

Abstract

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Genomewide Association Analysis of Coronary Artery Disease

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BACKGROUND: Modern genotyping platforms permit a systematic search for inherited components of complex diseases. We performed a joint analysis of two genomewide association studies of coronary artery disease.

METHODS: We first identified chromosomal loci that were strongly associated with coronary artery disease in the Wellcome Trust Case Control Consortium (WTCCC) study (which involved 1926 case subjects with coronary artery disease and 2938 controls) and looked for replication in the German MI [Myocardial Infarction] Family Study (which involved 875 case subjects with myocardial infarction and 1644 controls). Data on other single-nucleotide polymorphisms (SNPs) that were significantly associated with coronary artery disease in either study ($P < 0.001$) were then combined to identify additional loci with a high probability of true association. Genotyping in both studies was performed with the use of the GeneChip Human Mapping 500K Array Set.

RESULTS: Of thousands of chromosomal loci studied, the same locus had the strongest association with coronary artery disease in both the WTCCC and the German studies: chromosome 9p21.3 (SNP, rs1333049) ($P = 1.80 \times 10^{-14}$ and $P = 3.40 \times 10^{-6}$, respectively). Overall, the WTCCC study revealed nine loci that were strongly associated with coronary artery disease ($P < 1.2 \times 10^{-5}$ and less than a 50% chance of being falsely positive). In addition to chromosome 9p21.3, two of these loci were successfully replicated (adjusted $P < 0.05$) in the German study: chromosome 6q25.1 (rs6922269) and chromosome 2q36.3 (rs2943634). The combined analysis of the two studies identified four additional loci significantly associated with coronary artery disease ($P < 1.3 \times 10^{-6}$) and a high probability (>80%) of a true association: chromosomes 1p13.3 (rs599839), 1q41 (rs17465637), 10q11.21 (rs501120), and 15q22.33 (rs17228212).

CONCLUSIONS: We identified several genetic loci that, individually and in aggregate, substantially affect the risk of development of coronary artery disease.

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