Functional Analysis of the Coronary Heart Disease Risk Locus on Chromosome 21q22 - DTU Orbit (30/08/2017)

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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.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, University College London, St. George's University of London, University of Bristol, University of Edinburgh, MRC Unit for Lifelong Health and Ageing, MRC Epidemiology Unit, Karolinska Institutet
Number of pages: 11
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information
Journal: Disease Markers
Volume: 2017
Article number: 1096916
ISSN (Print): 0278-0240
Ratings:
BFI (2017): BFI-level 1
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 0.827 SNIP 0.783 CiteScore 2.3
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.791 SNIP 0.708 CiteScore 2.13
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.768 SNIP 0.67 CiteScore 1.99
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.933 SNIP 0.759 CiteScore 2.46
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.843 SNIP 0.716 CiteScore 2.4
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.78 SNIP 0.561 CiteScore 1.99
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.781 SNIP 0.674
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.824 SNIP 0.652
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.89 SNIP 0.693
Scopus rating (2007): SJR 0.61 SNIP 0.693
Scopus rating (2006): SJR 0.746 SNIP 0.857
Scopus rating (2005): SJR 0.597 SNIP 0.66