Eight genetic loci associated with variation in lipoprotein-associated phospholipase A2 mass and activity and coronary heart disease: meta-analysis of genome-wide association studies from five community-based studies.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) generates proinflammatory and proatherogenic compounds in the arterial vascular wall and is a potential therapeutic target in coronary heart disease (CHD). We searched for genetic loci related to Lp-PLA2 mass or activity by a genome-wide association study as part of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. In meta-analyses of findings from five population-based studies, comprising 13,664 subjects, variants at two loci (PLA2G7, CETP) were associated with Lp-PLA2 mass. The strongest signal was at rs1805017 in PLA2G7 [P = 2.4 x 10(-23), log Lp-PLA2 difference per allele (beta): 0.043]. Variants at six loci were associated with Lp-PLA2 mass. The additional variants with moderate effects are important targets for therapeutic interventions.
activity (PLA2G7, APOC1, CELSR2, LDL, ZNF259, SCARB1), among which the strongest signals were at rs4420638, near the APOE-APOC1-APOC4-APOC2 cluster \[P = 4.9 \times 10^{-30}; \log \text{Lp-PLA2 difference per allele (beta): -0.054}\]. There were no significant gene-environment interactions between these eight polymorphisms associated with Lp-PLA2 mass or activity and age, sex, body mass index, or smoking status. Four of the polymorphisms (in APOC1, CELSR2, SCARB1, ZNF259), but not PLA2G7, were significantly associated with CHD in a second study. Levels of Lp-PLA2 mass and activity were associated with PLA2G7, the gene coding for this protein. Lipoprotein-associated phospholipase A2 activity was also strongly associated with genetic variants related to low-density lipoprotein cholesterol levels.