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Coronary Heart Disease and Genetic Variants with Low Phospholipase A₂ Activity

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To the Editor

Genetic studies, particularly studies of rare loss-of-function variants, have been good predictors of the success of targeted drugs that lower levels of risk factors and the risk of disease.^{1,2} Lipoprotein-associated phospholipase A₂, which is encoded by the *PLA2G7* gene, hydrolyzes oxidized phosphatidylcholine to release oxidized nonesterified fatty acids and lysophosphatidylcholine, which up-regulate monocyte adhesion molecules and the chemotactic mediator, MCP-1.³ Elevated lipoprotein-associated phospholipase A₂ activity is positively associated with coronary heart disease.⁴

Following the lead of researchers who have conducted studies of proprotein convertase subtilisin/kexin type 9 (*PCSK9*) loss-of-function mutations,¹ we sequenced the exomes of 6325 participants in the Atherosclerosis Risk in Communities study in search of genetic variants that lower lipoprotein-associated phospholipase A₂ activity. We then tested the effects of these variants on the longitudinal risk of coronary heart disease and outcomes. Sequencing was performed at the Human Genome Sequencing Center at Baylor College of Medicine. DiaDexus donated all reagents for the measurements of lipoprotein-associated phospholipase A₂ but was not otherwise involved in either the conduct of the study or the preparation of this letter.

We considered a P value of less than 2.64×10^{-6} to be significant because this experiment-wise threshold accounts for the 17,944 genes with loss-of-function variants. The *PLA2G7* gene with four loss-of-function variants had the largest effect on lipoprotein-associated phospholipase A₂ activity in Americans of European ancestry ($P = 7.96 \times 10^{-13}$). We genotyped one variant, rs140020965 Q287X, in 8564 Americans of European ancestry (Table 1). These loss-of-function variants had no significant effect on levels of cardiovascular risk factors other than body-mass index. After an average of 25.1 years of

follow-up, there were 1533 incident cases of coronary heart disease. The rate of coronary heart disease was not significantly lower among carriers than among noncarriers (hazard ratio, 1.06; 95% confidence interval [CI], -0.33 to 2.45; $P = 0.93$), and there was no significant effect of loss-of-function variants on cardiovascular-related mortality (see Fig. S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

In Americans of African ancestry, a single low-frequency nonsynonymous variant, rs34159425 L389S, had a strong association with lower lipoprotein-associated phospholipase A₂ activity ($P = 2.23 \times 10^{-34}$) and no effect on other levels of cardiovascular risk factors (Table 1). There was no significant association of this variant with incident coronary heart disease (hazard ratio, 0.92; 95% CI, 0.35 to 1.49; $P = 0.78$) or cardiovascular-related mortality (see the Supplementary Appendix).

Mendelian randomization is an experimental design in which genetic variation is used to predict the effects of an intervention on risk-factor levels or disease. The positive association between lipoprotein-associated phospholipase A₂ activity and the risk of coronary heart disease in epidemiologic studies and the absence of an observed association in genetic studies indicate that lipoprotein-associated phospholipase A₂ activity may be a biomarker that is related to lipoprotein metabolism and inflammation, but not in the causal pathway of coronary heart disease.³

Recently, an international phase 3 drug trial of darapladib, an inhibitor of lipoprotein-associated phospholipase A₂ activity, showed no effect on combined cardiovascular outcomes in patients with stable coronary heart disease.⁵ In our study, we found that *PLA2G7* variants that reduce lipoprotein-associated phospholipase A₂ activity to a degree similar to activity associated with darapladib have no effect on the risk of coronary heart disease. These data bode poorly for inhibitors of lipoprotein-associated phospholipase A₂ with respect to lowering the risk of coronary heart disease in the general population, but the efficacy of a drug can be directly assessed only in appropriately controlled clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Loss-of-Function Mutations in PLA2G7 and Cardiovascular Risk Factors among Study Participants.*

Variable	Americans of European Ancestry		P Value [†]	Americans of African Ancestry		P Value [‡]
	Noncarriers (N = 8554)	Carriers (N = 10)		Noncarriers (N = 2301)	Carriers (N = 85)	
Lipoprotein-associated phospholipase A ₂ (nmol/min/ml)	238.5±60.7	84.6±49.4	<0.001	199.5±54.5	113.2±32.8	<0.001
Age (yr)	62.1±5.7	63.2±5.3	0.97	61.9±5.7	61.9±5.5	0.80
Male sex (%)	46.4	40.0	0.76	35.6	27.1	0.42
Body-mass index [‡]	28.3±5.3	34.1±5.6	0.001	30.6±6.4	30.7±6.8	0.85
Cholesterol (mg/dl)						
Total	201.1±36.3	198.0±34.1	0.79	199.4±38.4	205.8±36.0	0.13
LDL	122.3±32.6	118.5±37.4	0.71	123.4±36.1	129.4±33.4	0.13
HDL	49.0±16.3	47.3±11.9	0.74	53.2±16.9	52.7±16.7	0.80
Triglycerides (mg/dl)	151.7±88.4	161.0±54.2	0.74	115.7±65.6	118.2±62.3	0.73
Hypertension (%)	42.2	60.0	0.34	67.6	63.5	0.48
Diabetes (%)	13.8	10.0	1.00	27.2	32.1	0.32
Currently smoking (%)	14.0	20.0	0.64	17.7	14.8	0.66
Use of statin medication (%)	12.6	20.0	0.37	6.7	7.2	0.82
Prevalent coronary heart disease (%)	9.1	0.0	0.61	6.8	4.7	0.66

* Plus-minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. All measurements were obtained at clinic visit 4. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

[†] P values for mean differences between continuous variables were calculated with the use of the t-test, and P values for counts and percentages were calculated with the use of Fisher's exact test.

[‡] The body-mass index is the weight in kilograms divided by the square of the height in meters.