Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants.

Abstract:
Ischemic stroke (IS) and coronary artery disease (CAD) share several risk factors and each has a substantial heritability. We conducted a genome-wide analysis to evaluate the extent of shared genetic determination of the two diseases. Genome-wide
association data were obtained from the METASTROKE, Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDioGRAM), and Coronary Artery Disease (C4D) Genetics consortia. We first analyzed common variants reaching a nominal threshold of significance (P<0.01) for CAD for their association with IS and vice versa. We then examined specific overlap across phenotypes for variants that reached a high threshold of significance. Finally, we conducted a joint meta-analysis on the combined phenotype of IS or CAD. Corresponding analyses were performed restricted to the 2167 individuals with the ischemic large artery stroke (LAS) subtype. Common variants associated with CAD at P<0.01 were associated with a significant excess risk for IS and for LAS and vice versa. Among the 42 known genome-wide significant loci for CAD, 3 and 5 loci were significantly associated with IS and LAS, respectively. In the joint meta-analyses, 15 loci passed genome-wide significance (P<5×10(-8)) for the combined phenotype of IS or CAD and 17 loci passed genome-wide significance for LAS or CAD. Because these loci had prior evidence for genome-wide significance for CAD, we specifically analyzed the respective signals for IS and LAS and found evidence for association at chr12q24/SH2B3 (PIS=1.62×10(-7)) and ABO (PIS=2.6×10(-4)), as well as at HDAC9 (PLAS=2.32×10(-12)), 9p21 (PLAS=3.70×10(-6)), RAI1-PEMT-RASD1 (PLAS=2.69×10(-5)), EDNRA (PLAS=7.29×10(-4)), and CYP17A1-CNNM2-NT5C2 (PLAS=4.9×10(-4)). Our results demonstrate substantial overlap in the genetic risk of IS and particularly the LAS subtype with CAD.