

Abstract

Circ Cardiovasc Genet. 2010 Feb 1;3(1):15-21.

Genetic effects on carotid intima-media thickness: systematic assessment and meta-analyses of candidate gene polymorphisms studied in more than 5000 subjects.

Paternoster L, Martinez-Gonzalez NA, Charleton R, Chung M, Lewis S, Sudlow CL.

Division of Clinical Neurosciences, Centre for Molecular Medicine, Institute of Genetics and Molecular Medicine, and Medical School, University of Edinburgh, Edinburgh, United Kingdom.

BACKGROUND: Carotid intima-media thickness (CIMT) is highly heritable and associated with stroke and myocardial infarction, making it a promising quantitative intermediate phenotype for genetic studies of vascular disease. There have been many CIMT candidate gene association studies, but no systematic review to identify consistent, reliable findings.

METHODS AND RESULTS: We comprehensively sought all published studies of association between CIMT and any genetic polymorphism. We obtained additional unpublished data and performed meta-analyses for the 5 most commonly studied genes (studied in at least 2 studies in a total of >5000 subjects). We used a 3-step meta-analysis method: meta-analysis of variance; genetic model selection; and random effects meta-analysis of the mean CIMT difference between genotypes. We performed subgroup analyses to investigate effects of ethnicity, vascular risk status, and study size. We accounted for potential reporting bias by assessing qualitatively the possible effects of including unavailable data. Polymorphisms in 3 of the 5 genes (apolipoprotein E, angiotensin I converting enzyme, and 5,10-methylenetetrahydrofolate reductase) had an apparent association with CIMT, but for all these, we found evidence of small study bias. Apolipoprotein E epsilon2/epsilon3/epsilon4 was the only polymorphism with a persistent, statistically significant but modest association when we restricted analysis to larger studies (>1000 subjects).

CONCLUSIONS: Of the most extensively studied polymorphisms, apolipoprotein E epsilon2/epsilon3/epsilon4 is the only one so far with a convincing association with CIMT. Larger studies than have generally been performed so far may be needed to confirm the associations identified in future genome-wide association studies, and to investigate modification of effect according to characteristics such as ethnicity and vascular risk status.

PMID: 20160191