Impact of genetically determined differences in ECG parameters on risk of AF in c. 300,000 UK Biobank participants

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Background
An abnormal electrical substrate has been associated with atrial cardiomyopathy, atrial fibrillation (AF), and other supraventricular tachycardias (SVT). However, many risk factors for AF influence ECG parameters, potentially confounding the association. As ECG intervals are highly heritable, using genetic scores as proxies limits confounding and the effects of reverse causation.

Purpose
To establish the nature of any causal relationship between ECG parameters and risk of AF using Mendelian randomisation (MR) techniques.

Methods
Genetic scores for P-wave duration, PR interval and QT interval were constructed from published genome-wide association studies and logistic regression models used to estimate their associations with AF using individual participant data in UK Biobank (UKB) (15,311 AF cases and 262,320 controls). Validation was performed using summary data from the AFGEN consortium (15,979 AF cases and 102,776 controls). Sensitivity analyses exploring the impact of potential pleiotropy were performed using conventional MR techniques (e.g. weighted median, MR-Egger etc).

Results
As expected, the genetic scores were strongly associated with their specified ECG parameters. Longer genetically determined P-wave and PR interval durations were associated with lower risks of AF. By contrast, a longer genetically determined QT interval was not associated with AF risk (Figure). To investigate the role of changes in electrical pathways affecting the ECG and AF risk, scores for each parameter were generated limited to genetic proxies associated with genes for known ion channels. Ion channel limited scores lowered risks of AF per 5ms increases in P-wave duration (odds ratio [OR]: 0.83; 95% confidence interval [CI]: 0.78-0.89, P=2×10⁻⁸) and PR interval (OR: 0.92; 95% CI: 0.90-0.95, P=4×10⁻¹⁰) with no change in AF risk with longer score for QT interval (OR: 0.99; 95% CI: 0.96-1.03, P=0.68). These effects were consistently replicated in the AFGEN dataset and multiple sensitivity analyses supported the conclusions.

To test associations between the ECG genetic scores and a specific AF subtype, 3,843 participants with AF but without known coronary heart disease, heart failure, hypertension or diabetes and 273,788 controls were identified. Overall odds ratio estimates were similar to the primary outcomes for each of the ECG parameters investigated (Figure).

Conclusions
Genetically determined ECG parameters associated with shorter atrial electrical conduction times increased risk of AF and SVT. These findings provide a novel mechanistic insight into understanding the underlying pathophysiology of AF and potential development of therapeutic strategies.
To investigate the effects of altered electrical substrate on other related arrhythmias, 2,621 cases of SVT and 275,010 controls were identified. Longer genetic P-wave and PR intervals were associated with lower risks of SVT. The genetic QT interval was not associated with SVT risk (Figure).

Conclusions
Genetically determined ECG parameters associated with shorter atrial electrical conduction times increased risk of AF and SVT. These findings provide a novel mechanistic insight into understanding the underlying pathophysiology of AF and potential development of therapeutic strategies.