



UKE Paper of the Month Februar 2022

Tissue-specific multi-omics analysis of atrial fibrillation

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ABSTRACT:

Genome-wide association studies (GWAS) for atrial fibrillation (AF) have uncovered numerous disease-associated variants. Their underlying molecular mechanisms, especially consequences for mRNA and protein expression remain largely elusive. Thus, refined multi-omics approaches are needed for deciphering the underlying molecular networks. Here, we integrate genomics, transcriptomics, and proteomics of human atrial tissue in a cross-sectional study to identify widespread effects of genetic variants on both transcript (cis-eQTL) and protein (cis-pQTL) abundance. We further establish a novel targeted trans-QTL approach based on polygenic risk scores to determine candidates for AF core genes. Using this approach, we identify two trans-eQTLs and five trans-pQTLs for AF GWAS hits, and elucidate the role of the transcription factor NKX2-5 as a link between the GWAS SNP rs9481842 and AF. Altogether, we present an integrative multi-omics method to uncover trans-acting networks in small datasets and provide a rich resource of atrial tissue-specific regulatory variants for transcript and protein levels for cardiovascular disease gene prioritization.

STATEMENT:

Our study is the first world-wide that generates an integrated view of how atrial fibrillation associated genetic variation impacts on transcript and protein levels in the human heart. We developed a novel algorithmic approach to link genetic variation to disease through gene regulatory networks. This unique dataset allowed us to improve our understanding of how genetics are related to molecular changes in AF.

BACKGROUND:

This paper results from the cooperation of several research Institutes across Germany (University Heart and Vascular Center Hamburg, Helmholtz Munich, University Greifswald, University Lübeck), and highlights the importance of interdisciplinary work between medicine (Prof. Dr. Renate Schnabel), molecular biology (Prof. Dr. Tanja Zeller), and bioinformatics (Dr. Matthias Heinig). The project was part of the PhD thesis of Ines Assum and Julia Krause, who share the first authorship. The project was part of the e:Med consortium “symAtrial” funded by the BMBF. The aim of the consortium was to improve the understanding of molecular mechanisms underlying atrial fibrillation.