*International Classification of Diseases, Ninth Revision* codes 410*, 411*, 412*, 413*, and 414*) with angiographic evidence of obstructive coronary atherosclerosis (>50% stenosis in ≥1 major epicardial vessel from catheterization report). Participants were considered to have diabetes if they had at least 2 of the following: (1) a history of type 2 diabetes in the electronic health record, (2) antidiabetic medication use, or (3) fasting glucose level greater than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or hemoglobin A_{1c} level greater than 6.5% (to convert to proportion of total hemoglobin, multiply by 0.01). Participants were considered to have hypertension if they had a history of hypertension in the electronic health record, antihypertensive medication use, or systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg.

[b] Percentages indicative of participants with nonmissing values.

[c] At the time of lipid measurement.

[d] Total and LDL cholesterol values were divided by 0.8 and 0.7, respectively, in those receiving lipid-lowering medication to estimate untreated values.

by each of 5 computer prediction algorithms. Because any individual damaging mutation was rare (eTable 2 in the Supplement), the 52 damaging variants were aggregated for subsequent analyses of phenotypic consequences.

A total of 97 individuals in the Myocardial Infarction Genetics Consortium cohorts carried one of the 52 damaging *LPL* mutations, including 60 cases (0.59%; 95% CI, 0.46% to 0.77%) and 37 controls (0.30%; 95% CI, 0.21% to 0.42%) (eTable 3 in the Supplement). Circulating lipid levels were available in 16 200 participants (72%), including 72 of 97 mutation carriers (74%). Median triglyceride levels were 183 mg/dL (interquartile range, 135-274 mg/dL) in *LPL* mutation carriers vs 147 mg/dL (interquartile range, 99-217 mg/dL) in noncarriers (to convert to micromoles per liter, multiply by 0.0113). In an adjusted linear regression model, circulating triglyceride levels were 25.6 mg/dL (95% CI, −2.5 to 53.5 mg/dL) higher in mutation carriers as compared with noncarriers, although there was no significant association (P = .07) (**Figure 1** and eTable 4 in the Supplement). Furthermore, mutation carriers were at increased odds of having clinical hypertriglyceridemia (triglyceride levels ≥150 mg/dL) (odds ratio = 1.88; 95% CI, 1.13 to 3.20; P = .02).

The presence of a rare damaging *LPL* mutation was associated with an odds ratio for CAD of 1.96 (95% CI, 1.30-2.96; P = .001) in a combined analysis of the Myocardial Infarction Genetics Consortium studies (**Figure 2**). This association was most pronounced in those with a loss-of-function mutation in *LPL* (Table 2). Within the subgroup of 2592 CAD cases and 5341 controls free of CAD with an observed LDL-C level lower than 130 mg/dL (to convert to millimoles per liter, multiply by 0.0259), an increased odds of CAD among carriers of a damaging *LPL* mutation remained apparent (odds ratio = 2.15; 95% CI, 1.14-4.06; P = .02).

Independent replication of the increased circulating triglyceride levels and CAD was performed in 24 358 individuals from the Geisinger Health System DiscovEHR cohort (Table 1). This cohort included 4107 individuals with early-onset CAD (age <55 years in men or <65 years in women) as ascertained based on medical records as well as 20 251 CAD-free controls. Ninety-one individuals were heterozygous carriers of a damaging *LPL* mutation, including 23 individuals with CAD (0.56%; 95% CI, 0.36% to 0.85%) and 68 CAD-free controls (0.34%; 95% CI, 0.26% to 0.43%). Circulating triglyceride levels were 17.2 mg/dL (95% CI, −0.5 to 34.9 mg/dL; P = .06) higher in mutation carriers as compared with noncarriers (Figure 1 and Table 2). The mutation carriers had increased odds of early-onset CAD (odds ratio = 1.67; 95% CI, 1.04 to 2.69; P = .03).

In a combined analysis of the Myocardial Infarction Genetics Consortium and DiscovEHR cohorts, among 46 891

Table 2. Association of Damaging Lipoprotein Lipase Gene (*LPL*) Mutations With CAD by Rare Variant Class in the Myocardial Infarction Genetics Consortium Studies and Early-Onset CAD DiscovEHR Study

Outcome	Variant Class[a]			
	Loss-of-Function	ClinVar Pathogenic	Predicted Damaging Missense	Combined
Myocardial Infarction Genetics Consortium				
Variants, No.	8	6	38	52
Carriers, No. (%)				
Participants with CAD (n = 10 138)	7 (0.07)	15 (0.15)	38 (0.37)	60 (0.59)
CAD-free controls (n = 12 395)	2 (0.02)	5 (0.04)	30 (0.24)	37 (0.30)
Beta coefficient for difference in triglyceride concentrations (95% CI), mg/dL[b]	35.6 (-4.8 to 119.4)	18.2 (-50.3 to 86.7)	25.6 (-7.3 to 58.5)	25.6 (-2.5 to 53.5)
P Value	.41	.60	.13	.07
Odds ratio for CAD (95% CI)[c]	4.33 (0.85 to 21.96)	3.47 (1.25 to 9.58)	1.55 (0.96 to 2.50)	1.96 (1.30 to 2.96)
P Value	.08	.02	.07	.001
Geisinger Health System DiscovEHR Cohort				
Variants, No.	3	7	15	25
Carriers, No. (%)				
Participants with CAD (n = 4107)	1 (0.02)	6 (0.15)	16 (0.39)	23 (0.56)
CAD-free controls (n = 20 251)	2 (0.01)	28 (0.14)	38 (0.19)	68 (0.34)
Beta coefficient for difference in triglyceride concentrations (95% CI), mg/dL[b]	194.6 (92.7 to 296.4)	29.3 (-0.8 to 59.3)	2.4 (-20.1 to 24.9)	17.2 (-0.5 to 34.9)
P Value	.001	.06	.83	.06
Odds ratio for CAD (95% CI)[c]	2.47 (0.22 to 27.2)	1.06 (0.44 to 2.55)	2.08 (1.16 to 2.69)	1.67 (1.04 to 2.69)
P Value	.46	.90	.01	.03

Abbreviation: CAD, coronary artery disease.

[a] Rare variants refer to those with minor allele frequency less than 1% in the sequenced population. Loss-of-function variants were defined as single base changes that introduce a stop codon leading to premature truncation of a protein (nonsense), insertions or deletions (indels) of DNA that disrupt the translated protein's amino acid sequence beyond the variant site (frameshift), or point mutations at sites of pre–messenger RNA splicing that alter the splicing process (splice-site). Predicted damaging variants refer to those predicted to be deleterious or possibly deleterious by *each* of 5 in silico prediction algorithms (LRT score, MutationTaster, PolyPhen-2 HumDiv, PolyPhen-2 HumVar, and SIFT).

[b] Beta coefficients reflective of the difference in triglyceride concentrations between carriers of a damaging *LPL* mutation and noncarriers were derived from linear regression analysis that included adjustment for age, age squared, sex, cohort, and the first 5 principal components of ancestry. Principal components of ancestry were based on observed genotypic differences across subpopulations (eg, race or ethnicity) in the overall study. Inclusion of principal components as covariates in linear regression analyses increases statistical power for true relationships and minimizes confounding by ancestry.[27]

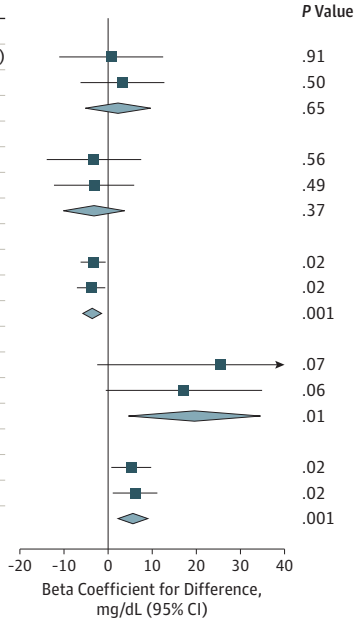
[c] The association of *LPL* mutations with risk of CAD was determined via meta-analysis implementing Cochran-Mantel-Haenszel statistics for stratified 2-by-2 tables.

individuals with *LPL* gene sequencing data available, the mean (SD) age was 50 (12.6) years and 51% were female. A damaging *LPL* mutation was present in 188 of 46 891 individuals (0.40%; 95% CI, 0.35% to 0.46%), including 105 of 32 646 control participants (0.32%) and 83 of 14 245 participants with early-onset CAD (0.58%). A meta-analysis of the association with lipid levels demonstrated that compared with 46 703 noncarriers, the 188 heterozygous carriers of an *LPL* damaging mutation displayed higher plasma triglyceride levels; these mutations were associated with a circulating triglycerides increase of 19.6 mg/dL (95% CI, 4.6 to 34.6 mg/dL), a high-density lipoprotein cholesterol decrease of 3.6 mg/dL (95% CI, −5.7 to −1.5 mg/dL), and a remnant cholesterol increase of 5.6 mg/dL (95% CI, 2.3 to 9.0 mg/dL) (Figure 1). These beta coefficients can be interpreted to suggest, for example, that an individual with a damaging *LPL* mutation would be predicted to have a 19.6-mg/dL higher level of circulating triglycerides as compared with an individual without such a mutation after correction for potential confounding related to age, sex, study cohort, and ancestry. These mutations were additionally associated with increased odds of early-onset CAD (odds ratio = 1.84; 95% CI, 1.35 to 2.51; $P < .001$) (Figure 2).

Beyond rare damaging mutations, common variants at the *LPL* locus were analyzed to assess for a similar link to triglyceride levels and CAD. In an analysis of up to 305 699 individuals, 6 common variants (minor allele frequency ranging from 1%-29%) were robustly ($P < 5 \times 10^{-8}$) and independently associated with plasma triglyceride levels. The minor (less common) alleles of 4 of these variants were associated with decreased triglyceride levels, suggesting gain of lipoprotein lipase activity, and 2 were linked to increased triglyceride levels, consistent with decreased activity. In an analysis of up to 120 600 individuals of CAD case-control studies, each of these variants was confirmed to be associated with odds of CAD ($P < .002$ for each) with the expected directionality. A roughly linear relationship was noted in this data set between association with triglyceride levels and odds of CAD (eFigure in the Supplement). A weighted analysis that combined these 6 variants demonstrated an odds ratio for CAD of 1.51 (95% CI, 1.39-1.64; $P = 1.1 \times 10^{-22}$) per 1-SD increase in triglycerides mediated by *LPL* locus variants.

Figure 1. Association of Damaging Lipoprotein Lipase Gene (*LPL*) Mutations With Circulating Lipid Concentrations

Lipid Phenotype	Participants, No.		Lipid Level, Median (IQR), mg/dL		Beta Coefficient for Difference, mg/dL (95% CI)	*P* Value
	Carriers	Noncarriers	Carriers	Noncarriers		
Total cholesterol						
Myocardial Infarction Genetics Consortium	73	16 367	203 (180-236)	203 (173-239)	0.7 (-11.1 to 12.5)	.91
Geisinger Health System DiscovEHR	66	17 111	198 (175-230)	200 (175-229)	3.4 (-6.3 to 12.8)	.50
Combined					2.2 (-5.2 to 9.6)	.65
LDL cholesterol						
Myocardial Infarction Genetics Consortium	69	14 880	120 (104-149)	127 (100-160)	-3.2 (-13.9 to 7.5)	.56
Geisinger Health System DiscovEHR	65	16 918	117 (90-140)	119 (97-144)	-3.2 (-12.3 to 5.9)	.49
Combined					-3.2 (-10.1 to 3.7)	.37
HDL cholesterol						
Myocardial Infarction Genetics Consortium	70	15 303	37 (30-42)	40 (32-50)	-3.4 (-6.2 to -0.6)	.02
Geisinger Health System DiscovEHR	66	17 141	45 (38-57)	49 (41-60)	-3.9 (-7.1 to -0.7)	.02
Combined					-3.6 (-5.7 to -1.5)	.001
Triglycerides						
Myocardial Infarction Genetics Consortium	72	16 128	183 (135-274)	147 (99-217)	25.6 (-2.5 to 53.5)	.07
Geisinger Health System DiscovEHR	66	17 112	133 (109-188)	126 (89-177)	17.2 (-0.5 to 34.9)	.06
Combined					19.6 (4.6 to 34.6)	.01
Remnant cholesterol						
Myocardial Infarction Genetics Consortium	68	14 601	37 (26-54)	30 (20-43)	5.2 (0.7 to 9.8)	.02
Geisinger Health System DiscovEHR	65	16 815	29 (22-42)	26 (17-38)	6.1 (1.1 to 11.2)	.02
Combined					5.6 (2.3 to 9.0)	.001



Beta coefficients reflective of the difference in lipid concentrations between carriers of a damaging *LPL* mutation and noncarriers were derived from linear regression models that included adjustment for age, age squared, sex, cohort, and the first 5 principal components of ancestry. Principal components of ancestry were based on observed genotypic differences across subpopulations (eg, race or ethnicity) in the overall study. Inclusion of principal components as covariates in linear regression analyses increases statistical power for true relationships and minimizes confounding by ancestry.[27] Fixed-effects meta-analysis was used to combine results across cohorts (*P* for heterogeneity > .50 for each lipid phenotype). The number of participants from each study cohort with lipid fraction values available is displayed. HDL indicates high-density lipoprotein; IQR, interquartile range; and LDL, low-density lipoprotein. To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

Discussion

The protein-coding exons of *LPL* were sequenced in 46 891 individuals from an international collaboration of CAD case-control cohorts and patients of a large health care organization. In this study, approximately 0.40% of individuals carried a rare damaging mutation in *LPL*. These carriers had increased circulating triglyceride levels (19.6 mg/dL) and an odds ratio of 1.84 for early-onset CAD. An analysis using common variants in *LPL* similarly demonstrated a significant association with CAD.

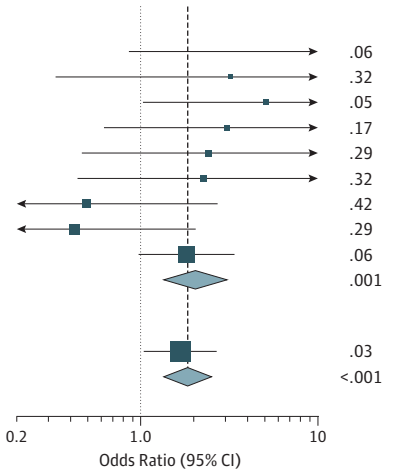
These results permit several conclusions. First, heterozygous LPL deficiency was associated with the presence of early-onset CAD. By identifying 188 carriers of a rare damaging mutation, an association with higher levels of triglycerides and remnant cholesterol and lower levels of high-density lipoprotein cholesterol was established along with an odds ratio for early-onset CAD of 1.84. This susceptibility to CAD may be due to impaired lipolysis of triglyceride-rich lipoproteins. Triglyceride-rich lipoproteins penetrate directly into the arterial wall and are selectively retained in the intima, thus promoting the development of cholesterol-rich foam cells and an inflammatory response that accelerate atherosclerosis.[33]

Second, a complementary common variant analysis involving 6 independent *LPL* variants confirmed the association of genetic variation in *LPL* with CAD. In an analysis in more than 300 000 individuals, each common variant's association with triglyceride levels was used as a proxy for influence on LPL activity. Association of these same variants with CAD in more than 120 000 individuals demonstrated an odds ratio for CAD of 1.51 per 1-SD increase in triglyceride levels associated with common *LPL* locus variants. These findings confirm and extend previous common variant studies that have suggested similar trends.[15,34,35]

Third, these data add to considerable recent genetic evidence that beyond LDL-C, LPL and its endogenous regulation—via facilitator (apolipoprotein A5 [APOA5]) and inhibitor (apolipoprotein C3 [APOC3], angiopoietin-like 4 [ANGPTL4]) proteins—represent an important determinant of human atherosclerosis. Similar approaches have been used to demonstrate that damaging mutations in *APOA5* are associated with a significant increase in odds of CAD.[7,20] By contrast, rare inactivating mutations in *APOC3* and *ANGPTL4* confer substantial vascular protection.[9,15,16,36] Ongoing research will seek to clarify the mechanistic interactions between these proteins. However, in each case, CAD risk is likely to be affected by lifelong alterations in LPL activity. Whether therapy to alter this pathway will decrease risk of CAD remains unknown.

Figure 2. Association of Damaging Lipoprotein Lipase Gene (*LPL*) Mutations With Coronary Artery Disease (CAD) Among 46 891 Individuals in 11 Studies

	LPL Mutation Carriers/Total, No.			
	CAD Cases	CAD-Free Controls	Odds Ratio for CAD (95% CI)	*P* Value
Myocardial Infarction Genetics Consortium				
JHS[8]	0/18	0/693	NA	
PROCARDIS[11]	7/914	0/910	15.05 (0.86-263.89)	.06
REGICOR[13]	3/369	1/391	3.20 (0.33-30.87)	.32
OHS[10]	6/572	2/968	5.12 (1.03-25.45)	.05
North German[15]	6/858	2/878	3.08 (0.62-15.32)	.17
ATVB[6]	5/1791	2/1719	2.40 (0.47-12.40)	.29
Leicester[14]	5/1201	2/1090	2.27 (0.44-11.75)	.32
South German[9]	2/400	4/398	0.49 (0.09-2.72)	.42
ESP-EOMI[7]	2/989	7/1471	0.42 (0.09-2.04)	.29
PROMIS[12]	24/3026	17/3877	1.82 (0.97-3.39)	.06
Combined Heterogeneity: $I^2 = 21\%$, $P = .26$	60/10 138	37/12 395	1.96 (1.30-2.96)	.001
Geisinger Health System				
DiscovEHR[16]	23/4107	68/20 251	1.67 (1.04-2.69)	.03
Overall Heterogeneity: $I^2 = 12\%$, $P = .33$	83/14 245	105/32 646	1.84 (1.35-2.51)	<.001



In each study, the relationship of rare damaging mutations in *LPL* with risk of CAD was determined. *P* values for association tests and confidence intervals were determined using exact methods. A meta-analysis across studies was performed using Cochran-Mantel-Haenszel statistics for stratified 2-by-2 tables. This method combines score statistics and is particularly useful when some observed odds ratios are 0. An odds ratio in the Jackson Heart Study (JHS) cohort was not available (NA) owing to absence of identified carriers of a damaging *LPL* mutation. ATVB indicates Atherosclerosis, Thrombosis, and Vascular Biology Italian Study; DiscovEHR, DiscovEHR project of the Regeneron Genetics Center and Geisinger Health System; ESP-EOMI, Exome Sequencing Project Early-Onset Myocardial Infarction study; Leicester, Leicester Myocardial Infarction study; North German, North German Myocardial Infarction study; OHS, Ottawa Heart Study; PROCARDIS, Precocious Coronary Artery Disease study; PROMIS, Pakistan Risk of Myocardial Infarction Study; REGICOR, Registre Gironí del COR (Gerona Heart Registry) study; South German, South German Myocardial Infarction study; and dashed line, overall meta-analysis effect estimate.

A key strength of the present analysis is that *LPL* was sequenced in a large number of individuals to analyze the entire spectrum of damaging mutations, each of which was rare in the population. Second, concordant results were demonstrated between CAD case-control studies of the Myocardial Infarction Genetics Consortium and the DiscovEHR study participants from the Geisinger Health System, in whom CAD status was ascertained based on EHRs. This reinforces the potential utility of ongoing efforts such as the UK Biobank and the All of Us Research Program (a cohort study within the Precision Medicine Initiative), which will facilitate large-scale interrogations of genetic variants as they relate to human disease.

Several limitations should be acknowledged. The approach to annotating rare missense variants in *LPL* using prediction algorithms and the ClinVar database has been previously validated and is fully reproducible.[7,23] However, because functional validation of each variant was not performed, this method may have led to misclassification in some cases. Second, because the effect of LPL activity on regulation of circulating triglyceride levels is most pronounced following a meal,[37] the degree of triglyceride level elevation among mutation carriers would likely have been greater if postprandial triglyceride levels were available. Third, this study assessed the association of *LPL* mutations with susceptibility to early-onset CAD; effect estimates might differ among individuals with later onset of disease. Fourth, levels of both triglycerides and calculated remnant cholesterol, the primary lipid components of triglyceride-rich lipoproteins, were increased in individuals harboring an *LPL* mutation. Because the level of remnant cholesterol was estimated and not directly measured in the present analysis, additional research is needed to determine the relative contributions of these components to human CAD.

Conclusions

The presence of rare damaging mutations in *LPL* was significantly associated with higher triglyceride levels and presence of CAD. However, further research is needed to assess whether there are causal mechanisms by which heterozygous LPL deficiency could lead to CAD.

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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Coronary Artery Disease Definitions Across Myocardial Infarction Genetics Consortium and DiscovEHR Cohorts

Cohort	Enrollment Location	Dates of Sequencing	CAD Cases	Controls	CAD Definition	Control Definition	N (%) with Lipid Levels Available
ATVB[1]	Italy	2013 – 2014	1791	1719	MI in men or women ≤45y	No history of thromboembolic disease	3180 (91%)
EOMI[2]	United States	2010 – 2014	989	1471	MI (men ≤50y or women ≤60y)	Hospital-based, no report of MI by history	1463 (59%)
JHS[3]	United States	2013 – 2014	18	693	Prevalent CHD (self-reported or electrocardiographic evidence of MI) and incident CHD (MI or coronary revascularization) in men ≤50y or women ≤60y	Free of CHD at baseline and during follow-up	616 (87%)
Leicester MI[4]	United Kingdom	2015	1201	1090	MI in men or women age ≤60y	Controls ≥64y without reported CAD history	459 (20%)
North German MI[5]	Germany	2014 – 2015	858	878	MI in men and women ≤60y	Controls without CAD; men and women ≤65y	0 (0%)
South German MI[6]	Germany	2014	400	398	MI in men ≤40y or women ≤55y	Controls without CAD, men ≥ 65y and women ≥75y	639 (80%)
OHS[7]	Canada	2013 – 2014	572	968	MI or CABG or angiographic disease (>50% stenosis) in men ≤50y or women ≤60y), without type 2 diabetes	Asymptomatic	1382 (90%)
PROCARDIS[8]	United Kingdom, Italy, Sweden, Germany	2013	914	910	MI (men ≤50y or women ≤60y)	No history of CAD	1430 (78%)
PROMIS[9]	Pakistan	2014 – 2015	3026	3877	MI, age ≤50y	Age and gender frequency-matched; no history of MI/CVD	6640 (96%)

REGICOR[10]	Spain	2013 – 2014	369	391	MI in men ≤50y or women ≤60y	Controls from a population-based study; free of MI, coronary revascularization; ≥55y and <80y	391 (51%)
DiscovEHR[11]	United States	2014 – 2015	4107	20251	History of coronary revascularization, acute coronary syndrome, ischemic heart disease, or exertional angina with angiographic evidence of obstructive coronary disease (>50% stenosis in at least one major epicardial vessel) in men <55y or women <65y	Absence of CAD case criteria or electronic health record problem list diagnosis code indicating CAD	17207 (71%)

ATVB: Atherosclerosis, Thrombosis and Vascular Biology Italian Study; EOMI: NHLBI Exome Sequencing Project Early-Onset Myocardial Infarction; JHS: Jackson Heart Study; Leicester MI: Leicester Myocardial Infarction Study; North German MI: North German Myocardial Infarction Study; South German MI; South German Myocardial Infarction Study; OHS: Ottawa Heart Study; PROCARDIS: Precocious coronary artery disease; PROMIS: Pakistan Risk of Myocardial Infarction Study; REGICOR: Registre Gironi del COR (Gerona Heart Registry) study.
CAD: coronary artery disease; MI: myocardial infarction; CHD**:** coronary heart disease; CABG: Coronary artery bypass grafting; CVD: cardiovascular disease.

eTable 2. Rare Damaging Mutations in *LPL* and Coronary Artery Disease in the Myocardial Infarction Genetics Consortium Cohorts

Variant (CHR:POS_REF/ALT)	dbSNP ID	Consequence	Protein Change or Splice Site	Median Triglyceride Level, mg/dL	N of 12,395 Controls	N of 10,138 CAD Cases	N of 22,533 Study Participants
Loss of Function Variants (n = 8)							
8:19797040_G/C		Splice Site	c.88+1G>C	137	0	2	2
8:19805729_C/CT		Frameshift	p.Arg44LysfsTer4	N/A	0	1	1
8:19805777_G/T	rs375484335	Premature Stop	p.Gly59Ter	105	1	0	1
8:19809303_G/A		Premature Stop	p.Trp91Ter	347	0	1	1
8:19809427_C/T	rs118204058	Premature Stop	p.Gln133Ter	229	1	0	1
8:19813360_C/T		Premature Stop	p.Gln262Ter	115	0	1	1
8:19816770_G/C		Splice Site	c.1019-1G>C	453	0	1	1
8:19818531_G/A		Premature Stop	p.Trp420Ter	205	0	1	1
ClinVar Pathogenic Variants (n = 6)							
8:19811733_G/A	rs118204057	Missense	p.Gly215Glu	N/A	3	9	12
8:19811790_C/T	rs118204060	Missense	p.Pro234Leu	136	0	2	2
8:19811844_T/C	rs118204080	Missense	p.Ile252Thr	N/A	1	2	3
8:19813384_C/T	rs118204077	Missense	p.Arg270Cys	172	0	1	1
8:19813405_G/A	rs118204068	Missense	p.Asp277Asn	249	0	1	1
8:19818446_C/G	rs118204078	Missense	p.Leu392Val	126	1	0	1
Predicted Damaging Missense Variants (n = 38)							
8:19805708_G/C	rs1801177	Missense	p.Asp36His	N/A	2	0	2
8:19805713_C/G	rs374067507	Missense	p.Ile37Met	186	1	0	1
8:19805715_A/G	rs142501489	Missense	p.Glu38Gly	49	1	0	1
8:19805736_C/A	rs143944126	Missense	p.Thr45Asn	N/A	2	0	2
8:19805844_G/A		Missense	p.Gly81Asp	154	0	1	1
8:19809298_A/G		Missense	p.Ser90Gly	N/A	1	1	2
8:19809316_G/C	rs373088068	Missense	p.Val96Leu	N/A	2	3	5
8:19809322_G/A	rs145657341	Missense	p.Ala98Thr	N/A	1	0	1
8:19809335_G/A		Missense	p.Arg102Lys	277	0	1	1

8:19809341_C/G		Missense	p.Pro104Arg	403	1	0	1
8:19809377_G/A		Missense	p.Arg116Gln	392	2	0	2
8:19809403_G/A	rs199675233	Missense	p.Ala125Thr	N/A	2	3	5
8:19809416_A/C	rs140903633	Missense	p.Lys129Thr	89	1	1	2
8:19809425_G/T		Missense	p.Gly132Val	273	0	1	1
8:19810916_A/C		Missense	p.Lys175Asn	N/A	1	0	1
8:19811636_G/C		Missense	p.Asp183His	N/A	0	1	1
8:19811642_G/A		Missense	p.Ala185Thr	112	0	1	1
8:19811678_C/T		Missense	p.Arg197Cys	428	1	0	1
8:19811679_G/A	rs372668179	Missense	p.Arg197His	N/A	1	0	1
8:19811679_G/T	rs372668179	Missense	p.Arg197Leu	829	0	1	1
8:19811711_G/A	rs568397156	Missense	p.Val208Ile	N/A	0	1	1
8:19811720_A/T		Missense	p.Thr211Ser	182	0	1	1
8:19811721_C/A		Missense	p.Thr211Lys	348	1	0	1
8:19811765_C/A		Missense	p.Pro226Thr	163	1	0	1
8:19811774_C/G		Missense	p.His229Asp	N/A	0	2	2
8:19811784_T/G		Missense	p.Ile232Ser	N/A	0	2	2
8:19813371_G/C		Missense	p.Lys265Asn	103	1	0	1
8:19813411_C/G	rs371282890	Missense	p.Leu279Val	250	1	1	2
8:19813438_G/C	rs1800011	Missense	p.Ala288Pro	63	0	1	1
8:19813448_G/T		Missense	p.Cys291Phe	532	0	1	1
8:19813534_G/T		Missense	p.Val320Phe	N/A	2	8	10
8:19816784_A/T		Missense	p.Gln344His	279	1	0	1
8:19816866_G/C		Missense	p.Glu372Gln	N/A	0	1	1
8:19816878_A/T		Missense	p.Ile376Phe	81	1	0	1
8:19818430_T/G		Missense	p.Asn386Lys	85	1	0	1
8:19818435_C/G		Missense	p.Thr388Ser	201	0	1	1
8:19818435_C/T		Missense	p.Thr388Ile	201	2	4	6
8:19818441_C/G	rs141502542	Missense	p.Ser390Cys	136	0	1	1

The carrier counts across coronary artery disease case and control participants of the Myocardial Infarction Genetics Consortium studies are provided for each of 52 *LPL* variants.
CHR: Chromosome; POS: Chromosomal positions based on the hg19 build of the human reference genome; REF: Reference allele; ALT: Alternate allele; N/A: Not available.

eTable 3. Baseline Characteristics of Myocardial Infarction Genetics Consortium Cohorts According to Damaging *LPL* Mutation Status

	***LPL* Mutation Negative (N = 22,436)**	***LPL* Mutation Positive (N = 97)**
Age, years	50 (44 – 64)	50 (44 – 59)
Male Gender	16,888 (75%)	75 (78%)
Race		
White	14,162 (63%)	54 (56%)
Black	1,286 (6%)	2 (2%)
South Asian	6,862 (31%)	41 (42%)
Other	126 (0.6%)	0 (0%)
Hypertension	6,626 (44%)	33 (45%)
Diabetes Mellitus	4,109 (22%)	23 (29%)
Current Smoking	6,692 (33%)	36 (41%)
Total Cholesterol, mg/dL	203 (173 – 239)	203 (180 – 236)
LDL Cholesterol, mg/dL	127 (100 – 160)	120 (104 – 149)
HDL Cholesterol, mg/dL	40 (32 – 50)	37 (30 – 42)
Triglycerides, mg/dL	147 (99 – 217)	183 (135 – 274)
Remnant Cholesterol, mg/dL	30 (20 – 43)	37 (26 – 54)
Lipid-lowering Medication	3,198 (17%)	14 (18%)
Coronary Artery Disease	10,078 (45%)	60 (62%)

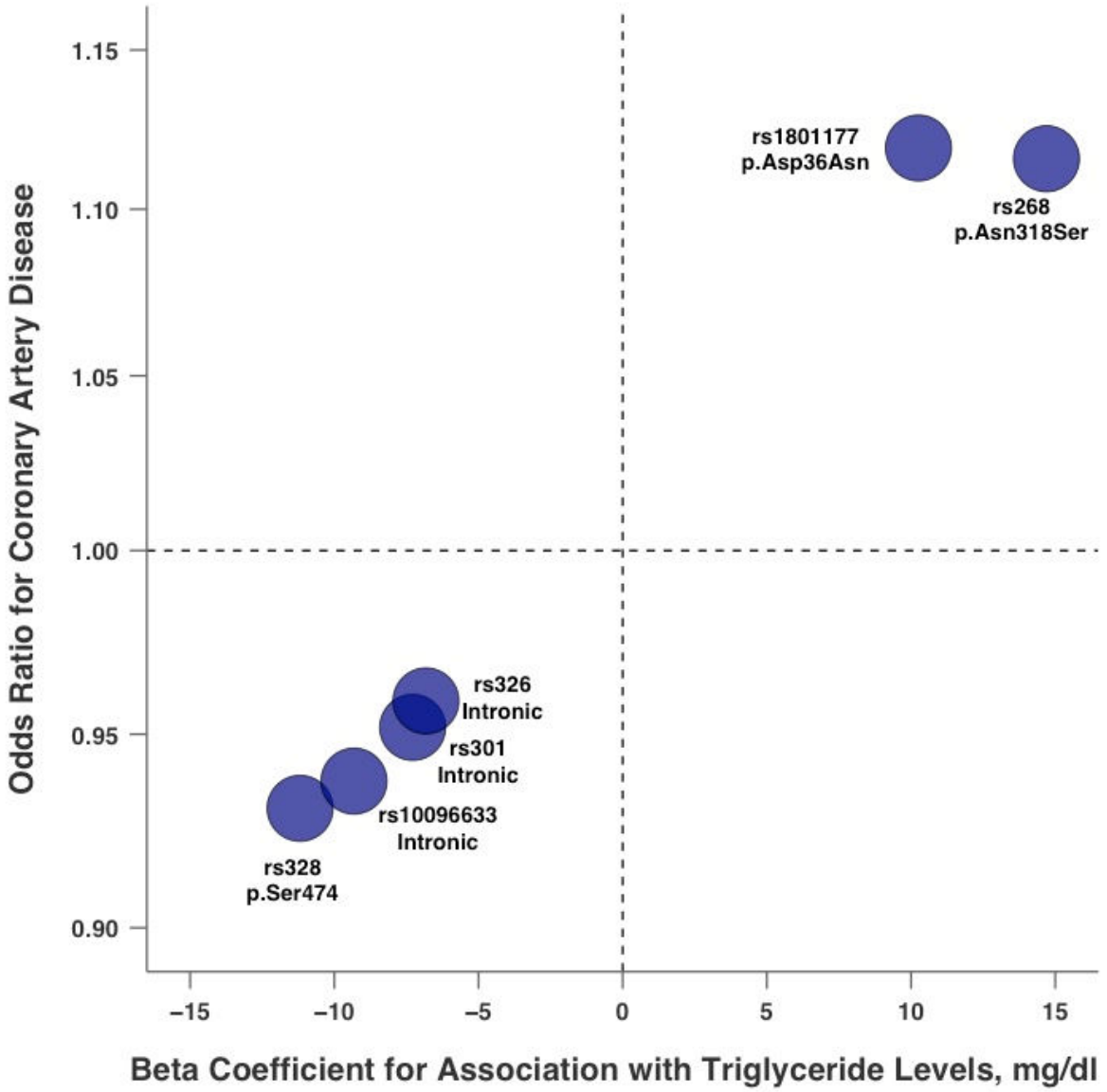
Values represent n (% of individuals with nonmissing data), or median (interquartile range, IQR). SI conversion factor: To convert cholesterol to mmol/L, multiply values by 0.0259. To convert triglyceride levels to mmol/l, multiple values by 0.01129.

eTable 4. Association of Damaging *LPL* Mutations With Circulating Lipids by Rare Variant Class in the Myocardial Infarction Genetics Consortium Studies

Variant Class	Loss of Function	ClinVar Pathogenic	Predicted Damaging Missense	Combined
Beta Coefficient for Association with Total Cholesterol Levels, mg/dlL (95% CI)	+ 30.4 (-5.0 – 65.9) P = 0.09	+ 8.1 (-20.9 – 37.1) P = 0.58	- 5.5 (-19.3 – 8.3) P = 0.44	+ 0.7 (-11.1 – 12.5) P = 0.91
Beta Coefficient for Association with LDL Cholesterol Levels, mg/dL (95% CI)	+ 22.5 (-11.0 – 5.6) P = 0.19	+ 6.9 (-18.7 – 32.6) P = 0.60	- 9.3 (-21.8 – 3.3) P = 0.15	- 3.2 (-13.9 – 7.5) P = 0.56
Beta Coefficient for Association with HDL Cholesterol Levels, mg/dL (95% CI)	- 4.0 (-13.0 – 4.9) P = 0.38	- 3.8 (-10.6 – 3.1) P = 0.28	- 3.2 (-6.5 – 0.1) P = 0.06	- 3.4 (-6.2 – -0.6) P = 0.02
Beta Coefficient for Association with Remnant Cholesterol Levels, mg/dL (95% CI)	+ 4.4 (-9.7 – 18.4) P = 0.54	+ 5.7 (-5.1 – 16.4) P = 0.30	+ 5.2 (-7.5 – 10.6) P = 0.05	+ 5.2 (0.7 – 9.8) P = 0.02
Beta Coefficient for Association with Triglyceride Levels, mg/dL (95% CI)	+35.6 (-4.8 – 119.4) P = 0.41	+ 18.2 (-50.3 – 86.7) P = 0.60	+ 25.6 (-7.3 – 58.5) P = 0.13	+ 25.6 (-2.5 – 53.5) P = 0.07

Beta coefficients derived from linear regression analysis that included adjustment for age, age^2, gender, cohort, and the first five principal components of ancestry. To convert cholesterol to mmol/L, multiply values by 0.0259. To convert triglyceride levels to mmol/L, multiple values by 0.01129.

eFigure. Association of Common Variants in *LPL* With Circulating Triglycerides and Odds of Coronary Artery Disease



Variant rsID	Variant Class	Protein Change	Minor Allele (Frequency)	TG Beta, mg/dl (95%CI)	CAD Odds Ratio (95%CI)	P Value (CAD)
rs1801177	Missense	Asp36Asn	A (1.9%)	10.3 (9.0 – 11.5)	1.12 (1.04 – 1.20)	0.002
rs268	Missense	Asn318Ser	G (2.1%)	14.7 (13.5 – 15.9)	1.12 (1.04 – 1.19)	0.0011
rs301	Intronic	--	C (23%)	-7.3 (-7.7 – -6.9)	0.95 (0.93 – 0.97)	8.7×10^{-6}
rs326	Intronic	--	G (29%)	-6.8 (-7.2 – -6.5)	0.96 (0.94 – 0.98)	5.0×10^{-5}
rs328	Premature Stop	Ser474Ter	G (1.0%)	-11.2 (-11.7 – -10.7)	0.93 (0.90 – 0.96)	5.0×10^{-6}
rs10096633	Intronic	NA	T (13%)	-9.3 (-9.8 – -8.9)	0.94 (0.91 – 0.96)	7.0×10^{-6}

For each variant, Beta coefficient for normalized triglyceride (TG) levels is plotted against odds ratio for coronary artery disease (CAD). Each of the six variants was an independent predictor of triglyceride concentrations in an analysis of up to 305,699 individuals from 73 cohorts of the Global Lipids Genetics Consortium. These same variants were linked to CAD in up to 120,600 individuals in the CARDIoGRAM Exome Consortium study.[5] *P-value < 5×10^{-8} for each.

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Additional information on the DiscovEHR study group is available at: http://discovehrshare.com.

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