Author's response to reviews

Title: Recent methods for polygenic analysis of genome-wide data implicate an important effect of common variants on cardiovascular disease risk

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Author's response to reviews: see over
Dear BMC Medical Genetics Editorial board,

We would like to resubmit our paper, “Recent methods for polygenic analysis of genome-wide data implicate an important effect of common variants on cardiovascular disease risk,” to BMC Medical Genetics as a research article. We have substantially revised the manuscript based on previous reviews, and we believe that the new manuscript is improved and clarified over the previous submission. **All authors have read and approved the final manuscript.**

Below is a copy of the cover letter from our original submission for your convenience:

Cardiovascular disease, the pathologies associated with the heart and its vascular structure, are a leading cause of death worldwide. Over the past decade, many large-scale efforts have attempted to find genetic factors associated with cardiovascular disease using single nucleotide polymorphism (SNP) markers. Several genome-wide association studies (GWAS) have been successful at identifying genetic variants associated with cardiovascular disease and related phenotypes. However, the effect sizes attributable to these variants are generally considered to be small. These results suggest that while GWAS studies have had some success, they currently only explain a very small amount of the genetic risk and heritability for many complex phenotypes, including cardiovascular disease.

We sought to use **both traditional GWAS methods, as well as more recently developed polygenic genome-wide analysis techniques** to identify subsets of single-nucleotide polymorphisms (SNPs) that may be involved in risk of cardiovascular disease, as well as estimate the heritability explained by common SNPs. Using data from the Framingham SNP Health Association Resource (SHARE), **three complimentary methods** were applied to examine the genetic factors associated with the Framingham Risk Score, a widely-accepted indicator of underlying cardiovascular disease risk.

This study demonstrates a novel approach for investigating heritability due to common SNPs in samples where individuals are unrelated, and shows that common SNPs can be used to predict risk for cardiovascular disease. We also provide evidence strongly consistent with the polygenic theory of cardiovascular disease and show that much of the genetic variation underlying this disease is likely to be due to common causal polymorphisms. Our results were also able to identify cardiovascular disease-related SNPs as reported by previous studies, which provides clear direction for future research. These results indicate that there remains much information in, and much to be learned from, the continued use of SNP panels in the investigation of cardiovascular phenotypes as well as other human diseases.

This research is original and we believe it will prove highly influential in the field of genetics. I will serve as the corresponding author, and all authors have agreed to the manuscript being submitted in its current form and to the order of authorship. This work has not been submitted to any other journal. Thank you for taking the time to consider this manuscript for publication.

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