Identifying genetic risk variants for coronary heart disease in familial hypercholesterolemia: an extreme genetics approach.

Mutations in the low-density lipoprotein receptor (LDLR) gene cause familial hypercholesterolemia (FH), a disorder characterized by coronary heart disease (CHD) at young age. We aimed to apply an extreme sampling method to enhance the statistical power to identify novel genetic risk variants for CHD in individuals with FH. We selected cases and controls with an extreme contrast in CHD risk from 17,000 FH patients from the Netherlands, whose functional LDLR mutation was unequivocally established. The
A genome-wide association (GWA) study was performed on 249 very young FH cases with CHD and 217 old FH controls without CHD (above 65 years for males and 70 years of age for females) using the Illumina HumanHap550K chip. In the next stage, two independent samples (one from the Netherlands and one from Italy, Norway, Spain, and the United Kingdom) of FH patients were used as replication samples. In the initial GWA analysis, we identified 29 independent single nucleotide polymorphisms (SNPs) with suggestive associations with premature CHD ($P < 1 \times 10^{-4}$). We examined the association of these SNPs with CHD risk in the replication samples. After Bonferroni correction, none of the SNPs either replicated or reached genome-wide significance after combining the discovery and replication samples. Therefore, we conclude that the genetics of CHD risk in FH is complex and even applying an 'extreme genetics' approach we did not identify new genetic risk variants. Most likely, this method is not as effective in leveraging effect size as anticipated, and may, therefore, not lead to significant gains in statistical power.