Functional Analysis of the Coronary Heart Disease Risk Locus on Chromosome 21q22 - DTU Orbit (03/05/2019)

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Background. The coronary heart disease (CHD) risk locus on 21q22 (lead SNP rs9982601) lies within a "gene desert." The aim of this study was to assess if this locus is associated with CHD risk factors and to identify the functional variant(s) and gene(s) involved. Methods. A phenome scan was performed with UCLEB Consortium data. Allele-specific protein binding was studied using electrophoretic mobility shift assays. Dual-reporter luciferase assays were used to assess the impact of genetic variation on expression. Expression quantitative trait analysis was performed with Advanced Study of Aortic Pathology (ASAP) and Genotype-Tissue Expression (GTEx) consortium data. Results. A suggestive association between QT interval and the locus was observed (rs9982601 p = 0.04). One variant at the locus, rs28451064, showed allele-specific protein binding and its minor allele showed 12% higher luciferase expression (p = 4.82 x 10^-3) compared to the common allele. The minor allele of rs9982601 was associated with higher expression of the closest upstream genes (SLC5A3 1.30-fold increase p = 3.98 x 10^-5; MRPS6 1.15-fold increase p = 9.60 x 10^-4) in aortic intima media in ASAP. Both rs9982601 and rs28451064 showed a suggestive association with MRPS6 expression in relevant tissues in the GTEx data. Conclusions. A candidate functional variant, rs28451064, was identified. Future work should focus on identifying the pathway(s) involved.

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