

This is an overview of an article entitled “ExomeChip-Wide Analysis of 95,626 Individuals Identifies 10 Novel Loci Associated with QT and JT Intervals”, published in the January 2018 issue of *Circulation: Genomic and Precision Medicine*.

The electrocardiographic QT interval spans from the beginning of the QRS complex to the end of the T wave, as shown in the schematic here. The QT interval is measured in order to assess the length of duration of ventricular repolarization. Abnormality of the QT interval in either direction, too long or too short, predisposes to arrhythmias and sudden cardiac death. The JT interval, as shown here, is a more precise measure of ventricular repolarization since it subtracts the QRS interval, which is when ventricular depolarization occurs, from the QT interval.

To assess for genetic factors that contribute to clinical traits, genetic association studies are performed. The most commonly done association study has been the genome-wide association study, or GWAS, which assesses common DNA variants throughout the genome for strength of association with the phenotype of interest. These common variants are for the most part noncoding variants. More recently, exome chips that can directly interrogate coding variants in genes have become available. While the exome chips do cover some noncoding variants, they are very comprehensive with respect to coding variants, covering all coding variants that were found in at least 3 individuals out of 12,000 individuals who had undergone exome sequencing. This comprises almost 200,000 coding variants in more than 17,000 genes.

The authors of the paper under discussion performed an exome chip genotyping association study in more than 95,000 individuals, most of whom were of European descent, although several other ethnicities were represented in smaller numbers. The rationale for using the exome chip is that GWASs tend to identify noncoding variants that often do not pinpoint specific genes, since noncoding variants can affect genes at a large distance, meaning that each GWAS hit might implicate numerous candidate genes in the vicinity of the locus. In contrast, exome chip studies tend to identify coding variants within genes, which implicate those specific genes as the causal genes.

Here are the results of the exome chip analysis with the QT interval. In this graph, the x-axis is the position in the genome, split into different chromosomes, and the y-axis is the strength of association. The green line indicates a stringent threshold for statistical significance, taking into account the hundreds of thousands of variants tested in the study. Many known loci implicated by previous association studies were validated in this study, indicated in yellow. In red are genes or loci being linked to the QT interval for the first time in this study.

Here are the genes or loci associated with the JT interval but not the QT interval. There were no prior loci linked only to the JT interval. This study found 4 novel genes or loci, indicated in red.

There were several key findings in this study. First, the exome chip analysis identified coding variants in two notable genes as being linked to the QT interval, *SCN10A* and *KCNQ1*. Both have previously been linked to cardiac repolarization—*SCN10A* to Brugada syndrome by GWAS, and *KCNQ1* is the well-established causal gene for long QT syndrome type 1. [pause] Second, the study found 4 hits associated only with the JT interval. Third, functional annotation of the various exome chip hits identified several known pathways—potassium, sodium, or calcium ion regulation, and autonomic control—and new pathways—the physical force of contraction of cardiomyocytes, as well as conduction of the electrical signal between cardiomyocytes.

In conclusion, this study identified a total of 10 new loci associated with the QT and/or JT interval. The exome chip analysis pinpointed variants in 17 genes, 7 of which are in new loci. These findings validated previously identified molecular pathways involved in cardiac repolarization and nominated new pathways. Finally, by identifying hits linked to the JT interval but not the QT interval, this study suggests that different genetic factors might influence the depolarization and repolarization phases of the ventricles. Together, these findings shed new light on normal cardiac electrophysiology, diseases with repolarization abnormalities, and potential treatments for the diseases.