

A PCSK9 Missense Variant Associated with a Reduced Risk of Early-Onset Myocardial Infarction

TO THE EDITOR: Cohen et al. (March 23, 2006, issue)¹ describe a missense variant in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene that was associated with reductions in low-density lipoprotein (LDL) cholesterol levels and in the risk of coronary heart disease. They report that among whites, the L allele at R46L (rs11591147) was associated with a 15% reduction in plasma levels of LDL cholesterol and a decreased risk of incident coronary heart disease (hazard ratio, 0.50; 95% confidence interval [CI], 0.32 to 0.79; $P=0.003$). Although the association of R46L with reduced LDL cholesterol levels has been convincingly replicated,² it remains unclear whether R46L is associated with a reduced risk of clinical events.

My colleagues and I designed a large-scale study to test the hypothesis that R46L is associated with the risk of early-onset myocardial infarction, a strongly heritable subtype of myocardial infarction. The Myocardial Infarction Genetics Consortium consists of 1454 cases of early-onset myocardial infarction (in men ≤ 50 years old or women ≤ 60 years old) and 1617 age- and sex-matched controls free of myocardial infarction from five international sites: Boston and Seattle in the United States as well as Sweden, Finland, and Spain. At each site, myocardial infarction was

diagnosed on the basis of autopsy evidence of fatal myocardial infarction or a combination of chest pain, electrocardiographic evidence of myocardial infarction, or elevation of one or more cardiac biomarkers (creatinine kinase or cardiac troponin). The mean age at the time of myocardial infarction was 41 years among the men and 47 years among the women. All participants were of self-reported European ancestry. All participants provided written informed consent, and the ethics review committees of the Massachusetts Institute of Technology and Massachusetts General Hospital approved the study. Genotyping was performed in a single laboratory with the use of the Sequenom MassARRAY platform. At each study site, Fisher's exact test was used to study the association of single-nucleotide polymorphisms with myocardial-infarction status. To summarize the statistical evidence across study sites, we performed a Cochran–Mantel–Haenszel test stratified by study site. PCSK9 R46L was associated with a reduced risk of early-onset myocardial infarction (Table 1). Specifically, the minor L allele (2.4% frequency in controls) of R46L was associated with a reduced risk of myocardial infarction (meta-analysis odds ratio, 0.40; 95% CI, 0.26 to 0.61; $P=0.00002$).

Table 1. Association of PCSK9 Missense Variant R46L with Early-Onset Myocardial Infarction.

Site	Study	No. of Case Patients	No. of Controls	Frequency of Minor L Allele		Odds Ratio for Early-Onset Myocardial Infarction (95% CI)*	P Value
				Case Patients %	Controls %		
Finland	FINRISK	209	210	1.3	4.1	0.30 (0.11–0.84)	0.02
Sweden	Malmö Diet and Cancer Study — cardiovascular cohort	150	149	0.7	2.0	0.32 (0.07–1.61)	0.17
Spain	Registre Gironi del Cor (REGICOR)	361	361	1.0	2.8	0.35 (0.15–0.82)	0.02
Seattle	Heart Attack Risk in Puget Sound	542	631	0.9	1.9	0.45 (0.21–0.98)	0.049
Boston	Massachusetts General Hospital Pre-mature Coronary Artery Disease Study	192	266	1.4	2.3	0.59 (0.21–1.69)	0.46
Combined analysis		1454	1617	0.99	2.4	0.40 (0.26–0.61)	0.00002

* CI denotes confidence interval.

We conducted several secondary analyses. First, this association remained significant after further adjustment for traditional risk factors, including treated hyperlipidemia (data not shown). Second, among women (545 case patients and 662 controls) and men (909 case patients and 955 controls), the odds ratio was similar (odds ratio for women, 0.56; 95% CI, 0.30 to 1.07; odds ratio for men, 0.31; 95% CI, 0.17 to 0.56). Finally, the association was consistent across all five study sites (Breslow–Day test for heterogeneity, $P=0.92$) and was similar in magnitude to that found by Cohen et al.

Our study provides strong replication evidence that a missense variant in *PCSK9* reduces the risk of early-onset myocardial infarction. Our confirmation that a *PCSK9* loss-of-function allele not only

decreases LDL cholesterol levels but also provides protection against myocardial infarction in humans should increase confidence in *PCSK9* as a valid target for pharmacologic therapy.

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2. Kathiresan S, Melander O, Guiducci C, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet* 2008;40:189-97.

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