Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction.

Myocardial infarction (MI), a leading cause of death around the world, displays a complex pattern of inheritance. When MI occurs early in life, genetic inheritance is a major component to risk. Previously, rare mutations in low-density lipoprotein (LDL) genes have been shown to contribute to MI risk in individual families, whereas common variants at more than 45 loci have been associated with MI risk in the population. Here we evaluate how rare mutations contribute to early-onset MI risk in the population. We sequenced the protein-coding regions of 9,793 genomes from patients with MI at an early age (190 mg dl⁻¹). At apolipoprotein A-V (APOA5), carriers of rare non-synonymous mutations were at 2.2-fold increased risk for MI. When compared with non-carriers, LDLR mutation carriers had higher plasma LDL cholesterol, whereas APOA5 mutation carriers had higher plasma triglycerides. Recent evidence has connected MI risk with coding-sequence mutations at two genes functionally related to APOA5, namely lipoprotein lipase and apolipoprotein C-III (refs 18, 19). Combined, these observations suggest that, as well as LDL cholesterol, disordered metabolism of triglyceride-rich lipoproteins contributes to MI risk.