

# Abstract

N Engl J Med. 2009 Dec 24;361(26):2518-28.

## Genetic variants associated with Lp(a) lipoprotein level and coronary disease.

Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M; PROCARDIS Consortium.

Clinical Trial Service Unit, University of Oxford, Oxford, United Kingdom

**BACKGROUND:** An increased level of Lp(a) lipoprotein has been identified as a risk factor for coronary artery disease that is highly heritable. The genetic determinants of the Lp(a) lipoprotein level and their relevance for the risk of coronary disease are incompletely understood.

**METHODS:** We used a novel gene chip containing 48,742 single-nucleotide polymorphisms (SNPs) in 2100 candidate genes to test for associations in 3145 case subjects with coronary disease and 3352 control subjects. Replication was tested in three independent populations involving 4846 additional case subjects with coronary disease and 4594 control subjects.

**RESULTS:** Three chromosomal regions (6q26-27, 9p21, and 1p13) were strongly associated with the risk of coronary disease. The LPA locus on 6q26-27 encoding Lp(a) lipoprotein had the strongest association. We identified a common variant (rs10455872) at the LPA locus with an odds ratio for coronary disease of 1.70 (95% confidence interval [CI], 1.49 to 1.95) and another independent variant (rs3798220) with an odds ratio of 1.92 (95% CI, 1.48 to 2.49). Both variants were strongly associated with an increased level of Lp(a) lipoprotein, a reduced copy number in LPA (which determines the number of kringle IV-type 2 repeats), and a small Lp(a) lipoprotein size. Replication studies confirmed the effects of both variants on the Lp(a) lipoprotein level and the risk of coronary disease. A meta-analysis showed that with a genotype score involving both LPA SNPs, the odds ratios for coronary disease were 1.51 (95% CI, 1.38 to 1.66) for one variant and 2.57 (95% CI, 1.80 to 3.67) for two or more variants. After adjustment for the Lp(a) lipoprotein level, the association between the LPA genotype score and the risk of coronary disease was abolished.

**CONCLUSIONS:** We identified two LPA variants that were strongly associated with both an increased level of Lp(a) lipoprotein and an increased risk of coronary disease. Our findings provide support for a causal role of Lp(a) lipoprotein in coronary disease.

PMID: 20032323