Abstract: P578

Integrative functional annotation of 52 genetic loci influencing myocardial mass

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Duration of the QRS complex on the electrocardiogram (ECG) represents cardiac depolarization and conduction of the electrical signal through the ventricular muscle and is correlated with left ventricular mass as measured by echocardiography. Moreover, prolonged QRS duration is associated with an increased risk of cardiovascular mortality. Identification of specific genes influencing the QRS complex may thus enhance our understanding of the human heart and ultimately lead to the prevention of cardiovascular disease and death. A recent large-scale genome-wide association study (GWAS) and meta-analysis identified 52 loci associated to QRS traits (p<1x10⁻⁸). However, the precise identification of disease-causing variants remains an important challenge. We hypothesised that we can find causal variants and prioritize genes using specific tissue and disease information. We used both public and in-house generated genomic and epigenomic data to identify exons, promoters and enhancers (and putative target genes) affected by ECG-associated SNPs and vicinity (linkage disequilibrium of r²>0.8) in the relevant tissue and disease context. Six non-synonymous variants predicted as potentially damaging were found to overlap exons. Thirtyone SNPs may confer risk to disease due to their location at the promoter region (2500bp from transcription start site) of differentially expressed genes between RNA-seq data of hypertrophic cardiomyopathy (HCM) patients compared to controls (FDR<0.05). Finally, 123 SNPs overlap relevant enhancer regions, highlighted by down or up-acetylation (H3K27ac ChIP-seq) between HCM patients and controls (FDR<0.05), or super-enhancers specific to healthy or hypertrophic heart. Sixteen motifs predicted to be altered by SNPs overlapping enhancer regions showed differential expression in disease. As a next step, CRISPR-Cas9 deletion will be carried out on some of these candidate causal SNPs on differentiated cardiomyocytes, in order to identify additional candidate genes likely to affect cardiac mass and function. The results of this integrative approach further advance our understanding of non-coding regulatory variation in cardiac hypertrophy.