Rare Coding Variants Associated With Electrocardiographic Intervals Identify Monogenic Arrhythmia Susceptibility Genes A Multi-Ancestry Analysis

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Rare Coding Variants Associated With Electrocardiographic Intervals Identify Monogenic Arrhythmia Susceptibility Genes

A Multi-Ancestry Analysis

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Nonstandard Abbreviation and Acronyms

<table>
<thead>
<tr>
<th>LOF</th>
<th>loss-of-function</th>
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<tbody>
<tr>
<td>LQTS</td>
<td>long QT syndrome</td>
</tr>
<tr>
<td>QTc</td>
<td>corrected QT interval</td>
</tr>
<tr>
<td>SCD</td>
<td>sudden cardiac death</td>
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<tr>
<td>TOPMed</td>
<td>Trans-Omics in Precision Medicine</td>
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Nearly 1 in 3 adults will experience an arrhythmia and up to 10% will die of sudden cardiac death (SCD) during their lifetime.1,2 The ECG is an inexpensive, noninvasive, and widely used screening test for abnormalities in cardiac conduction. Previous work has demonstrated that electrocardiographic intervals are quantitative markers for arrhythmias and SCD3–5 and have a considerable heritable basis.9

Monogenic mutations underlying many conduction disorders and arrhythmia syndromes, such as the long QT syndrome (LQTS),10,11 have been the focus of extensive study over the past 2 decades. Typically, these studies have focused on sequencing a modest number of affected patients or families to identify the causative genes. In contrast, large-scale genome-wide association studies have identified a multitude of loci associated with electrocardiographic traits by studying common variants in large study samples comprising thousands of individuals.12–15 However, the effect of discovered genome-wide association studies variants is inherently small and direct implication of any particular gene tagged by an identified common variant is difficult.

To date, a missing gap in our understanding of common electrocardiographic traits and related diseases has been whether rare coding variants have a substantial contribution to variation at the population level. Rare variants may have substantial effect sizes, confer pathogenicity, and have a measurable impact on disease risk. Yet, identifying such variants has been technically challenging since this analysis requires both the sequencing of large study samples and the availability of electrocardiographic data.

To address this challenge, we used a unique resource of over 130,000 individuals with whole-exome or -genome sequencing, and a rigorous 3-stage design, to examine the associations between rare coding genetic variation and several routinely collected electrocardiographic traits, including the heart rate, maximum P-wave duration, PR interval, QRS duration, and corrected QT interval (QTc). We then specifically assessed the frequency, magnitude of association, and penetrance of clinically pathogenic variation in select SCD genes that are associated with electrocardiographic variation.

RESULTS

An overview of the study design and sample selection flow is presented in Figure 1 and Figures I through III in the Data Supplement. Characteristics of the included studies are displayed in the Table and Tables I through III and Figure IV in the Data Supplement.

Once we had aggregated electrocardiographic and genetic data for participants in TOPMed, we began by performing genome-wide association studies for common variants related to 5 electrocardiographic traits (Figure 2A and Table IV in the Data Supplement). As expected, we observed associations at 44 previously reported loci (Results in the Data Supplement). Cross-trait pleiotropy was particularly notable at the SCN5A-10A locus and the CAV1 locus, which demonstrated robust associations across multiple electrocardiographic traits.

We then performed an analysis of the protein-coding regions of the genome and identified a low-frequency coding variant in PAM that was associated with PR interval duration (p.Ser539Trp, rs78408340_G, MAF=0.5%, $\beta$=8 ms, $P=1.9\times10^{-7}$, Figure 2B and Table V in the Data Supplement). This finding was replicated in the UK Biobank ($\beta$=2 ms, $P=0.01$) and in MyCode ($\beta$=3 ms, $P=1.8\times10^{-5}$). Variants in PAM were also associated with PR interval duration in gene-based testing in TOPMed ($P=4.5\times10^{-7}$, Figure 3, Table VI in the Data Supplement), an association driven by p.Ser539Trp (Figure V in the Data Supplement). We did not observe consistent associations between rare high-confidence loss-of-function (LOF) variants in PAM and PR interval duration across data sets (Results, Tables VII and VIII, and Figure VIA in the Data Supplement). Low-frequency coding variant testing also identified a synonymous variant in MFGEB (p.Ser52=rs141997845_T, MAF=0.1%, $\beta$=19 ms, $P=4.9\times10^{-8}$), which was associated with marked PR interval prolongation in TOPMed (Figure 2B, Results and Table V in the Data Supplement). Only one carrier was identified in the UK Biobank, who had a first-degree atrioventricular block (PR=200 ms). In MyCode, the association was replicated ($\beta$=15 ms, $P=1.6\times10^{-3}$).
Gene-based testing in TOPMed also identified 3 genes established as important for cardiac conduction, arrhythmias, and SCD (SCN5A [PR interval, \(P=7.6 \times 10^{-7}\), KCNQ1 [QTc, \(P=2.3 \times 10^{-12}\), KCNH2 [QTc, \(P=3.2 \times 10^{-8}\), Figure 3, Table VI in the Data Supplement]. Rare LOF variants in SCN5A conferred a 38 ms (\(P=4.3 \times 10^{-32}, N\) carriers=70) increase in PR interval duration across all data sets (Results, Figure VIA, and Tables VII and VIII in the Data Supplement). Furthermore, gene-based testing highlighted pleiotropy of SCN5A, as rare variants also associated with prolonged P-wave duration and QRS duration (Results and Figure VII in the Data Supplement). Similarly, rare LOF variants in KCNQ1 were associated with marked prolongation of the QTc (\(\beta=42\) ms, \(P=3.9 \times 10^{-44}, N\) carriers=78), as were rare LOF variants in KCNH2 (\(\beta=38\) ms, \(P=8.5 \times 10^{-15}, N\) carriers=21, Results, Figure VIB, and Tables VII and VIII in the Data Supplement). In exploratory exome-wide analyses, a number of genes reached significance (Results and Table IX in the Data Supplement). Of these genes, none reached \(P<0.05\) in replication among UK Biobank participants, except for SCN5A (PR interval), PAM (PR interval), KCNQ1 (QTc), and KCNH2 (QTc).

In an analysis of 17 genes included on a typical clinical sequencing panel for long QT syndrome, 16 in addition to KCNQ1 and KCNH2, we also identified an association between QTc and predicted-deleterious variants in KCNE1 in TOPMed (\(P=1.2 \times 10^{-6}\), which was replicated in the UK Biobank (\(P=9.0 \times 10^{-5}\); Results and Table X in the Data Supplement). No KCNE1 LOF variants were identified in TOPMed or the UK Biobank, although rare predicted-deleterious missense variants in these data sets were associated with a 16 ms (\(P=3.3 \times 10^{-7}\)) prolongation of the QTc (Results and Tables XI and XII in the Data Supplement). In contrast to the large effect sizes observed for deleterious variation in the aforementioned genes, the top variants in common variant analyses for PR interval and QTc conferred effect sizes of 4 and 3 ms, respectively (Table IV in the Data Supplement).

We observed similar findings for pathogenic or likely pathogenic variants adjudicated by clinical testing laboratories and submitted to ClinVar. Among 54,355 TOPMed and UK Biobank participants, 239 (0.44\%) carried such a variant in a LQTS gene from the panel cited above. Half were located in one of the 3 most validated susceptibility genes, KCNQ1, KCNH2, and SCN5A (Table XIII in the Data Supplement). Pathogenic or likely pathogenic variants in KCNQ1 and KCNH2 were associated with substantially prolonged QTc values across all studies (Figure VIII and Table VII in the Data Supplement). Pathogenic and likely pathogenic variants in SCN5A were not associated with QTc prolongation, likely owing to heterogeneity of allele effects, although were associated with substantially prolonged PR intervals (Results and Figure IXA in the Data Supplement). When aggregated together, LOF, pathogenic, or likely pathogenic variants in KCNQ1 and KCNH2 were associated with a 30 ms (\(P=1.1 \times 10^{-6}\)) and 27 ms (\(P=1.0 \times 10^{-16}\)) prolongation of the QTc, respectively (Figure 4).
Despite the marked effect of deleterious variation on electrocardiographic intervals, incomplete penetrance was common (Table XIV in the Data Supplement). LOF, pathogenic, or likely pathogenic variants in **SCN5A**, which were carried by 0.1% of individuals, and were associated with an ≈6-fold increased odds of first-degree atrioventricular block in TOPMed and the UK Biobank (*P*=8.4×10⁻⁵), and 12-fold increased odds in MyCode (*P*=2.7×10⁻¹²; Tables XV in the Data Supplement). Nevertheless, about 70% of carriers had a PR interval of <200 ms, indicating absence of first-degree atrioventricular block (Results and Figure IX in the Data Supplement).

Similarly, deleterious **KCNQ1** and **KCNH2** variants were carried by 0.2% of individuals and were associated with an almost 23-fold increased odds of a QTc duration of at least 480 ms in TOPMed and UK Biobank (*P*=4.5×10⁻²⁵) and 9-fold increased odds in MyCode (*P*=2.7×10⁻¹²; Tables XV in the Data Supplement). Nevertheless, about 70% of carriers had a PR interval of <200 ms, indicating absence of first-degree atrioventricular block (Results and Figure IX in the Data Supplement).

DISCUSSION

Using a unique resource of high-depth genomic sequence data from over 130,000 individuals, we identified low-frequency and rare genetic variants underlying variability in 5 routinely collected electrocardiographic traits. Our findings indicate that pathogenic variation in arrhythmia and SCD genes are associated with marked PR (**SCN5A**) and QTc (**KCNQ1**, **KCNH2**, and **KCNE1**) prolongation in the general population. Nevertheless, over 70% of individuals with deleterious variation had normal electrocardiographic intervals, indicating that routinely measured electrocardiographic intervals may be insensitive for the detection of such carriers. Moreover, <3% of individuals with marked PR interval or QTc variation carried a known deleterious variant in **SCN5A** or **SCN5A** gene.

Few individuals with prolonged intervals carried known deleterious variation. For example, among individuals with first-degree atrioventricular block, only 0.3% carried a LOF, pathogenic, or likely pathogenic variant in **SCN5A** in TOPMed and the UK Biobank, and 0.5% in MyCode. Similarly, among individuals with marked QTc prolongation (eg, ≥480ms), only 2.4% carried a LOF or known deleterious variant in **KCNQ1** or **KCNH2** in TOPMed and UK Biobank, and 1.2% in MyCode (Figure 5). Extended analyses summarizing the frequency of additional rare protein-coding variation are displayed in Table XVII in the Data Supplement. Notably, fewer than 11% of individuals with QTc≥480ms or QTc≥500 ms carried any rare **KCNQ1** or **KCNH2** protein-altering variant across TOPMed and UK Biobank.

### Table. Baseline Characteristics of TOPMed Participants

<table>
<thead>
<tr>
<th>ECG traits</th>
<th>RR interval</th>
<th>P-wave duration*</th>
<th>PR interval</th>
<th>QRS duration</th>
<th>QTc†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>27 967</td>
<td>23 567</td>
<td>28 008</td>
<td>27 874</td>
<td>26 976</td>
</tr>
<tr>
<td>Ancestry, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>16 749 (59.9)</td>
<td>15 801 (67)</td>
<td>16 707 (59.7)</td>
<td>16 644 (59.7)</td>
<td>16 074 (59.6)</td>
</tr>
<tr>
<td>African</td>
<td>5034 (18.0)</td>
<td>4149 (17.6)</td>
<td>5063 (18.1)</td>
<td>5019 (18.0)</td>
<td>4887 (18.1)</td>
</tr>
<tr>
<td>Amish</td>
<td>1028 (3.7)</td>
<td>1024 (3.7)</td>
<td>1025 (3.7)</td>
<td>998 (3.7)</td>
<td>1008 (3.7)</td>
</tr>
<tr>
<td>East Asian</td>
<td>727 (2.6)</td>
<td>700 (3.0)</td>
<td>727 (2.6)</td>
<td>727 (2.6)</td>
<td>715 (2.7)</td>
</tr>
<tr>
<td>Ad Mixed American</td>
<td>615 (2.2)</td>
<td>520 (2.2)</td>
<td>616 (2.2)</td>
<td>610 (2.2)</td>
<td>596 (2.2)</td>
</tr>
<tr>
<td>South Asian</td>
<td>56 (0.2)</td>
<td>57 (0.2)</td>
<td>57 (0.2)</td>
<td>53 (0.2)</td>
<td>53 (0.2)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>3758 (13.4)</td>
<td>2397 (10.2)</td>
<td>3814 (13.6)</td>
<td>3792 (13.6)</td>
<td>3653 (13.5)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>18 077 (65)</td>
<td>15 566 (68)</td>
<td>18 140 (65)</td>
<td>18 069 (65)</td>
<td>17 644 (65)</td>
</tr>
<tr>
<td>Mean age at ECG, y (SD)</td>
<td>60.2 (12.5)</td>
<td>61.1 (11.3)</td>
<td>60.1 (12.5)</td>
<td>60.1 (12.5)</td>
<td>59.8 (12.5)</td>
</tr>
<tr>
<td>Mean interval length, ms (SD)</td>
<td>937.9 (148.9)</td>
<td>109.5 (13.3)</td>
<td>164.9 (26.1)</td>
<td>91.0 (12.7)</td>
<td>423.8 (22.9)</td>
</tr>
<tr>
<td>Mean height, cm (SD)</td>
<td>166.0 (9.8)</td>
<td>165.1 (9.4)</td>
<td>165.0 (9.6)</td>
<td>165.0 (9.6)</td>
<td>165.0 (9.5)</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>79.6 (18.8)</td>
<td>79.3 (18.3)</td>
<td>79.6 (18.8)</td>
<td>79.6 (18.9)</td>
<td>79.5 (18.9)</td>
</tr>
<tr>
<td>Myocardial infarction, N (%)</td>
<td>2521 (9.8)</td>
<td>2198 (9.2)</td>
<td>2503 (9.8)</td>
<td>2493 (9.8)</td>
<td>2361 (9.6)</td>
</tr>
<tr>
<td>Heart failure, N (%)</td>
<td>1925 (8.1)</td>
<td>1558 (6.7)</td>
<td>1914 (8.0)</td>
<td>1913 (8.1)</td>
<td>1788 (7.8)</td>
</tr>
<tr>
<td>β-Blocker, N (%)</td>
<td>3651 (13)</td>
<td>2740 (12)</td>
<td>3628 (13)</td>
<td>3638 (13)</td>
<td>3415 (13)</td>
</tr>
<tr>
<td>Calcium channel blocker, N (%)</td>
<td>3220 (12)</td>
<td>2632 (11)</td>
<td>3203 (12)</td>
<td>3198 (12)</td>
<td>3043 (12)</td>
</tr>
</tbody>
</table>

TOPMed indicates Trans-Omics in Precision Medicine.

*The maximum P-wave duration was obtained from the ECG leads.

†QTc is corrected QT interval using the Bazett method.
value of large-scale sequencing efforts to identify novel genes, such as PAM and MFGE8, which we implicated in atrioventricular conduction.

Our study complements and extends prior literature. To date, most genome-wide association studies of electrocardiographic traits have largely been focused on common genetic variants, have studied these traits individually,12,13,15,18–20 or have relied on sequencing in smaller samples with imputation of low-frequency variants.14 In contrast, the recent and rapid innovation in sequencing technology has enabled the analysis of very rare and potentially deleterious coding variation in relation to cardiac traits. Such rare variants are likely to directly implicate genes in cardiac physiology and may confer large effect sizes which could be of clinical relevance.

Our findings have 3 important implications. First, rare variants in arrhythmia and SCD susceptibility genes are associated with large effects on the ECG in the population, yet routinely measured electrocardiographic intervals may not be a reliable method for identifying most carriers. Incomplete electrocardiographic penetrance was common among individuals carrying deleterious variation. Indeed, it is likely that pathogenic variation in arrhythmia and SCD genes exhibits lower penetrance than was reported previously in family-based analyses,21–23 consistent with reports for arrhythmogenic cardiomyopathy genes.24 Considering the frequency of

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**Figure 2. Manhattan plots for 5 electrocardiographic traits.**

A illustrates circular Manhattan plot illustrating genome-wide association testing results between 5 electrocardiographic traits and common variants with minor allele frequency (MAF) >1%. Loci that reached a conventional genome-wide significant threshold (P = 5 × 10⁻⁸; red dotted lines) are annotated with the nearest genes. B shows associations between low-frequency (0.1% ≤ MAF <1%) variants and PR interval. The gray dotted line is the significant threshold (0.05/83994 variants = 6.0 × 10⁻⁷).
second hits that can predispose to QTc prolongation and lethal ventricular arrhythmias, the consequences of subclinical genetic predisposition to arrhythmias requires prospective evaluation, particularly given the adoption of genome-first approaches for which return of incidental findings in several arrhythmia and SCD genes is encouraged.\(^2\) Since electrocardiographic intervals may vary over time, future analyses that leverage repeated electrocardiographic measures may provide more accurate estimates of rare variant penetrance. Moreover, analysis of additional electrocardiographic features beyond standard intervals is warranted. Importantly, whether a genome-first approach to identifying pathogenic variant carriers will have a material impact on SCD risk requires prospective evaluation.

Second, our observations suggest that quantitative traits measured in population-based studies are endophenotypes for pathogenic variation. Analyzing low-frequency and rare genetic variation in relation to commonly ascertained electrocardiographic traits is an efficient approach for identifying important genes, both established and novel, that are related to cardiac conduction and arrhythmia risk. For example, variation in SCN5A was associated with PR duration. SCN5A encodes the α-subunit of the cardiac sodium channel and comprises the major inward sodium current responsible for cardiomyocyte depolarization during phase 0. Mutations in SCN5A are responsible for several conditions, including atrial fibrillation, bradyarrhythmias, cardiomyopathy, Brugada syndrome, LOTS, and SCD.\(^3\) Additionally, low-frequency and rare coding variants in KCNQ1, KCNH2, and KCNE1 were associated with QTc. KCNQ1 and KCNH2 encode voltage-gated potassium channel subunits responsible for the outward rectifier currents \(I_{Ks}\) and \(I_{Kr}\).
respectively, which govern cardiomyocyte repolarization during phases 2 and 3 of the action potential. Mutations in KCNQ1 and KCNH2 represent the most common forms of LQTS.10 KCNE1 encodes a β-subunit that interacts with KCNQ1 to form the IKs current. Notably, KCNE1 has recently been considered a controversial susceptibility gene for typical monogenic LQTS.10,26 Examination of sequence data in relation to ECGs can also identify novel pathways involved in cardiac physiology. PAM encodes peptidylglycine-alpha-amidating-monooxygenase, an enzyme expressed in atrial cardiomyocytes, where it colocalizes with atrial natriuretic peptide.27–29 MFGE8 encodes the milk fat globule-epidermal growth factor 8 that is involved in phagocytic signaling and has been implicated in neovascularization,30 cardiac hypertrophy,31 and atrial fibrosis.32 These novel conduction genes have not been examined extensively in relation to cardiovascular disease. Future work is necessary to characterize the relations between genetic variation in these genes and disease, as well as their mechanistic roles in cardiovascular biology. Larger discovery samples anticipated in the near future are likely to identify additional arrhythmias and SCD susceptibility genes, emphasizing the importance of high-throughput functional characterization of new genes.

Third, few individuals with markedly abnormal electrocardiographic intervals had known deleterious variation in classic arrhythmia and SCD genes, indicating that the causes of such electrocardiographic variability remain unclear. We suspect that multiple factors may account for prolonged electrocardiographic intervals, including rare variants in genes not traditionally implicated in arrhythmias and SCD, polygenic susceptibility to electrocardiographic interval prolongation, and other factors, such as electrolyte abnormalities or medication exposures, that were not accounted for in our analysis. We included individuals on antiarrhythmic medications, individuals with paced rhythms, and pathological QRS prolongation which may confound some intervals (eg, QTc). The yield of contemporary panel-based genetic evaluations in individuals with isolated electrocardiographic interval prolongation is, therefore, likely low. The cause, prognosis, and optimal management of these genotype-negative individuals in the community warrants evaluation considering the adverse prognosis traditionally associated with both prolonged PR interval and QTc.3,8,33–36

Our results should be evaluated in the context of the study design. The sample consisted mainly of middle-aged individuals of European ancestry, limiting generalizability of results beyond the ancestral groups and age strata represented. We used single time point electrocardiographic analyses and intervals may vary over time, although for the studied traits 10 second ECGs have been determined to be reliable.37,38 We did not account for all medications that may affect cardiac conduction, which requires future investigation. Finally, we cannot exclude a survival bias since included participants were adults at the time of enrollment.
In conclusion, we demonstrate the value of large-scale high-depth sequence analysis for interrogating the genetic basis of the ECG. As bio Repositories grow in the near future, similar approaches will undoubtedly uncover additional rare variants with other high-impact on cardiovascular diseases.

**ARTICLE INFORMATION**

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**Whole-genome sequencing for NHLBI TOPMed:**

- **Cardiovascular Health Research Unit** (3R01HL121907-01S1).
- **whole-genome sequencing for NHLBI TOPMed:**
  - **Women's Health Initiative** (phs001364.v1.p1) was performed at the Baylor Human Genome Sequencing Center (3U54HG003067-12S2) and (HHSN2682016000039).
  - **whole-genome sequencing for NHLBI TOPMed:** Framingham Heart Study (phs000974.v1.p1) was performed at the Broad Institute of MIT and Harvard (3R01HL092577-06S1) and 3U54HG003067-12S2).
  - **whole-genome sequencing for NHLBI TOPMed:**
    - **Jackson Heart Study** (phs000964.v1.p1) was performed at the University of Washington Northwest Genomics Center (3R01HL098433-05S1 and HSN268201100037C).
  - **whole-genome sequencing for NHLBI TOPMed:**
    - **Multi-Ethnic Study of Atherosclerosis** (phs001416.v1.p1) was performed at the Broad Institute of MIT and Harvard (3U54HG003067-13S1).

- **whole-genome sequencing for NHLBI TOPMed:**
  - **Women’s Health Initiative** (phs001237.v1.p1) was performed at the Broad Institute of MIT and Harvard (HHSN268201600014C). Centralized read mapping and genotype calling, along with variant quality metrics and filtering were provided by the TOPMed Informatics Core (3R01HL117925-02S1; contract HHSN268201600021; contract HHSN268201600022; contract HHSN268201600024; contract HHSN268201600025; contract HHSN268201600026; contract HHSN268201600027).

- **topmed data coordinating center** (phs001235.v1.p1) was performed at the Broad Institute of MIT and Harvard (3U54HG003067-13S1).

- **whole-genome sequencing for NHLBI TOPMed:**
  - **Women’s Health Initiative** (phs001237.v1.p1) was performed at the Broad Institute of MIT and Harvard (HHSN268201600014C). Centralized read mapping and genotype calling, along with variant quality metrics and filtering were provided by the TOPMed Informatics Core (3R01HL117925-02S1; contract HHSN268201600021; contract HHSN268201600022; contract HHSN268201600024; contract HHSN268201600025; contract HHSN268201600026; contract HHSN268201600027).

- **topmed data coordinating center** (phs001235.v1.p1) was performed at the Broad Institute of MIT and Harvard (3U54HG003067-13S1).
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