**Multi-ancestry genome-wide association meta-analysis of 293,000 individuals identifies 217 regions for the electrocardiographic PR interval**

Authors

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Abstract

**Introduction:** The electrocardiographic PR interval represents cardiac atrioventricular conduction, a critical physiological process that is associated with arrhythmias and all-cause mortality. Yet the biological determinants of the PR interval remain incompletely understood. We conducted the largest genetic association study of the PR interval to date. **Methods:** We combined genome-wide association results for the PR interval from 55 studies encompassing 293,051 individuals (271,570 European, 8,173 African, 12,823 Hispanic, and 763 Asian ancestry) using fixed-effect meta-analysis. Analyses included ~12 million variants (minor allele frequency, MAF>0.1%) imputed using the 1000 Genomes Project reference panel. **Results:** We identified 217 regions (152 novel) associated with PR interval exceeding genome-wide significance (p<5x10-8). Among novel regions, we identified 3 missense variants annotated as deleterious and/or possibly damaging in *KIAA1755*, *ARHGEF40*, and *SPSB3*;and 7 variants in high LD (r2>0.8) with missense variants in *DERL3, DUSP13, DNAH11, C10orf71, ACCN4, CHPF, OBSL1* and *DALRD3*. Expression quantitative trait locus (eQTL) analysis using the GTEx portal revealed 5 variants associated with gene expression levels in right atrial appendage (*TRAK1*, *SMARCB1*, *SYNE2*, *DEK,* *DNAH11*). Gene Ontology enrichment analysis including only the nearest genes to both known and novel variants indicated further enrichment of biological processes involving heart and cardiac muscle tissue development with the addition of the newly identified genes. **Conclusions:** Our results implicate specific genes which determine PR interval and highlight the complex polygenic nature of atrioventricular conduction. Future analyses will assess the relations between genetic determinants of the PR interval and cardiac arrhythmias.