Rare Coding Variation in Atrial Fibrillation: Results from 52K cases

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with substantial morbidity and mortality. AF is known to be highly heritable and prior genome-wide association studies (GWAS) have identified over 100 genomic loci associated with AF. While GWAS studies for AF and other disease have rapidly expanded there are many inherent limitations with this approach. For example, the disease associated variants identified by GWAS typically confer only small effects and identifying the correct gene at a GWAS locus can be challenging. In contrast, whole genome- and whole exome-sequencing studies provide a greater resolution for genetic discovery and enable the discovery of rare variants conferring large genetic effects. However, due to the high cost of sequencing, many prior studies were performed within small sample sizes or with low sequencing depth, both of which greatly reduce the resolution for genetic discovery.

In recent years, large international collaborations have facilitated a massive expansion in available sequencing data. The National Heart Lung and Blood Institute and the National Health Genetic Research Institute have built the *Trans-Omics for Precision Medicine Program* (TOPMed) and the *Centers for Common Disease Genomics* (CCDG) to perform deep coverage whole genome sequencing for a range of complex diseases. The CCDG has further produced whole exome sequencing data to identify the genetic underpinning for several common diseases, including AF. Finally, the UK Biobank, a population-based study from the United Kingdom, released over 200,000 whole-exome sequencing samples in December 2020, following an industry-funded partnership.

To date, only a limited number of studies were able to leverage sequencing data to identify reproducible rare variant associations for AF. In 2018, a family-based study and an early-onset AF study identified the important association between rare loss-of-function (LOF) variants in *TTN* and early-onset AF. The association between rare mutations in *TTN* to AF risk has been subsequently replicated, yet these variants only explain ~0.2% of the variance in AF susceptibility.

Here, we present a meta-analysis of over 52K AF cases and 267K controls from sequenced samples from TOPMed-CCDG, CCDG, four TIMI trials, and the UK Biobank. This project leverages the largest scale of sequencing data for this complex trait to date and allows us to assess the role of rare genetic variants in AF risk, through exome-wide tests of protein-coding genes. Our results identify several novel associations with AF and highlight a shared biological basis between AF and various inherited forms of cardiomyopathy. This finding may have implications for the diagnosis, longitudinal evaluation, and treatment of this common arrhythmia. More broadly, our findings underscore the value of large-scale sequencing to understand the rare genetic underpinnings of complex, adult-onset diseases.