The novel genetic variant predisposing to coronary artery disease in the region of the PSRC1 and CELSR2 genes on chromosome 1 associates with serum cholesterol.

Abstract:
Through genome-wide association studies, we have recently identified seven novel loci that confer a substantial increase in risk for coronary artery disease (CAD). Elucidating the mechanisms by which these loci affect CAD risk could have important clinical utility. Here, we investigated whether these loci act through mechanisms involving traditional cardiovascular risk factors. We genotyped 2,037 adult individuals from 520 nuclear families characterised for body mass index, waist-hip ratio, 24-h ambulatory blood pressure, total cholesterol, high-density lipoprotein cholesterol and glucose for the lead single nucleotide polymorphisms (SNPs) in the seven CAD-associated loci. SNP rs599839, representing the locus in the vicinity of the PSRC1 and CELSR2 genes on chromosome 1p13.3, showed a strong association with total cholesterol. The CAD-associated risk allele A of rs599839 (allele frequency 0.78) was associated with a 0.17-mmol/l (95% CI 0.10 to 0.24 mmol/l) higher serum cholesterol level per allele copy (P = 3.84 x 10(-6)). The association of the A allele with higher total cholesterol was confirmed in an independent cohort (n = 847) of healthy adults (P = 1.0 x 10(-4)) and related to an effect
on low-density lipoprotein (LDL) cholesterol ($P = 8.56 \times 10^{-5}$). An association of rs599839 with LDL cholesterol was also shown in 1,090 cases with myocardial infarction ($P = 0.0026$). None of the other variants showed a strong association with the measured cardiovascular risk factors, suggesting that these loci act through other mechanisms. However, the novel CAD-associated locus in the vicinity of the PSRC1 and CELSR2 genes on chromosome 1 probably enhances CAD risk through an effect on plasma LDL cholesterol. The findings support further investigation of the role of these genes in cholesterol metabolism and coronary risk.