Journal of the American Heart Association

ORIGINAL RESEARCH

Screening for Rare Coding Variants That Associate With the QTc Interval in Iceland

Gardar Sveinbjornsson , MSc*; Bara D. Benediktsdottir, MD, MRCP*; Gunnlaugur Sigfusson, MD;
Kristjan Norland, MSc; Olafur B. Davidsson , MSc; Rosa B. Thorolfsdottir, MD, PhD; Vinicius Tragante , PhD;
Gudny A. Arnadottir , MSc; Brynjar O. Jensson, MSc; Hildigunnur Katrinardottir, MSc;
Run Fridriksdottir, MSc; Hallbera Gudmundsdottir, MD; Hildur M. Aegisdottir, MD; Brynjar Fridriksson, BA;
Gudmundur Thorgeirsson , MD, PhD; Vidar Magnusson, MD; Asmundur Oddsson , PhD; Patrick Sulem , MD;
Daniel F. Gudbjartsson, PhD; Hilma Holm , MD; David O. Arnar , MD, PhD, MPH; Kari Stefansson, MD, PhD

BACKGROUND: Long-QT syndrome (LQTS) is a cardiac repolarization abnormality that can lead to sudden cardiac death. The most common causes are rare coding variants in the genes *KCNQ1*, *KCNH2*, and *SCN5A*. The data on LQTS epidemiology are limited, and information on expressivity and penetrance of pathogenic variants is sparse.

METHODS AND RESULTS: We screened for rare coding variants associated with the corrected QT (QTc) interval in Iceland. We explored the frequency of the identified variants, their penetrance, and their association with severe events. Twelve variants were associated with the QTc interval. Five in *KCNQ*1, 3 in *KCNH2*, 2 in cardiomyopathy genes *MYBPC3* and *PKP2*, and 2 in genes where coding variants have not been associated with the QTc interval, *ISOC1* and *MYOM2.* The combined carrier frequency of the 8 variants in the previously known LQTS genes was 530 per 100 000 individuals (1:190). p.Tyr315Cys and p.Leu273Phe in *KCNQ1* were associated with having a mean QTc interval longer than 500 ms ($P=4.2\times10^{-7}$; odds ratio [OR], 38.6; $P=8.4\times10^{-10}$, OR, 26.5; respectively), and p.Leu273Phe was associated with sudden cardiac death ($P=0.0034$; OR, 2.99). p.Val215Met in *KCNQ1* was carried by 1 in 280 Icelanders, had a smaller effect on the QTc interval ($P=1.8\times10^{-44}$; effect, 22.8 ms), and did not associate with severe clinical events.

CONCLUSIONS: The carrier frequency of associating variants in LQTS genes was higher than previous estimates of the prevalence of LQTS. The variants have variable effects on the QTc interval, and carriers of p.Tyr315Cys and p.Leu273Phe have a more severe disease than carriers of p.Val215Met. These data could lead to improved identification, risk stratification, and a more precise clinical approach to those with QTc prolongation.

Key Words: genetic epidemiology ■ genetics ■ long-QT syndrome ■ precision medicine

The primary electrophysiological disorders of the heart are a group of mostly inherited arrhythmia syndromes usually defined by electrocardiographic patterns that frequently occur in the absence of structural cardiac abnormalities. They are almost exclusively inherited as autosomal dominant traits and are well-established causes of ventricular arrhythmias and sudden unexpected death, not least in younger individuals.[1]

Among these disorders is the long-QT syndrome (LQTS), a cardiac repolarization abnormality characterized by a prolonged corrected QT (QTc) interval on a 12-lead ECG. A prolonged QTc interval can result in an arrhythmia termed torsade de pointes. LQTS

1

RESEARCH PERSPECTIVE

What Is New?
- The study provides unique information on the genetic epidemiology, penetrance of sequence variants, and the association with serious events of long-QT syndrome.
- The prevalence of sequence variants associated with corrected QT prolongation was higher than prior estimates that have relied on ECG screening alone and the most frequent sequence variant in Iceland, P.Val215Met in the *KCNQ1* gene, a founder mutation, is associated with a less severe phenotype than other variants.

What Question Should Be Addressed Next?
- Improved knowledge about the genotype–phenotype relationship of sequence variants that can lead to QTc prolongation might facilitate better identification and risk stratification of individuals.

Nonstandard Abbreviations and Acronyms

AF	allele frequency
dHS	deCODE Health Study
LQTS	long-QT syndrome
PVC	premature ventricular complex
QTc	corrected QT interval
SCD	sudden cardiac death

can be either congenital or acquired, the latter most commonly considered multifactorial, with contributing factors including certain medications and electrolyte disturbances.[2] The congenital LQTS was the first inherited arrhythmia syndrome to be extensively described. International guidelines are not in complete agreement on the degree of QT prolongation required to diagnose LQTS. The European Society of Cardiology recommends that in the absence of secondary factors, congenital LQTS can be diagnosed if the QTc interval is >480 ms, and considered if the interval is >460 ms when unexplained syncope has occurred.[3] The Heart Rhythm Society guidelines are more rigorous, recommending QTc cutoff of 500 ms in the absence of other factors that prolong the QT interval, or >480 ms when presented with syncope.[4] Both guidelines agree that LQTS can also be diagnosed if an individual has a Schwartz score, which is a clinical risk score, >3 or if a pathogenic sequence variant associated with LQTS is identified, regardless of QTc interval.[5]

Genetic information is not a part of the Schwartz score,[5] and up to 40% of LQTS variant carriers have a normal QTc interval.[6] Thus, an asymptomatic carrier of a LQTS variant without prolongation of the QTc interval can easily be missed without genetic testing. This is of considerable importance, because studies show that even carriers with a normal QTc have increased risk of serious cardiac events, particularly under certain clinical circumstances such as electrolyte disturbances or when taking medications that may prolong the QTc.[7,8] Further complicating the diagnosis of LQTS is that the QTc interval can be dynamic and vary between normal and abnormal in the same individual.

Although 8 genes have to date been implicated in LQTS, the most common causes are rare coding variants in the genes *KCNQ1* (LQTS1), *KCNH2* (LQTS2), and *SCN5A* (LQTS3).[9] These 3 genes contribute to >88% of genotype-positive cases,[10] but genetic testing has a diagnostic yield of 47% to 72% in suspected LQTS.[11,12] In addition to LQTS genes, several sequence variants with smaller effects, most notably at *NOS1AP*, have been associated with the QTc interval through genome-wide association studies.[13,14]

Different genetic subtypes of the LQTS have specific clinical and ECG characteristics, including triggers for arrhythmia, and also a variable response to treatment.[4,15] This underscores both the complexity of this disorder and the importance of genetic testing in the evaluation of individuals with LQTS and their relatives.

The prevalence of congenital LQTS, defined as a prolonged QTc interval on an ECG, in some instances also confirmed by genotyping, has been estimated to be in the range of 1 in 2000 to 1 in 5000.[16,17] A study from Norway suggested that the prevalence of LQTS mutation carriers may be closer to 1 in 1000,[18] but data on both clinical and genetic epidemiology of LQTS are limited.

The goal of this study was to search for rare coding variants (minor allele frequency <1%) associated with the QTc interval in Iceland; to explore their phenotypic effects, penetrance, and pathogenicity; and to map the genetic epidemiology of QTc prolonging sequence variants in Iceland. It should be emphasized that variants that cause mild QTc prolongation do not necessarily equate a diagnosis of LQTS. We performed an exome-wide association study testing 290 589 rare coding variants for association with automated QTc interval measures in 450 502 ECGs from 95 112 individuals.

METHODS

The Icelandic Data Protection Authority and the National Bioethics Committee of Iceland (number VSNb2015030024/03.01 and VSNb2015030022/03.01) approved the study, which complies with the Declaration

of Helsinki. All patients and controls who donated DNA samples signed informed consent. Personal identifiers of the patient data and biological samples were encrypted with a third-party system monitored by the Data Protection Authority. The authors declare that the data supporting the findings of this study are available within this article, its Supplemental Material, and on request.

Study Population

This study was based on whole-genome sequence data from 63 118 Icelanders participating in various studies at deCODE Genetics. Variants were imputed, down to a minor allele frequency <0.01%, into 173 025 individuals genotyped with Illumina single nucleotide polymorphism chips, and genotype probabilities for nontyped relatives were calculated based on Icelandic genealogy. The whole-genome sequencing of the Icelandic population, and the subsequent imputation, have been extensively described in prior publications.[19]

ECG Data

The ECG data were obtained from Landspitali–The National University Hospital in Reykjavik, Iceland (Landspitali) and included all ECGs obtained and digitally stored from 1998 to 2015 and ECGs from the deCODE Health Study (dHS). There were 16 502 ECGs obtained from the dHS and 434 000 from Landspitali. The ECGs at Landspitali were obtained in all hospital departments, from both inpatients and outpatients, and digitally recorded with the Philips PageWriter and stored in the Philips TraceMaster ECG Management System. Digitally measured parameters were extracted for analysis. Individuals with pacemakers at the time of measurement were excluded from the analysis. The Philips PageWriter Trim III QT interval measurement algorithm has been previously described and shown to fulfill industrial ECG measurement accuracy standards.[20] The QTc interval was corrected using the Fridericia formula.[21] Although the exact definition of a prolonged QTc interval may vary,[22] a QTc interval of >460 ms for both men and women was defined as prolonged in this study, and the mean measured QTc interval per individual was considered for phenotype ascertainment.

Phenotypic Data

To explore the phenotype of carriers of variants associating with the QTc interval, we used *International Classification of Diseases, Eighth, Ninth, and Tenth Revision* (*ICD-8*, *ICD-9*, *ICD-10*) diagnostic codes collected through various studies since 1987, and medical record review was performed for selected subsets of carriers. Syncope was defined as those individuals with a diagnosis of R55 in *ICD-9* and *ICD-10*, ventricular tachycardia as I47.2, and sudden cardiac death (SCD) as I46.0–46.9.

To have information about SCD as complete as possible, data from the Capital District Fire and Rescue Service about individuals who suffered from out-of-hospital cardiac arrest from 2008 until 2018 and data from the Icelandic Causes of Death Registry were used along with appropriate diagnostic codes. The available Icelandic Causes of Death Registry data included the main cause of death of individuals dying after 1975, and medical records were evaluated in an attempt to complete information about deceased carriers as much as possible.

Medical records were also evaluated of all carriers of QTc variants who died before the age of 75 years with a cardiac-related main cause of death or unspecified causes of death (*ICD-10* codes R.00.0-R00.9, I20-I79, R95-R99). Evaluation of medical records confirmed all SCD cases of the p.Leu273Phe and p.Cys315Tyr sequence variants in *KCNQ1* and validated the accuracy of cause of death in the Causes of Death Registry.

Information about use of β-blockers (*Anatomical Therapeutic Chemical* code C07*) was obtained from the Prescriptions Medicines Registry, an electronic database for outpatient prescriptions in Iceland initiated in 2002. A total of 101 individuals have been given the *ICD* codes 426.82 or I45.81 (LQTS).

Statistical Analysis

Quantitative traits were tested using a BOLT linear mixed model[23] and binary traits with a logistic regression model. We assumed an additive model, treating disease status as the response and expected genotype counts from imputation as covariates. This was done using software developed at deCODE Genetics.[19] Sex, county of birth, current age or age at death (first- and second-order terms included), blood sample availability for the individual, and an indicator function for the overlap of the lifetime of the individual with the time span of the phenotype collection were adjusted for in the regression when analyzing case–control traits, and age and sex when analyzing the quantitative traits. The first 10 principal components correlate with county of birth, only explain 0.085% of the variance in the QTc measures, and it was not necessary to include them as covariates.[24] When multiple measurements were available for individuals, the mean value was used in association analysis. Because LQTS-causing variants are not common, we tested rare coding sequence variants (minor allele frequency <1%) for associations and applied a Bonferroni correction for 290 589 variants tested (Figure S1). This resulted in a significance threshold of 1.7×10^{-7}. Given prior

knowledge, we specifically analyzed the association between the QTc interval and rare coding variants in the well-established LQTS genes *KCNQ1*, *KCNH2*, and *SCN5A*, and adjusted for significance using the number of coding variants in these genes with a false discovery rate procedure.

RESULTS

To search for rare (minor allele frequency <1%) protein coding variants that associate with the QT interval, we tested for association between the mean automated QTc interval measurements derived from 95 112 individuals and 290 589 rare protein coding variants. The mean analyzed QTc interval was 414.0 ms (SD, 25.3 ms), 419.2 ms in the Landspitali data and 413.3 ms in the dHS data. In the Landspitali data, 4.9 QTc interval measures were available per individual, and mean age at the median measurement was 57.6 years. The mean QTc interval was >460 ms for 4.4% of individuals and >500 ms for 0.5%. In the dHS data, the age at measure was 54.8 years, and the QTc interval was >460 ms for 3.7% of individuals and >500 ms for 0.5% (Table S1; Figure S2).

Eight variants were associated with the QTc interval (Table 1; Figure). Four were in the LQTS gene *KCNQ1*, 2 in known cardiomyopathy genes, *MYBPC3* and *PKP2*, and 2 in genes where coding variants have up to this time not been associated with the QTc interval or other cardiac diseases, *ISOC1* and *MYOM2*. Common intronic variants in *MYOM2* have previously been associated with the JT and QRS duration.[25] For rare coding variants in the well-established LQTS genes *KCNQ1*, *KCNH2*, and *SCN5A*, we specifically analyzed association with the QTc interval and adjusted for significance using the 94 tested variants. Using this approach ($P<0.0043$), 1 other variant in *KCNQ1*, and 3 in *KCNH2* associated with the QTc interval resulted in 12 significant variants in total. Out of 43 rare coding variants in *SCN5A* that were tested in the study, none were associated with the QTc interval.

Rare Sequence Variants Associated With the QTc Interval

Of the variants tested in known LQTS genes, p.Tyr315Cys (allele frequency [AF], 0.015%), p.Leu273Phe (AF, 0.037%), p.Val215Met (AF, 0.18%), p.Arg594Ter (AF, 0.024%), and p.Ile263LysfsTer26 (AF, 0.004%) in *KCNQ1* and p.Pro968AlafsTer151 (AF, 0.006%), p.Trp412Arg (AF, 0.002%), and p.Cys66Ser (AF, 0.001%) in *KCNH2* were associated with a prolonged QTc. p.Tyr315Cys, carried by 1 in 3330 Icelanders, conferred the largest effect ($P=3.3\times10^{-28}$; effect, 56.7 ms). The more common p.Val215Met, carried by 1 in 280 Icelanders,

had the smallest effect among the variants in *KCNQ1* and *KCNH2* ($P=1.8\times10^{-44}$; effect, 22.8 ms). The other rare coding variants in *KCNQ1* and *KCNH2* had an effect range from 30.8 to 55.7 ms.

We looked up the reported classification of pathogenicity from the ClinVar database[26] (downloaded on May 11, 2021) for all 94 coding variants tested in the established LQTS genes and compared it with their association with the QTc interval (Table S2). Of the 8 variants in these genes that were associated with the QTc interval in our study, 4 are reported as pathogenic/likely pathogenic in ClinVar, 1 is of unknown significance, and 3 have not been classified (Table 1). The most frequent of these variants, which also had the smallest effect on the QTc interval, p.Val215Met in *KCNQ1*, is reported as of unknown significance. When applying the American College of Medical Genetics and Genomics classification,[27] all variants apart from p.Val215Met and p.Trp412Arg were classified as pathogenic or likely pathogenic for LQTS. When classifying the variants, we did not use evidence from the associations with the QTc interval, which would add even more support to their classification as pathogenic for LQTS (Table S3).

Of the 94 variants, 40 are likely benign for LQTS given their frequency and small effect on the QTc interval, resulting in a 95% CI upper bound <15 ms from the mean. We consider other variants to be of unknown significance. Four of the associating variants are in non-LQTS genes. The missense variant p.Gly256Arg (AF, 0.58%) in *ISOC1*, carried by 1 in 80 Icelanders, associated most significantly of all variants with the QTc interval and resulted in a 14.6 ms prolongation on average ($P=1.5\times10^{-58}$), which is significantly smaller than those of the variants in the LQTS genes. The variant is not correlated with top expression quantitative loci in publicly available Genotype-Tissue Expression project data.[28] A stop-gain variant, p.Gln1386Ter (AF, 0.13%) in *MYOM2*, carried by 1 in 420 Icelanders, was associated with a shortening of the QTc interval ($P=7.1\times10^{-11}$; effect, −11.4 ms; Figure S3). Two variants in cardiac genes, 1 in *MYBPC3* ($P=7.4\times10^{-28}$; effect, 15.6 ms) and 1 in *PKP2* ($P=2.1\times10^{-8}$; effect, 11.4 ms), that are known to cause hypertrophic cardiomyopathy[15] and arrhythmogenic right ventricular cardiomyopathy,[16] respectively, were also associated with a prolonged QTc interval (Table 1). Because premature ventricular complexes (PVCs) on an ECG can interfere with QT measurement, and *PKP2* variant carriers have frequent PVCs, we explored if ECG statement codes that show PVCs affect the QTc association. Excluding individuals with PVCs does not explain the QTc variant association, with carriers without PVCs having on average 10.4-ms longer QTc than noncarriers. The *PKP2* carriers that had ventricular tachycardia, had their ECGs

Table 1. Variants Found in Iceland That Associate With the Corrected QT Interval

Chr	Pos (hg38)	P value	Effect, ms	rs no.	AF %	Carriers, n	Amin	Amaj	Gene	Coding effect	Coding change	ClinVar classification
Chr5	129 112 870	1.46E-58	14.60 (12.83 to 16.37)	rs372435009	0.58	2513	C	A	ISOC1	Missense	NP_057132.2:p.Gly256Arg	Not available
Chr11	2571 363	1.37E-44	22.80 (19.61 to 25.99)	rs17215479	0.178	769	A	G	KCNQ1	Missense	NP_000209.2:p.Val215Met	Unknown significance
Chr11	2572 882	1.20E-39	43.00 (36.60 to 49.40)	rs120074180	0.037	142	T	C	KCNQ1	Missense	NP_000209.2:p.Leu273Phe	Pathogenic (LQTS)
Chr11	2583 457	3.27E-28	56.70 (46.61 to 66.79)	rs74462309	0.015	67	G	A	KCNQ1	Missense	NP_000209.2:p.Tyr315Cys	Pathogenic/likely pathogenic (LQTS)
Chr11	47346372	7.36E-28	15.61 (12.81 to 18.41)	rs397516082	0.18	788	T	C	MYBPC3	Splice acceptor	NM_000256.3:c.927-2A>G	Pathogenic (HCM)
Chr8	2 144 739	7.06E-11	−11.56 (−15.04 to −8.08)	rs201108083	0.13	564	C	T	MYOM2	Stop gained	NP_003961.3:p.Gln1386Ter	Not available
Chr11	2778 023	7.98E-09	31.90 (21.06 to 42.74)	rs794728537	0.024	103	T	C	KCNQ1	Stop gained	NP_000209.2:p.Arg594Ter	Pathogenic (LQTS)
Chr12	32802 499	2.11E-08	11.39 (7.41 to 15.37)	rs759179184	0.10	405	GGGTGT	G	PKP2	Frameshift	NP_001005242.2:p.His689ProfsTer8	Pathogenic (ARVC)
Chr7	150 947 670	0.00026	30.80 (14.27 to 47.33)	rs786204101	0.006	23	CG	C	KCNH2	Frameshift	NP_000229.1:p.Pro968AlafsTer151	Pathogenic (LQTS)
Chr11	2572 852	0.00030	38.00 (17.40 to 58.60)	...	0.004	19	A	AT	KCNQ1	Frameshift	NP_000229.2:p.Ile263LysfsTer26	Not classified
Chr7	150 952 748	0.00031	50.00 (22.83 to 77.17)	...	0.002	7	G	A	KCNH2	Missense	NP_000229.1:p.Trp412Arg	Not classified
Chr7	150 974 821	0.00033	55.70 (25.29 to 86.11)	...	0.001	4	G	C	KCNH2	Missense	NP_000229.1:p.Cys66Ser	Not classified

The associations are shown for both the 8 variants identified in the exome-wide association study approach and the 4 variants found when LQTS genes *KCNQ1*, *KCNH2*, and *SCN5A* were specifically analyzed. Classification of the variants in ClinVar is shown. AF indicates allele frequency; Amaj, major allele; Amin, minor allele, which is the effect allele; ARVC, arrhythmogenic right ventricular cardiomyopathy; Chr, chromosome; HCM, hypertrophic cardiomyopathy; LQTS, long-QT syndrome; and Pos, position in build hg38.
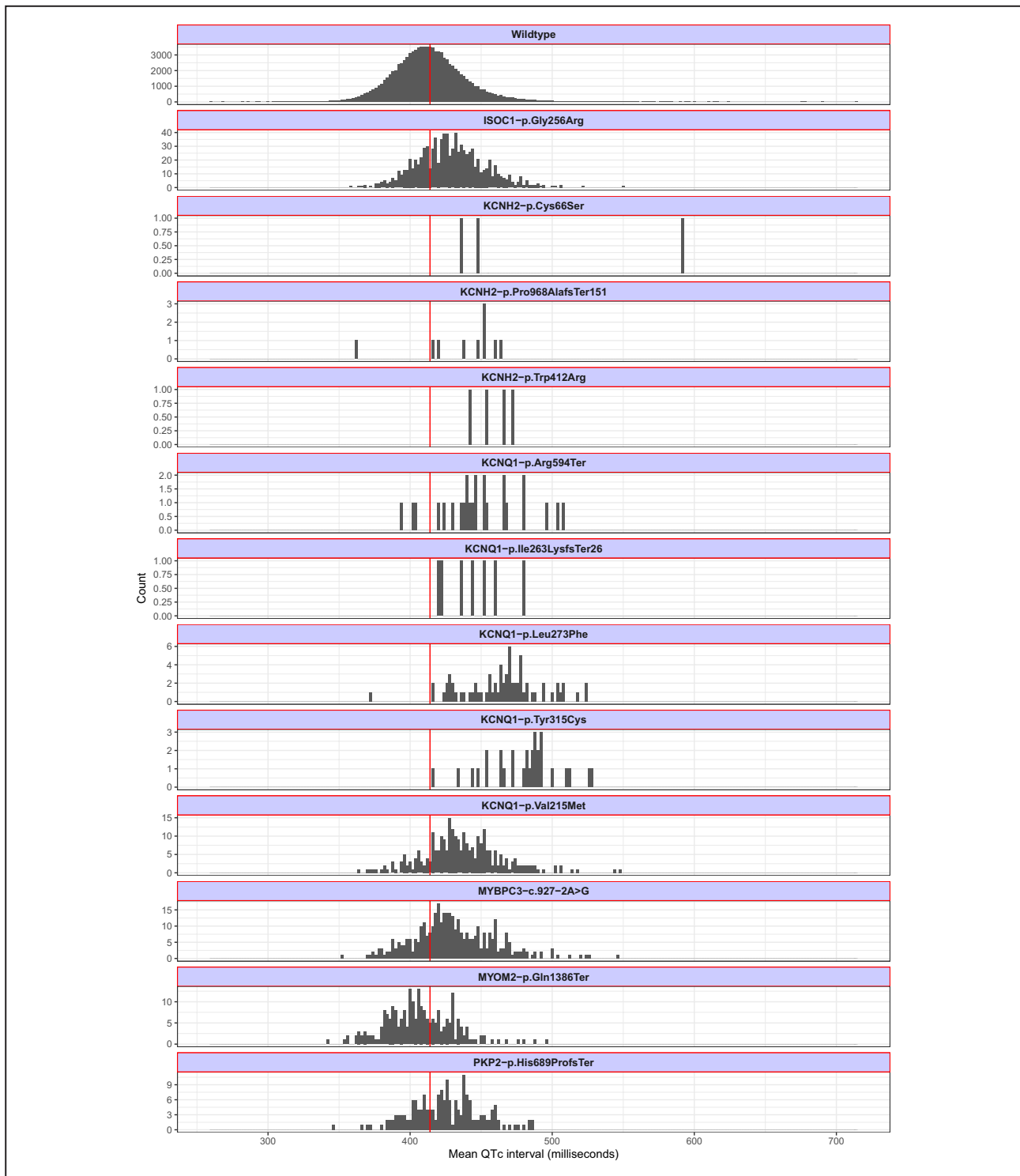
Figure 1.   Histogram of the mean observed QTc interval in individuals carrying QTc interval-associating mutations in Iceland.
The red line indicates a 414-ms mean of the population where carriers of QTc interval variants have been excluded. QTc indicates corrected QT.

manually reviewed, and had monomorphic ventricular tachycardia. This would suggest that the arrhythmia is more likely associated with structural heart disorder than the prolonged QTc.

Genetic Epidemiology of LQTS Based on Associating Variants in LQTS Genes

The combined frequency of the 8 coding sequence variants in the established LQTS genes that prolonged

the QTc interval was 530 per 100 000 individuals (1:190). If we omit p.Val215Met in *KCNQ1*, which is a founder mutation in the Icelandic population, the frequency decreases to 180 per 100 000 individuals (1:560) (Table 2).

Among individuals with available ECGs, the fraction of carriers with mean QTc interval ≥460 ms was 140 per 100 000 or 87 per 100 000 if omitting p.Val215Met in *KCNQ1*. Of carriers of QT variants in the known LQTS genes and available ECGs, 32.9% (141/429) had a mean QTc interval ≥460 ms. ECG data were not available for 62% of carriers. The prevalence of mean QTc interval ≥460 ms was similar in the dHS and Landspitali data sets (3.7% compared with 4.4%).

Evaluation of the Phenotypic Effects of Associating Variants

To explore the phenotypic effects of the 12 variants in more detail, we tested them for association with lifespan, SCD (N_{cases}=4763), ventricular tachycardia (N_{cases}=1110), syncope and collapse (N_{cases}=19 723), having mean QTc interval ≥460 and 500 ms, and having an *ICD* code used for LQTS (*ICD-9* 426.82 and *ICD-10* I45.81) (Table 3).

After accounting for number of variants tested using a false discovery rate procedure, all QTc variants in *KCNQ1* and *KCNH2* were associated with a mean QTc interval ≥460 ms. p.Tyr315Cys and p.Leu273Phe in *KCNQ1* were the only ones that were associated with having a LQTS *ICD* code diagnosis ($P=7.2\times10^{-15}$; odds ratio [OR], 228.9; and $P=4.2\times10^{-32}$; OR, 328.5, respectively). Both of these variants were also associated with a mean QTc interval ≥500 ms ($P=4.2\times10^{-7}$; OR, 38.6; and $P=8.4\times10^{-10}$; OR, 26.5, respectively), a value that is associated with a high risk of ventricular tachycardia. In total, 16.6% of p.Tyr315Cys and 11.4% of p.Leu273Phe carriers, with available ECGs, had a mean QTc interval ≥500 ms. Respectively, 76.6% and 61.4% of carriers of these variants had a mean QTc interval ≥460 ms, suggesting high penetrance (Table 2). Carriers of these variants also had a higher proportion of β-blocker prescriptions than carriers of other variants (Table 2). The p.Leu273Phe variant in *KCNQ1* was associated with the risk of SCD ($P=0.0066$; OR, 3.16), and p.Tyr315Cys was associated with syncope and collapse ($P=0.0034$; OR, 2.99). A lower percentage of p.Val215Met carriers had mean QTc ≥460 ms (19.3%) and mean QTc interval ≥500 ms (2.9%), suggesting a milder phenotype for this most frequent variant. p.Val215Met in *KCNQ1* was not associated with SCD ($P=0.85$; OR, 1.05), but there was statistical power to detect association with OR above 1.58 for this variant. p.Cys66Ser in *KCNH2* was the only LQTS gene variant that was associated with shorter lifespan ($P=0.0052$; effect, −1.86 SD). c.927-2A>G in *MYBPC3* was associated with SCD ($P=0.0040$; OR,

Table 2. Characteristics of Carriers of the Sequence Variants in the Established LQTS Genes in Iceland

Gene	Coding effect	Identified carriers, n	Coding change	AF %	Icelanders, n	Carriers with available ECG, %	Mean QTc >460 ms (% among those with available ECG)	Mean QTc >500 ms (% among those with available ECG)	Carriers on β-blockers (compared with 8.9% of all individuals), n
KCNQ1	Missense	769	NP_000209.2:p.Val215Met	0.178	1:280	36.4	19.3	2.9	17.8
KCNQ1	Missense	142	NP_000209.2:p.Leu273Phe	0.037	1:1350	49.3	61.4	11.4	31.0
KCNQ1	Stop gained	103	NP_000209.2:p.Arg594Ter	0.024	1:2080	24.3	36.0	4.0	13.6
KCNQ1	Missense	67	NP_000209.2:p.Tyr315Cys	0.015	1:3330	44.8	76.6	16.6	29.9
KCNH2	Frameshift	23	NP_000229.1:p.Pro968AlafsTer151	0.006	1:8330	43.5	20.0	0	17.4
KCNQ1	Frameshift	19	NP_000209.2:p.Ile263LysfsTer26	0.004	1:12 500	36.8	42.9	0	15.8
KCNH2	Missense	7	NP_000229.1:p.Trp412Arg	0.002	1:25 000	57.1	50.0	0	28.9
KCNH2	Missense	4	NP_000229.1:p.Cys66Ser	0.001	1:50 000	75.0	33.3	33.3	0
			Combined (with p.Val215Met)	530 per 100 000	1:190				
			Combined (without p.Val215Met)	180 per 100 000	1:560				

Percent of carriers with extreme risk (mean QTc >500 ms) and penetrance of LQTS (mean QTc intervals >460 ms) are reported among carriers with available ECGs. β-blocker prescription rate among carriers is regardless of indication. AF is shown for each variant and combined. AF indicates allele frequency; LQTS, long-QT syndrome; and QTc, corrected QT.

Table 3. Associations of the Identified Variants With Binary End Points

Chr	Pos (hg38)	AF %	Amin	Amaj	Gene	Coding effect	Coding change	QTc effect, ms	SCD (N cases=4763)		VT (N cases=1110)		Lifespan (N=124512)		QTc >460ms		QTc >500ms		LQTS/ICD code 426.82 (ICD-9) or I45.81 (ICD-10) (N cases=101)		Syncope and collapse (N cases=19723)	
									P value	OR	P value	OR	P value	β SD	P value	OR	P value	OR	P value	OR	P value	OR
Chr5	129112870	0.58	C	A	ISOC1	Missense	NP_057132.2:p.Gly256Arg	14.6	0.28	0.84 (0.61 to 1.15)	0.35	0.72 (0.36 to 1.43)	0.34	0.03 (−0.03 to 0.09)	1.01E-14	2.55 (2.01 to 3.23)	0.08	1.93 (0.92 to 4.03)	0.27	0.0 (0.00 to 26.12)	0.85	1.02 (0.83 to 1.25)
Chr7	150947670	0.006	CG	C	KCNH2	Frameshift variant	NP_000229.1:p.Pro968AlafsTer151	30.8	0.073	5.42 (0.85 to 34.39)	0.67	0.0 (0.00 to >1000)	0.11	−0.56 (−1.25 to 0.13)	0.014	9.81 (1.59 to 60.63)	0.79	0.0 (0.00 to >1000)	0.9	0.0 (0.00 to >1000)	0.44	1.67 (0.45 to 6.14)
Chr7	150952748	0.002	G	A	KCNH2	Missense variant	NP_000229.1:p.Trp412Arg	50	0.63	0.0 (0.00 to >1000)	0.76	0.0 (0.00 to >1000)	0.7	0.21 (−0.86 to 1.28)	0.0081	25.80 (2.33 to 286.10)	0.84	0.0 (0.00 to >1000)	0.95	0.0 (0.00 to >1000)	0.58	2.01 (0.17 to 23.83)
Chr7	150974821	0.001	G	C	KCNH2	Missense variant	NP_000229.1:p.Cys66Ser	55.7	0.67	0.0 (0.00 to >1000)	0.82	0.0 (0.00 to >1000)	0.0052	−1.86 (−3.16 to −0.56)	0.004	52.30 (3.53 to 774.08)	0.0061	85.00 (3.55 to 2034.23)	0.96	0.0 (0.00 to >1000)	0.19	4.59 (0.47 to 44.83)
Chr8	2144739	0.13	C	T	MYOM2	Stop gained	NP_003961.3:p.Gln1386Ter	−11.56	0.89	0.96 (0.54 to 1.71)	0.2	0.34 (0.07 to 1.77)	0.83	0.01 (−0.10 to 0.12)	0.09	0.49 (0.21 to 1.12)	0.13	0.0 (0.00 to 3.44)	0.38	4.18 (0.17 to 101.86)	0.15	1.26 (0.92 to 1.73)
Chr11	47346372	0.18	T	C	MYBPC3	Splice acceptor	NM_000256.3:c.927-2A>G	15.61	0.004	1.93 (1.23 to 3.02)	8.00E-15	8.12 (4.79 to 13.77)	3.42E-05	−0.22 (−0.32 to −0.12)	4.14E-15	4.40 (3.04 to 6.37)	2.80E-06	7.78 (3.30 to 18.35)	0.55	0.0 (0.00 to >1000)	0.061	1.31 (0.99 to 1.74)
Chr11	2571363	0.178	A	G	KCNQ1	Missense variant	NP_000209.2:p.Val15Met	22.8	0.85	1.05 (0.63 to 1.74)	0.68	1.24 (0.45 to 3.45)	0.66	−0.02 (−0.13 to 0.08)	1.23E-19	5.05 (3.56 to 7.17)	0.00042	4.91 (2.03 to 11.89)	0.019	10.62 (1.47 to 76.49)	0.041	1.33 (1.01 to 1.75)
Chr11	2572882	0.037	T	C	KCNQ1	Missense variant	NP_000209.2:p.Leu273Phe	43	0.0066	3.16 (1.38 to 7.25)	0.06	3.84 (0.94 to 15.61)	0.93	−0.01 (−0.26 to 0.23)	4.83E-44	35.50 (21.48 to 58.68)	8.37E-10	26.50 (9.31 to 75.46)	4.22E-32	328.50 (125.40 to 860.54)	0.22	1.45 (0.80 to 2.63)
Chr11	2583457	0.015	G	A	KCNQ1	Missense variant	NP_000209.2:p.Tyr315Cys	56.7	0.067	3.11 (0.92 to 10.47)	0.32	3.34 (0.31 to 35.98)	0.059	−0.34 (−0.69 to 0.01)	4.72E-27	47.40 (23.49 to 95.66)	4.17E-07	38.60 (9.38 to 158.87)	7.21E-15	228.90 (58.24 to 899.60)	0.0034	2.99 (1.44 to 6.22)
Chr11	2778023	0.024	T	C	KCNQ1	Stop gained	NP_000209.2:p.Arg594Ter	31.9	0.47	0.54 (0.10 to 2.87)	0.25	3.24 (0.44 to 24.01)	0.72	0.05 (−0.24 to 0.35)	0.00034	5.24 (2.12 to 12.97)	0.32	3.34 (0.31 to 35.98)	0.8	0.0 (0.00 to >1000)	0.96	0.98 (0.44 to 2.16)
Chr11	2572852	0.004	A	AT	KCNQ1	Frameshift variant	NP_000209.2:p.Ile263LysfsTer26	38	0.44	0.0 (0.00 to 639.12)	0.69	0.0 (0.00 to >1000)	0.27	−0.47 (−1.31 to 0.37)	0.0025	15.90 (2.65 to 95.55)	0.8	0.0 (0.00 to >1000)	0.94	0.0 (0.00 to >1000)	0.63	1.51 (0.28 to 8.08)
Chr12	32802499	0.1	GGGTGT	G	PKP2	Frameshift	NP_001005242.2:p.His689ProfsTer8	11.39	0.86	1.07 (0.50 to 2.27)	0.00076	4.58 (1.89 to 11.11)	0.42	−0.06 (−0.21 to 0.09)	0.0054	2.30 (1.28 to 4.14)	0.19	0.0 (0.00 to 8.01)	0.31	5.46 (0.21 to 144.69)	0.38	0.83 (0.55 to 1.26)

P values, ORs, and effects are shown for each variant. AF indicates allele frequency; Amaj, major allele; Amin, minor allele, which is the effect allele; Chr, chromosome; ICD, *International Classification of Diseases*; LQTS, long-QT syndrome; OR, odds ratio; Pos, position in build hg38; QTc, corrected QT; SCD, sudden cardiac death; and VT, ventricular tachycardia.

1.93), ventricular tachycardia ($P=8.0\times10^{-15}$; OR, 8.12), and lifespan ($P=3.4\times10^{-5}$; effect, −0.22 SD), and p.His-689ProfsTer8 in *PKP2* with ventricular tachycardia ($P=0.00076$; OR, 4.58). These variants likely prolong the QTc interval due to conduction abnormalities secondary to hypertrophic cardiomyopathy[29] and arrhythmogenic right ventricular cardiomyopathy.[16]

Rare Sequence Variants in the LQTS Genes

Because it is difficult to impute rare variants in the whole-genome sequencing set (eg, singletons and de novo variants), they cannot be tested for association with QTc interval. Using the whole-genome sequencing data of 63 118 individuals, we screened for rare variants in the LQTS genes that were reported as pathogenic in ClinVar. Three sequence variants, p.Asp446Asn and p.Arg231Ser in *KCNQ1* and p.Ile593Thr in *KCNH2* were carried by fewer than 5 individuals each, with at least 1 carrier with a mean QTc >460 ms.

DISCUSSION

In this study, whole-genome sequence data were used to search for rare coding variants that were associated with the QTc interval in Iceland. We found 12 variants that were associated with the QTc interval and explored their association with severe events. Five in the LQTS gene *KCNQ*1, 3 in *KCNH2*, 2 in known cardiomyopathy genes, *MYBPC3* and *PKP2*, and 2 in genes where rare coding variants have not been associated with the QTc interval, *ISOC1* and *MYOM2*. The results also provide new information on the genotype–phenotype relationship of these sequence variants and the variable risk of serious adverse effects. In addition, these data give new insight into the allelic frequency of sequence variants in LQTS genes. The prevalence of this disorder, restricting the analysis to known LQTS genes, was shown to be higher than previously reported based on clinical studies only. The results could have implications for risk stratification of carriers of these sequence variants and provide an opportunity to implement a precision medicine approach to QTc prolongation in Iceland.

Guidelines agree that LQTS can be diagnosed if a pathogenic sequence variant is identified, regardless of the QTc interval as evaluated on ECG.[4] However, it is not well established which variants are pathogenic. The variants found in this study have a variable effect on the QTc interval and risk of serious event. It is also not clear how large the effect on the QTc interval needs to be for a variant to be classified as pathogenic, and our data suggest that a more detailed risk stratification than simply classifying them as pathogenic or not is needed.

The prevalence of LQTS has previously been estimated using large prospective ECG studies and was found to be 1 in 2000 to 2500 in Italian and Japanese infants.[17,30] In this Icelandic cohort, the prevalence of rare sequence variants in *KCNQ1* and *KCNH2* that were associated with QTc prolongation was found to be substantially higher, both the number of carriers alone and even when restricting the analysis to carriers with an ECG with mean QTc >460 ms. The prevalence of sequence variants in this study is closer to that reported in a Norwegian genotyped cohort, where it was ≈1 in 1000.[18] Individuals who are genotype positive may have a normal QTc interval on ECG, and the proportion of phenotype-negative carriers has been estimated to be as high as 40%.[6,8] These carriers might easily be missed with ECG screening alone, and therefore the true prevalence of LQTS is most certainly underestimated in studies that are only based on ECG screening.

We chose a different approach (ie, genetic screening) to try to estimate the carrier frequency of QTc prolonging variants. In this study, we identified all carriers in a large genetic data set of rare coding variants associated with QTc interval. Although known sequence variants are believed to account for up to 70% of all inherited cases, this number, however, may be an underestimate due to previous evaluation of individuals with a borderline phenotype or limitations to the methodology of genotyping.

The high prevalence of sequence variants in LQTS genes in Iceland may in large part be explained by the p.Val215Met in the *KCNQ*1 founder mutation, but after exclusion of this variant, mutations in these genes are, nevertheless, more common than previously reported, 180 per 100.000 individuals (1:560). However, this information should be interpreted with some caution, not least the genetic epidemiology data that included p.Val215Met, because these findings do not necessarily equate to a diagnosis of LQTS. Geographical variation in prevalence of the QTc prolongation is perhaps to be expected, but with the advent of high-throughput genomic technologies, it is likely that the estimated prevalence will begin to increase.

The p.Val215Met variant has been reported in association with LQTS, but only in a few individuals[31–33] and is reported as a variant of uncertain clinical significance in ClinVar. Functional studies have reported that p.Val215Met alters potassium channel current function and may have a destabilizing effect on the S3 subunit of the *KCNQ1* protein.[34,35] Because of its high frequency in the Icelandic population, this study provides new information about its phenotypic manifestations and clinical significance. The p.Val215Met variant in *KCNQ1* does have a significant effect on the QTc interval (>20 ms) but does not associate with increased rate of serious events such as SCD. It has been reported

that p.Tyr111Cys in *KCNQ1*, a founder variant in the Swedish population, has not been associated with high incidence of life-threatening events showing similarities to p.Val215Met in the Icelandic population.[36,37]

Of note, early-onset SCD was seen in 2 female patients with the p.Val215Met variant suffering from eating disorders and severe hypokalemia at the time of cardiac arrest. It is known that LQTS carriers are more susceptible to LQTS-triggered cardiac events when hypokalemic.[38,39] There are reports that severe hypokalemia may be of critical importance in triggering lethal arrhythmias in a subset of patients with LQTS and a mild phenotype, as described in our p.Val215Met variant cohort.[40] Therefore, we conclude that this variant is unlikely to confer increased risk of SCD in the baseline state but may render the individual more susceptible to serious events under certain clinical circumstances such as electrolyte disturbance and possibly when taking QT-prolonging medications. Thus, the p.Val215VMet variant may be considered more as a risk factor than a pathogenic LQTS variant in the classical sense.

Knowing the effect size of a variant on the QTc is valuable when assessing pathogenicity. In this study, p.Val215Met is a relatively frequent coding variant in *KCNQ1* associating with the QTc interval, and we did not see a large effect on severe events and outcomes. Carriers of the variant have on average ≈20-ms longer QTc interval. If variants' mean effect of an association is below that, it might be viewed as a risk factor rather than being pathogenic for LQTS until additional evidence would imply pathogenicity. The variant is, in our opinion, a genetic risk factor but does not fit well into current classification systems for LQTS that do not acknowledge different risk among pathogenic variants.

In this study, only 1 of the rare coding variants in the *KCNQ1* gene, p.Leu273Phe, was associated with a risk of SCD. p.Leu273Phe causes on average a large prolongation in the QTc interval, and as such supports previous findings that a longer QTc interval predisposes to an elevated risk of SCD.[7] Approximately 60% of carriers had a QTc interval exceeding 460 ms.[41] Just >75% of the carriers of p.Tyr315Cys and 60% of the p.Leu273Phe carriers in our data have a mean QTc interval that exceeds 460 ms. Our results, therefore, do provide insights into high-risk variants that can be useful in the general context outside of Iceland. p.Tyr315Cys has been identified in studies elsewhere, and Mazzanti et al have described the penetrance of a LQTS phenotype in *KCNQ1* p.Tyr315Cys carriers.[41]

The association of a rare variant with prolongation of the QTc interval does not necessarily mean that it is pathogenic for LQTS. However, all of the associating variants in LQTS genes identified in the study, apart from p.Val215Met and p.Trp412Arg, were classified as pathogenic or likely pathogenic for LQTS using American College of Medical Genetics and Genomics guidelines. In addition, they have a large effect on the QTc interval in the population, which supports that they are pathogenic for LQTS.

It has been demonstrated that individuals with sequence variants that carry the highest risk for SCD could benefit most from treatment with β-blockers.[42] However, it has been suggested that those with low-risk variants might only need to observe preventative lifestyle measures, such as avoiding situations that are known to be potential triggers for an arrhythmia, drugs that can prolong the QT interval, and certain clinical circumstances such as hypokalemia.[43] Although international guidelines currently recommend that β-blockers should be considered for everyone with LQTS, regardless of the QTc interval or symptoms, side effects of this therapy are common.

Most Icelanders who carry mutations associated with LQTS are unaware of it. On the other hand, some have been diagnosed clinically with LQTS. Knowledge of LQTS mutation carrier status might be an opportunity for timely intervention to prevent sudden death. Extensive accumulation of data on genetics and other contributors to human diversity form the backbone of precision medicine, which has the goal of providing more efficient and effective care, but also to reduce complications and limit cost from unnecessary or inappropriate treatment.[44] Risk stratification is of considerable importance for individuals with sequence variants associated with QTc prolongation. The phenotypic expression and clinical consequences of the sequence variants found in this study were variable and provide valuable information on the clinical spectrum of sequence variants associated with QTc prolongation in Iceland. The value of knowledge of the genetic make-up of diseases in specific populations is underscored by the findings that the most common QTc prolonging variant in Iceland, p.Val215Met, has been reported elsewhere only on rare occasions. The data also point toward the possibility of basing specific therapeutic recommendations on genotype information in the future.

A limitation of the study is that the classification of rare variants, such as singletons or de novo mutations, as pathogenic can be difficult. Also, when exploring association between rare variants and SCD, there may be insufficient statistical power to detect significant associations. Mutations causing severe LQTS may also be removed quickly from the population through natural selection, and the variants may only be present in the pediatric population, which was outside the scope of this study. When analyzing the QT interval, there were on average 4.9 ECGs available per individuals, and the mean QTc was used in the analysis. This can potentially lead to a bias in effect estimates but will underestimate the effects of pathogenic variants rather than overestimate.

CONCLUSIONS

In summary, the prevalence of sequence variants associated with QTc prolongation in Iceland is higher than previous estimates using ECGs and partial molecular screening only. The most frequent variant, p.Val215Met in *KCNQ1*, a founder mutation, has a less severe phenotype than other variants. Ultimately, extensive knowledge about genotype–phenotype relationship, such as presented here, could lead to improved identification and risk stratification of individuals with QT prolonging variants and potentially a more effective clinical approach.

Affiliations

deCODE Genetics/Amgen, Inc., Reykjavik, Iceland (G.S., K.N., O.B.D., R.B.T., V.T., G.A.A., B.O.J., H.K., R.F., H.G., H.M.A., G.T., A.O., P.S., D.F.G., H.H., D.O.A., K.S.); Internal Medicine, Landspitali–The National University Hospital of Iceland, Reykjavik, Iceland (B.D.B.); Children's Medical Center, Landspítali–The National University Hospital of Iceland, Reykjavík, Iceland (G.S.); The Capital District Fire and Rescue Service, Reykjavik, Iceland (B.F., V.M.); Department of Anesthesia, Landspitali, The National University Hospital of Iceland, Reykjavik, Iceland (V.M.); Faculty of Electrical and Computer Engineering (D.F.G.); Faculty of Medicine, University of Iceland, Reykjavik, Iceland (D.O.A.); and Cardiovascular Center, Landspitali, The National University Hospital of Iceland, Reykjavik, Iceland (D.O.A.).

Disclosures

All authors affiliated with deCODE Genetics/Amgen, Inc. are employed by the company. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S3
Figures S1–S3

REFERENCES

1. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. *Am Heart J*. 1975;89:378–390. doi: 10.1016/0002-8703(75)90089-7
2. Schwartz PJ, Woosley RL. Predicting the unpredictable: drug-induced QT prolongation and torsades de pointes. *J Am Coll Cardiol*. 2016;67:1639–1650. doi: 10.1016/j.jacc.2015.12.063
3. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43:3997–4126. doi: 10.1093/eurheartj/ehac262
4. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932–1963. doi: 10.1016/j.hrthm.2013.05.014
5. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. *Circulation*. 1993;88:782–784. doi: 10.1161/01.cir.88.2.782
6. Hofman N, Tan HL, Alders M, van Langen IM, Wilde AA. Active cascade screening in primary inherited arrhythmia syndromes: does it lead to prophylactic treatment? *J Am Coll Cardiol*. 2010;55:2570–2576. doi: 10.1016/j.jacc.2009.12.063
7. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, et al. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348:1866–1874. doi: 10.1056/NEJMoa022147
8. Goldenberg I, Horr S, Moss AJ, Lopes CM, Barsheshet A, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, et al. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. *J Am Coll Cardiol*. 2011;57:51–59. doi: 10.1016/j.jacc.2010.07.038
9. Adler A, Novelli V, Amin AS, Abiusi E, Care M, Nannenberg EA, Feilotter H, Amenta S, Mazza D, Bikker H, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. *Circulation*. 2020;141:418–428. doi: 10.1161/CIRCULATIONAHA.119.043132
10. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Effect of clinical phenotype on yield of long QT syndrome genetic testing. *J Am Coll Cardiol*. 2006;47:764–768. doi: 10.1016/j.jacc.2005.09.056
11. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, Moss AJ, Schwartz PJ, Towbin JA, Vincent GM, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation*. 2000;102:1178–1185. doi: 10.1161/01.CIR.102.10.1178
12. Hofman N, Tan HL, Alders M, Kolder I, de Haij S, Mannens MM, Lombardi MP, Dit Deprez RH, van Langen I, Wilde AA. Yield of molecular and clinical testing for arrhythmia syndromes: report of 15 years' experience. *Circulation*. 2013;128:1513–1521. doi: 10.1161/CIRCULATIONAHA.112.000091
13. Arking DE, Pulit SL, Crotti L, van der Harst P, Munroe PB, Koopmann TT, Sotoodehnia N, Rossin EJ, Morley M, Wang X, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. *Nat Genet*. 2014;46:826–836. doi: 10.1038/ng.3014
14. Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, et al. Common variants at ten loci influence QT interval duration in the QTGEN study. *Nat Genet*. 2009;41:399–406. doi: 10.1038/ng.364
15. Wilde AAM, Amin AS, Postema PG. Diagnosis, management and therapeutic strategies for congenital long QT syndrome. *Heart*. 2021;108:332–338. doi: 10.1136/heartjnl-2020-318259
16. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. *Circ Arrhythm Electrophysiol*. 2012;5:868–877. doi: 10.1161/CIRCEP.111.962019
17. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, Gabbarini F, Goulene K, Insolia R, Mannarino S, et al. Prevalence of the congenital long-QT syndrome. *Circulation*. 2009;120:1761–1767. doi: 10.1161/CIRCULATIONAHA.109.863209
18. Berge KE, Haugaa KH, Fruh A, Anfinsen OG, Gjesdal K, Siem G, Oyen N, Greve G, Carlsson A, Rognum TO, et al. Molecular genetic analysis of long QT syndrome in Norway indicating a high prevalence of heterozygous mutation carriers. *Scand J Clin Lab Invest*. 2008;68:362–368. doi: 10.1080/00365510701765643
19. Gudbjartsson DF, Helgason H, Gudjonsson SA, Zink F, Oddson A, Gylfason A, Besenbacher S, Magnusson G, Halldorsson BV, Hjartarson E, et al. Large-scale whole-genome sequencing of the Icelandic population. *Nat Genet*. 2015;47:435–444. doi: 10.1038/ng.3247
20. Norland K, Sveinbjornsson G, Thorolfsdottir RB, Davidsson OB, Tragante V, Rajamani S, Helgadottir A, Gretarsdottir S, van Setten J, Asselbergs FW, et al. Sequence variants with large effects on cardiac electrophysiology and disease. *Nat Commun*. 2019;10:4803. doi: 10.1038/s41467-019-12682-9
21. Vandenberk B, Vandael E, Robyns T, Vandenberghe J, Garweg C, Foulon V, Ector J, Willems R. Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc*. 2016;5:5. doi: 10.1161/JAHA.116.003264
22. Giudicessi JR, Ackerman MJ. Genotype- and phenotype-guided management of congenital long QT syndrome. *Curr Probl Cardiol*. 2013;38:417–455. doi: 10.1016/j.cpcardiol.2013.08.001
23. Loh PR, Tucker G, Bulik-Sullivan BK, Vilhjalmsson BJ, Finucane HK, Salem RM, Chasman DI, Ridker PM, Neale BM, Berger B, et al. Efficient

Bayesian mixed-model analysis increases association power in large cohorts. *Nat Genet*. 2015;47:284–290. doi: 10.1038/ng.3190

24. Price AL, Helgason A, Palsson S, Stefansson H, St Clair D, Andreassen OA, Reich D, Kong A, Stefansson K. The impact of divergence time on the nature of population structure: an example from Iceland. *PLoS Genet*. 2009;5:e1000505. doi: 10.1371/journal.pgen.1000505

25. Young WJ, Lahrouchi N, Isaacs A, Duong T, Foco L, Ahmed F, Brody JA, Salman R, Noordam R, Benjamins JW, et al. Genetic analyses of the electrocardiographic QT interval and its components identify additional loci and pathways. *Nat Commun*. 2022;13:5144. doi: 10.1038/s41467-022-32821-z

26. Landrum MJ, Lee JM, Benson M, Brown G, Chao C, Chitipiralla S, Gu B, Hart J, Hoffman D, Hoover J, et al. ClinVar: public archive of interpretations of clinically relevant variants. *Nucleic Acids Res*. 2016;44:D862–D868. doi: 10.1093/nar/gkv1222

27. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424. doi: 10.1038/gim.2015.30

28. GTEx project maps wide range of normal human genetic variation: a unique catalog and follow-up effort associate variation with gene expression across dozens of body tissues. *Am J Med Genet A*. 2018;176:263–264. doi: 10.1002/ajmg.a.38426

29. Adalsteinsdottir B, Teekakirikul P, Maron BJ, Burke MA, Gudbjartsson DF, Holm H, Stefansson K, DePalma SR, Mazaika E, McDonough B, et al. Nationwide study on hypertrophic cardiomyopathy in Iceland: evidence of a MYBPC3 founder mutation. *Circulation*. 2014;130:1158–1167. doi: 10.1161/CIRCULATIONAHA.114.011207

30. Yoshinaga M, Kucho Y, Nishibatake M, Ogata H, Nomura Y. Probability of diagnosing long QT syndrome in children and adolescents according to the criteria of the HRS/EHRA/APHRS expert consensus statement. *Eur Heart J*. 2016;37:2490–2497. doi: 10.1093/eurheartj/ehw072

31. Napolitano C, Priori SG, Schwartz PJ, Bloise R, Ronchetti E, Nastoli J, Bottelli G, Cerrone M, Leonardi S. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA*. 2005;294:2975–2980. doi: 10.1001/jama.294.23.2975

32. Kapplinger JD, Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Pollevick GD, Wilde AA, Ackerman MJ. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION long QT syndrome genetic test. *Heart Rhythm*. 2009;6:1297–1303. doi: 10.1016/j.hrthm.2009.05.021

33. Stattin EL, Bostrom IM, Winbo A, Cederquist K, Jonasson J, Jonsson BA, Diamant UB, Jensen SM, Rydberg A, Norberg A. Founder mutations characterise the mutation panorama in 200 Swedish index cases referred for long QT syndrome genetic testing. *BMC Cardiovasc Disord*. 2012;12:95. doi: 10.1186/1471-2261-12-95

34. Eldstrom J, Xu H, Werry D, Kang C, Loewen ME, Degenhardt A, Sanatani S, Tibbits GF, Sanders C, Fedida D. Mechanistic basis for LQT1 caused by S3 mutations in the KCNQ1 subunit of IKs. *J Gen Physiol*. 2010;135:433–448. doi: 10.1085/jgp.200910351

35. Liin SI, Larsson JE, Barro-Soria R, Bentzen BH, Larsson HP. Fatty acid analogue N-arachidonoyl taurine restores function of IKs channels with diverse long QT mutations. *Elife*. 2016;5:5. doi: 10.7554/eLife.20272

36. Winbo A, Diamant UB, Rydberg A, Persson J, Jensen SM, Stattin EL. Origin of the Swedish long QT syndrome Y111C/KCNQ1 founder mutation. *Heart Rhythm*. 2011;8:541–547. doi: 10.1016/j.hrthm.2010.11.043

37. Winbo A, Diamant UB, Stattin EL, Jensen SM, Rydberg A. Low incidence of sudden cardiac death in a Swedish Y111C type 1 long-QT syndrome population. *Circ Cardiovasc Genet*. 2009;2:558–564. doi: 10.1161/CIRCGENETICS.108.825547

38. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon V. Risk factors for QTc-prolongation: systematic review of the evidence. *Int J Clin Pharm*. 2017;39:16–25. doi: 10.1007/s11096-016-0414-2

39. Kapoor JR. Inherited long QT syndromes: be mindful of the potassium level. *J Am Coll Cardiol*. 2008;52:1605; author reply 1605-1606. doi: 10.1016/j.jacc.2008.07.053

40. Imai M, Nakajima T, Kaneko Y, Niwamae N, Irie T, Ota M, Iijima T, Tange S, Kurabayashi M. Novel KCNQ1 splicing mutation in patients with forme fruste LQT1 aggravated by hypokalemia. *J Cardiol*. 2014;64:121–126. doi: 10.1016/j.jjcc.2013.11.014

41. Mazzanti A, Maragna R, Vacanti G, Monteforte N, Bloise R, Marino M, Braghieri L, Gambelli P, Memmi M, Pagan E, et al. Interplay between genetic substrate, QTc duration, and arrhythmia risk in patients with long QT syndrome. *J Am Coll Cardiol*. 2018;71:1663–1671. doi: 10.1016/j.jacc.2018.01.078

42. Barsheshet A, Goldenberg I, O-Uchi J, Moss AJ, Jons C, Shimizu W, Wilde AA, McNitt S, Peterson DR, Zareba W, et al. Mutations in cytoplasmic loops of the KCNQ1 channel and the risk of life-threatening events: implications for mutation-specific response to beta-blocker therapy in type 1 long-QT syndrome. *Circulation*. 2012;125:1988–1996. doi: 10.1161/CIRCULATIONAHA.111.048041

43. MacIntyre CJ, Rohatgi RK, Sugrue AM, Bos JM, Ackerman MJ. Intentional nontherapy in long QT syndrome. *Heart Rhythm*. 2020;17:1147–1150. doi: 10.1016/j.hrthm.2020.02.017

44. Arnar DO, Palsson R. Precision medicine and advancing clinical care: insights from Iceland. *JAMA Intern Med*. 2019;179:139–140. doi: 10.1001/jamainternmed.2018.6729

SUPPLEMENTAL MATERIAL

Table S1. Study characteristics

	N ECGs	N indivduals	Mean N ECGs per individual (SD)	Mean of individual mean QTc (SD)	Mean YOB	% Females	% Individuals with mean ECG QTc > 460ms	% Individuals mean ECG QTc > 500ms
dHS	16534	16534	NA	419.2 (22.4)	1964	56%	3.7%	0.5%
LSH	432841	89331	4.9 (7.2)	413.3 (25.9)	1952	49%	4.4%	0.5%

Table S2. Associations of 94 coding variants with the QTc interval and overlap with Clinvar

Chr	Pos	P-value	Effect (SD)	Effect (ms)	Name	CI lower (ms)	CI upper (ms)	Rs #	MAF %	Info	Effect allele	other allele	gene	consequence	coding effect	Clinvar REF	Clinvar ALT	Clinvar Name	Clinvar clinical significance
chr11	2571363	1.4E-44	0.904	22.8712	chr11:2571363:SG	19.67	26.07	rs17215479	0.178	0.99777	A	G	KCNQ1	missense_variant	NP_000209.2:p.Val215Met,NP_861463.1:p.Val88Met	G	A	NM_181798.1(KCNQ1): c.262G>A (p.Val88Met)	Uncertain_significance
chr11	2572882	1.2E-39	1.698	42.9594	chr11:2572882:SG	36.57	49.35	rs120074180	0.037	0.98308	T	C	KCNQ1	missense_variant	NP_000209.2:p.Leu273Phe,NP_861463.1:p.Leu146Phe	C	T	NM_181798.1(KCNQ1): c.436C>T (p.Leu146Phe)	Pathogenic
chr11	2583457	3.3E-28	2.241	56.6973	chr11:2583457:SG	46.61	66.79	rs74462309	0.015	0.99996	G	A	KCNQ1	missense_variant	NP_000209.2:p.Tyr315Cys,NP_861463.1:p.Tyr188Cys	A	G	NM_181798.1(KCNQ1): c.563A>G (p.Tyr188Cys)	Pathogenic/Likely_pathogenic
chr11	2778023	8E-09	1.262	31.9286	chr11:2778023:SG	21.08	42.78	rs794728537	0.024	0.99363	T	C	KCNQ1	stop_gained	NP_000209.2:p.Arg594Ter,NP_861463.1:p.Arg467Ter	C	T	NM_181798.1(KCNQ1): c.1399C>T (p.Arg467Ter)	Pathogenic
chr7	150947670	0.00026	1.216	30.7648	chr7:150947670:IG	14.24	47.29	rs786204101	0.006	0.95026	CG	C	KCNH2	frameshift_variant	NP_000229.1:p.Pro968AlafsTer151,NP_742054.1:p.Pro628AlafsTer151	CG	C	NM_172057.2(KCNH2): c.1880dup (p.Pro628fs)	Pathogenic
chr11	2572852	0.0003	1.502	38.0006	chr11:2572852:IG	17.39	58.62	.	0.004	0.9647	A	AT	KCNQ1	frameshift_variant	NP_000209.2:p.Ile263LysfsTer26,NP_861463.1:p.Ile136LysfsTer26				
chr7	150952748	0.00031	1.975	49.9675	chr7:150952748:SG	22.84	77.09	.	0.002	0.97976	G	A	KCNH2	missense_variant	NP_000229.1:p.Trp412Arg,NP_001191727.1:p.Trp72Arg,NP_742053.1:p.Trp412Arg,NP_742054.1:p.Trp72Arg				
chr7	150974821	0.00033	2.203	55.7359	chr7:150974821:SG	25.31	86.16	.	0.001	0.99051	G	C	KCNH2	missense_variant	NP_000229.1:p.Cys66Ser,NP_742053.1:p.Cys66Ser				
chr11	2585297	0.00624	1.152	29.1456	chr11:2585297:SG	8.26	50.03	.	0.008	0.94312	A	C	KCNQ1	stop_gained	NP_000209.2:p.Ser373Ter,NP_861463.1:p.Ser246Ter				
chr7	150959602	0.01583	0.194	4.9082	chr7:150959602:SG	0.92	8.9	rs139544114	0.123	0.99613	A	G	KCNH2	missense_variant	NP_000229.1:p.Arg148Trp,NP_742053.1:p.Arg148Trp	G	A	NM_000238.4(KCNH2): c.442C>T (p.Arg148Trp)	Conflicting_interpretations_of_pathogenicity
chr11	2445168	0.03427	0.36	9.108	chr11:2445168:SG	0.68	17.54	rs990778345	0.027	0.99148	T	C	KCNQ1	missense_variant	NP_000209.2:p.Arg24Trp	C	T	NM_000218.3(KCNQ1): c.70C>T (p.Arg24Trp)	Uncertain_significance
chr3	38554306	0.05211	-1.258	-31.8274	chr3:38554306:SG	-63.95	0.29	rs199473278	0.001	1	T	A	SCN5A	missense_variant	NP_000326.2:p.Phe1595Ile,NP_001092874.1:p.Phe1596Ile,NP_001092875.1:p.Phe1578Ile,NP_001153633.1:p.Phe1542Ile,NP_001341630.1:p.Phe1577Ile,NP_932173.1:p.Phe1596Ile	T	A	NM_000335.5(SCN5A): c.4783T>A (p.Phe1595Ile)	Uncertain_significance
chr11	2587630	0.06288	1.047	26.4891	chr11:2587630:SG	-1.42	54.4	rs199472776	0.005	0.99396	T	C	KCNQ1	missense_variant	NP_000209.2:p.Arg397Trp,NP_861463.1:p.Arg270Trp	C	T	NM_181798.1(KCNQ1): c.808C>T (p.Arg270Trp)	Conflicting_interpretations_of_pathogenicity
chr3	38562443	0.07183	0.922	23.3266	chr3:38562443:SG	-2.07	48.72	.	0.003	0.94132	G	C	SCN5A	missense_variant	NP_000326.2:p.Arg1311Thr,NP_001092874.1:p.Arg1312Thr,NP_001092875.1:p.Arg1312Thr,NP_001153632.1:p.Arg1311Thr,NP_001153633.1:p.Arg1258Thr,NP_001341630.1:p.Arg1311Thr,NP_932173.1:p.Arg1312Thr				
chr7	150947864	0.07437	0.152	3.8456	chr7:150947864:SG	-0.38	8.07	rs199473669	0.097	0.99848	T	C	KCNH2	missense_variant	NP_000229.1:p.Gly903Arg,NP_742054.1:p.Gly563Arg	C	T	NM_000238.4(KCNH2): c.2707G>A (p.Gly903Arg)	Uncertain_significance
chr3	38603887	0.09303	0.131	3.3143	chr3:38603887:SG	-0.55	7.18	rs36210423	0.124	0.99578	T	G	SCN5A	missense_variant	NP_000326.2:p.Ala572Asp,NP_001092874.1:p.Ala572Asp,NP_001092875.1:p.Ala572Asp,NP_001153632.1:p.Ala572Asp,NP_001153633.1:p.Ala572Asp,NP_001341630.1:p.Ala572Asp,NP_932173.1:p.Ala572Asp	T	G	NM_000335.5(SCN5A): c.1715C>A (p.Ala572Asp)	Benign/Likely_benign
chr11	2445150	0.09348	0.088	2.2264	chr11:2445150:SG	-0.38	4.83	.	0.248	0.99626	T	G	KCNQ1	missense_variant	NP_000209.2:p.Gly18Cys				
chr3	38633205	0.1188	0.128	3.2384	chr3:38633205:SG	-0.83	7.31	rs199473552	0.111	0.99623	T	C	SCN5A	missense_variant	NP_000326.2:p.Gly35Ser,NP_001092874.1:p.Gly35Ser,NP_001092875.1:p.Gly35Ser,NP_001153632.1:p.Gly35Ser,NP_001153633.1:p.Gly35Ser,NP_001341630.1:p.Gly35Ser,NP_932173.1:p.Gly35Ser	T	C	NM_198056.2(SCN5A): c.103G>A (p.Gly35Ser)	Conflicting_interpretations_of_pathogenicity
chr7	150948477	0.11945	-0.359	-9.0827	chr7:150948477:SG	-20.52	2.35	rs140279503	0.009	0.99362	A	!	KCNH2	missense_variant	NP_000229.1:p.Arg887Cys,NP_742054.1:p.Arg547Cys	A		NM_000238.3(KCNH2): c.2659C>T (p.Arg887Cys)	Uncertain_significance
chr11	2847803	0.12432	0.723	18.2919	chr11:2847803:SG	-5.04	41.62	rs147445322	0.003	0.9902	A	G	KCNQ1	missense_variant	NP_000209.2:p.Asp611Asn,NP_861463.1:p.Asp484Asn	G	A	NM_181798.1(KCNQ1): c.1450G>A (p.Asp484Asn)	Conflicting_interpretations_of_pathogenicity
chr3	38586037	0.12832	0.428	10.8284	chr3:38586037:SG	-3.13	24.78	rs199473584	0.008	0.95448	T	C	SCN5A	missense_variant	NP_000326.2:p.Arg814Gln,NP_001092874.1:p.Arg814Gln,NP_001092875.1:p.Arg814Gln,NP_001153632.1:p.Arg814Gln,NP_001153633.1:p.Arg814Gln,NP_001341630.1:p.Arg814Gln,NP_932173.1:p.Arg814Gln	C	T	NM_000335.5(SCN5A): c.2441G>A (p.Arg814Gln)	Conflicting_interpretations_of_pathogenicity
chr3	38620877	0.13528	1.64	41.492	chr3:38620877:SG	-12.96	95.94	rs1288302782	0	1	G	A	SCN5A	missense_variant	NP_000326.2:p.Trp193Arg,NP_001092874.1:p.Trp193Arg,NP_001092875.1:p.Trp193Arg,NP_001153632.1:p.Trp193Arg,NP_001153633.1:p.Trp193Arg,NP_001341630.1:p.Trp193Arg,NP_932173.1:p.Trp193Arg				
chr3	38551477	0.13625	1.359	34.3827	chr3:38551477:SG	-10.85	79.61	rs199473286	0.003	0.95068	T	C	SCN5A	missense_variant	NP_000326.2:p.Arg1631His,NP_001092874.1:p.Arg1632His,NP_001092875.1:p.Arg1614His,NP_001153632.1:p.Arg1599His,NP_001153633.1:p.Arg1578His,NP_001341630.1:p.Arg1613His,NP_932173.1:p.Arg1632His	T	C	NM_198056.2(SCN5A): c.4895G>A (p.Arg1632His)	Conflicting_interpretations_of_pathogenicity
chr7	150952678	0.15915	0.535	13.5355	chr7:150952678:SG	-5.31	32.38	rs759305745	0.003	0.97463	C	T	KCNH2	missense_variant	NP_000229.1:p.Glu435Gly,NP_001191727.1:p.Glu95Gly,NP_742053.1:p.Glu435Gly,NP_742054.1:p.Glu95Gly				
chr3	38604031	0.18536	-0.819	-20.7207	chr3:38604031:SG	-51.38	9.94	rs41313691	0.003	1	T	G	SCN5A	missense_variant	NP_000326.2:p.Ser524Tyr,NP_001092874.1:p.Ser524Tyr,NP_001092875.1:p.Ser524Tyr,NP_001153632.1:p.Ser524Tyr,NP_001153633.1:p.Ser524Tyr,NP_001341630.1:p.Ser524Tyr,NP_932173.1:p.Ser524Tyr	T	G	NM_000335.5(SCN5A): c.1571C>A (p.Ser524Tyr)	Benign/Likely_benign

chr	pos				locus			rsID			ref	alt	gene	consequence	protein	a1	a2	cDNA	clinical
chr3	38613799	0.19381	-1.426	-36.0778	chr3:38613799:SG	-90.5	18.34	rs41276525	0.001	0.99801	A	G	SCN5A	missense_variant	NP_000326.2:p.Ser216Leu,NP_932173.1:p.Ser216Leu	G	A	NM_000335.5(SCN5A): c.647C>T (p.Ser216Leu)	Conflicting_interpretations_of_pathogenicity
chr7	150957497	0.19527	-0.429	-10.8537	chr7:150957497:SG	-27.28	5.57	rs1393487302	0.004	1	C	T	KCNH2	missense_variant	NP_000229.1:p.Met308Val,NP_742053.1:p.Met308Val				
chr7	150951602	0.22161	0.963	24.3639	chr7:150951602:SG	-14.71	63.43	rs1439981248	0.001	0.92722	T	G	KCNH2	stop_gained	NP_000229.1:p.Tyr597Ter,NP_001191727.1:p.Tyr257Ter,NP_742053.1:p.Tyr597Ter,NP_742054.1:p.Tyr257Ter				
chr3	38550895	0.22987	-0.201	-5.0853	chr3:38550895:SG	-13.39	3.22	rs137854610	0.028	0.98861	T	C	SCN5A	missense_variant	NP_000326.2:p.Arg1825His,NP_001092874.1:p.Arg1826His,NP_001092875.1:p.Arg1808His,NP_001153632.1:p.Arg1793His,NP_001153633.1:p.Arg1772His,NP_001341630.1:p.Arg1807His,NP_932173.1:p.Arg1826His	T	C	NM_000335.5(SCN5A): c.5474G>A (p.Arg1825His)	Uncertain_significance
chr3	38566414	0.23346	0.39	9.867	chr3:38566414:SG	-6.36	26.1	rs199473341	0.009	0.99607	T	C	SCN5A	missense_variant	NP_000326.2:p.Val1278Ile,NP_001092874.1:p.Val1279Ile,NP_001092875.1:p.Val1279Ile,NP_001153632.1:p.Val1278Ile,NP_001153633.1:p.Val1225Ile,NP_001341630.1:p.Val1278Ile,NP_932173.1:p.Val1279Ile	C	T	NM_000335.4(SCN5A): c.3832G>A (p.Val1278Ile)	Uncertain_significance
chr3	38579473	0.23996	-0.607	-15.3571	chr3:38579473:SG	-40.97	10.26	rs1370492279	0.005	0.95983	T	C	SCN5A	missense_variant	NP_000326.2:p.Gly1083Asp,NP_001092874.1:p.Gly1084Asp,NP_001092875.1:p.Gly1084Asp,NP_001153632.1:p.Gly1083Asp,NP_001341630.1:p.Gly1083Asp,NP_932173.1:p.Gly1084Asp				
chr7	150958110	0.25285	-0.723	-18.2919	chr7:150958110:SG	-49.65	13.06	rs199472880	0.001	0.97725	T	C	KCNH2	missense_variant	NP_000229.1:p.Glu289Lys,NP_742053.1:p.Glu289Lys	C	T	NM_172056.2(KCNH2): c.865G>A (p.Glu289Lys)	Uncertain_significance
chr3	38581170	0.25297	0.61	15.433	chr3:38581170:SG	-11.03	41.89	rs137854609	0.002	0.88998	T	C	SCN5A	missense_variant	NP_000326.2:p.Ala997Thr,NP_001092874.1:p.Ala997Thr,NP_001092875.1:p.Ala997Thr,NP_001153632.1:p.Ala997Thr,NP_001153633.1:p.Ala997Thr,NP_001341630.1:p.Ala997Thr,NP_932173.1:p.Ala997Thr	T	C	NM_000335.5(SCN5A): c.2989G>A (p.Ala997Thr)	Conflicting_interpretations_of_pathogenicity
chr3	38550569	0.26279	-0.462	-11.6886	chr3:38550569:SG	-32.15	8.77	rs199473637	0.003	0.96336	T	C	SCN5A	missense_variant	NP_000326.2:p.Gly1934Ser,NP_001092874.1:p.Gly1935Ser,NP_001092875.1:p.Gly1917Ser,NP_001153632.1:p.Gly1902Ser,NP_001153633.1:p.Gly1881Ser,NP_001341630.1:p.Gly1916Ser,NP_932173.1:p.Gly1935Ser	T	C	NM_198056.2(SCN5A): c.5803G>A (p.Gly1935Ser)	Uncertain_significance
chr3	38597728	0.27022	0.215	5.4395	chr3:38597728:SG	-4.23	15.11	rs772841571	0.025	0.99955	T	C	SCN5A	splice_donor_variant	NM_000335.5:c.2262+1G>A,NM_001099404.1:c.2262+1G>A,NM_001099405.1:c.2262+1G>A,NM_001160160.2:c.2262+1G>A,NM_001160161.1:c.2262+1G>A,NM_001354701.2:c.2262+1G>A,NM_198056.2:c.2262+1G>A				
chr7	150947797	0.27447	-0.395	-9.9935	chr7:150947797:IG	-27.92	7.93	.	0.005	0.92437	C	CCCCCC	KCNH2	inframe_deletion	NP_000229.1:p.Ala915_Gly924del,NP_742054.1:p.Ala575_Gly584del	CCCCCC	C	NM_000238(KCNH2): c.2744_2773del (p.Ala915_Gly924del)	Uncertain_significance
chr3	38614031	0.28871	0.179	4.5287	chr3:38614031:SG	-3.84	12.89	rs201002736	0.024	0.99961	A	G	SCN5A	missense_variant	NP_001092874.1:p.Ser216Leu,NP_001092875.1:p.Ser216Leu,NP_001153632.1:p.Ser216Leu,NP_001153633.1:p.Ser216Leu,NP_001341630.1:p.Ser216Leu	G	A	NM_000335.5(SCN5A): c.612-197C>T	Benign/Likely_benign
chr7	150947761	0.28954	0.673	17.0269	chr7:150947761:SG	-14.48	48.54	rs199473540	0.002	0.99719	T	C	KCNH2	missense_variant	NP_000229.1:p.Ser937Asn,NP_742054.1:p.Ser597Asn	C	T	NM_000238.4(KCNH2): c.2810G>A (p.Ser937Asn)	Uncertain_significance
chr7	150947371	0.29792	0.804	20.3412	chr7:150947371:SG	-17.96	58.64	rs199473023	0.001	0.93181	T	C	KCNH2	missense_variant	NP_000229.1:p.Asp1037Asn,NP_742054.1:p.Asp697Asn	C	T	NM_000238.4(KCNH2): c.3109G>A (p.Asp1037Asn)	Uncertain_significance
chr7	150950077	0.30661	-0.201	-5.0853	chr7:150950077:SG	-14.83	4.66	rs1457616755	0.019	0.99998	T	C	KCNH2	stop_gained	NP_001191727.1:p.Trp490Ter,NP_742053.1:p.Trp830Ter				
chr7	150947623	0.32365	-0.285	-7.2105	chr7:150947623:SG	-21.53	7.11	rs149955375	0.012	0.97348	A	G	KCNH2	missense_variant	NP_000229.1:p.Thr983Ile,NP_742054.1:p.Thr643Ile	G	A	NM_000238.4(KCNH2): c.2948C>T (p.Thr983Ile)	Conflicting_interpretations_of_pathogenicity
chr3	38562471	0.32546	-0.414	-10.4742	chr3:38562471:SG	-31.35	10.4	rs200334972	0.003	0.83813	A	G	SCN5A	missense_variant	NP_000326.2:p.Arg1302Trp,NP_001092874.1:p.Arg1303Trp,NP_001092875.1:p.Arg1303Trp,NP_001153632.1:p.Arg1302Trp,NP_001153633.1:p.Arg1249Trp,NP_001341630.1:p.Arg1302Trp,NP_932173.1:p.Arg1303Trp				
chr7	150952652	0.32879	0.087	2.2011	chr7:150952652:SG	-2.22	6.62	rs201268831	0.09	0.99182	T	C	KCNH2	missense_variant	NP_000229.1:p.Glu444Lys,NP_001191727.1:p.Glu104Lys,NP_742053.1:p.Glu444Lys,NP_742054.1:p.Glu104Lys	C	T	NM_172056.2(KCNH2): c.1330G>A (p.Glu444Lys)	Uncertain_significance
chr3	38560330	0.3406	0.624	15.7872	chr3:38560330:SG	-16.68	48.26	.	0.002	0.9379	T	G	SCN5A	missense_variant	NP_000326.2:p.Asn1353Lys,NP_001092874.1:p.Asn1354Lys,NP_001092875.1:p.Asn1354Lys,NP_001153632.1:p.Asn1353Lys,NP_001153633.1:p.Asn1300Lys,NP_001341630.1:p.Asn1353Lys,NP_932173.1:p.Asn1354Lys				
chr7	150945441	0.34735	0.62	15.686	chr7:150945441:SG	-17.03	48.4	rs199473547	0.002	0.90062	T	C	KCNH2	missense_variant	NP_000229.1:p.Arg1135His,NP_742054.1:p.Arg795His	T	C	NM_000238.3(KCNH2): c.3404G>A (p.Arg1135His)	not_provided
chr11	2570719	0.3544	1.015	25.6795	chr11:2570719:SG	-28.67	80.03	rs120074178	0.001	0.93864	T	G	KCNQ1	missense_variant	NP_000209.2:p.Arg190Leu,NP_861463.1:p.Arg63Leu			NM_181798.1(KCNQ1): c.188G>T (p.Arg63Leu)	Pathogenic/Likely_pathogenic
chr11	2527989	0.37507	0.182	4.6046	chr11:2527989:SG	-5.57	14.78	rs794728577	0.021	0.9929	A	G	KCNQ1	missense_variant	NP_000209.2:p.Ala150Thr,NP_861463.1:p.Ala23Thr	G	A	NM_181798.1(KCNQ1): c.67G>A (p.Ala23Thr)	Uncertain_significance
chr7	150947833	0.38751	0.158	3.9974	chr7:150947833:SG	-5.07	13.06	rs77331749	0.023	0.99393	A	G	KCNH2	missense_variant	NP_000229.1:p.Ala913Val,NP_742054.1:p.Ala573Val	G	A	NM_000238.4(KCNH2): c.2738C>T (p.Ala913Val)	Conflicting_interpretations_of_pathogenicity

chr	pos				variant			rsid			ref	alt	gene	consequence	protein	a1	a2	transcript	classification
chr3	38597917	0.40893	0.644	16.2932	chr3:38597917:SG	-22.38	54.97	rs45553235	0.001	1	T	G	SCN5A	missense_variant	NP_000326.2:p.Gln692Lys,NP_001092874.1:p.Gln692Lys,NP_001092875.1:p.Gln692Lys,NP_001153632.1:p.Gln692Lys,NP_001153633.1:p.Gln692Lys,NP_001341630.1:p.Gln692Lys,NP_932173.1:p.Gln692Lys	G	T	NM_000335.5(SCN5A): c.2074C>A (p.Gln692Lys)	Conflicting_interpretations_of_pathogenicity
chr11	2445315	0.4208	0.882	22.3146	chr11:2445315:SG	-32.01	76.64	rs199472676	0.002	0.99983	A	C	KCNQ1	missense_variant	NP_000209.2:p.Pro73Thr	C	A	NM_000218.2(KCNQ1): c.217C>A (p.Pro73Thr)	Uncertain_significance
chr3	38566522	0.44104	0.372	9.4116	chr3:38566522:SG	-14.53	33.35	rs199473599	0.002	0.83251	T	C	SCN5A	missense_variant	NP_000326.2:p.Asp1242Asn,NP_001092874.1:p.Asp1243Asn,NP_001092875.1:p.Asp1243Asn,NP_001153632.1:p.Asp1242Asn,NP_001153633.1:p.Asp1189Asn,NP_001341630.1:p.Asp1242Asn,NP_932173.1:p.Asp1243Asn	T	C	NM_000335.5(SCN5A): c.3724G>A (p.Asp1242Asn)	Conflicting_interpretations_of_pathogenicity
chr7	150948477	0.4444	0.538	13.6114	chr7:150948477:SG	-21.27	48.49	rs140279503	0.001	0.82609	C	!	KCNH2	missense_variant	NP_000229.1:p.Arg887Gly,NP_742054.1:p.Arg547Gly	C	G	NM_000238.4(KCNH2): c.2659C>G (p.Arg887Gly)	Uncertain_significance
chr11	2847958	0.45039	0.113	2.8589	chr11:2847958:SG:	-4.57	10.28	rs11601907	0.028	0.99913	G	!	KCNQ1	stop_gained	NP_000209.2:p.Tyr662Ter,NP_861463.1:p.Tyr535Ter	C	G	NM_000218.3(KCNQ1): c.1986C>G (p.Tyr662Ter)	Conflicting_interpretations_of_pathogenicity
chr7	150952442	0.45634	-0.389	-9.8417	chr7:150952442:SG	-35.74	16.05	rs555734087	0.003	0.99934	T	C	KCNH2	missense_variant	NP_000229.1:p.Gly514Ser,NP_001191727.1:p.Gly174Ser,NP_742053.1:p.Gly514Ser,NP_742054.1:p.Gly174Ser				
chr3	38587500	0.46222	-0.22	-5.566	chr3:38587500:SG	-20.4	9.27	.	0.007	0.97472	G	T	SCN5A	missense_variant	NP_000326.2:p.Gln779Pro,NP_001092874.1:p.Gln779Pro,NP_001092875.1:p.Gln779Pro,NP_001153632.1:p.Gln779Pro,NP_001153633.1:p.Gln779Pro,NP_001341630.1:p.Gln779Pro,NP_932173.1:p.Gln779Pro				
chr11	2588797	0.46752	0.337	8.5261	chr11:2588797:SG	-14.48	31.53	rs149089817	0.003	0.84154	A	G	KCNQ1	missense_variant	NP_000209.2:p.Asp446Asn,NP_861463.1:p.Asp319Asn	A	G	NM_181798.1(KCNQ1): c.955G>A (p.Asp319Asn)	Conflicting_interpretations_of_pathogenicity
chr3	38633208	0.48135	-0.355	-8.9815	chr3:38633208:SG	-33.98	16.02	rs6791924	0.007	1	A	G	SCN5A	missense_variant	NP_000326.2:p.Arg34Cys,NP_001092874.1:p.Arg34Cys,NP_001092875.1:p.Arg34Cys,NP_001153632.1:p.Arg34Cys,NP_001153633.1:p.Arg34Cys,NP_001341630.1:p.Arg34Cys,NP_932173.1:p.Arg34Cys	G	A	NM_000335.5(SCN5A): c.100C>T (p.Arg34Cys)	Benign/Likely_benign
chr3	38550634	0.49842	0.055	1.3915	chr3:38550634:SG	-2.64	5.42	rs199473327	0.124	0.99903	T	C	SCN5A	missense_variant	NP_000326.2:p.Arg1912His,NP_001092874.1:p.Arg1913His,NP_001092875.1:p.Arg1895His,NP_001153632.1:p.Arg1880His,NP_001153633.1:p.Arg1859His,NP_001341630.1:p.Arg1894His,NP_932173.1:p.Arg1913His	G	T	NM_198056.2(SCN5A): c.5738G>A (p.Arg1913His)	Uncertain_significance
chr3	38614041	0.51077	-0.055	-1.3915	chr3:38614041:SG	-5.54	2.76	rs748294482	0.1	0.99748	T	C	SCN5A	missense_variant	NP_001092874.1:p.Gly213Ser,NP_001092875.1:p.Gly213Ser,NP_001153632.1:p.Gly213Ser,NP_001153633.1:p.Gly213Ser,NP_001341630.1:p.Gly213Ser	C	T	NM_198056.2(SCN5A): c.612-207G>A	Uncertain_significance
chr7	150950938	0.55044	0.462	11.6886	chr7:150950938:SG	-26.68	50.06	.	0.001	0.99277	T	C	KCNH2	missense_variant	NP_000229.1:p.Gly710Ser,NP_001191727.1:p.Gly370Ser,NP_742053.1:p.Gly710Ser,NP_742054.1:p.Gly370Ser	T	A	NM_172056.2(KCNH2): c.2128G>A (p.Gly710Ser)	Uncertain_significance
chr7	150951772	0.55679	0.206	5.2118	chr7:150951772:SG	-12.17	22.6	rs764666519	0.006	0.96129	A	G	KCNH2	missense_variant	NP_000229.1:p.Arg541Cys,NP_001191727.1:p.Arg201Cys,NP_742053.1:p.Arg541Cys,NP_742054.1:p.Arg201Cys	A	T	NM_000238.4(KCNH2): c.1621C>T (p.Arg541Cys)	Uncertain_significance
chr7	150957380	0.5759	-0.614	-15.5342	chr7:150957380:SG	-69.96	38.9	rs138776684	0.001	1	A	G	KCNH2	missense_variant	NP_000229.1:p.Pro347Ser,NP_742053.1:p.Pro347Ser	A	G	NM_000238.4(KCNH2): c.1039C>T (p.Pro347Ser)	Conflicting_interpretations_of_pathogenicity
chr11	2587620	0.57712	-0.413	-10.4489	chr11:2587620:SG	-47.18	26.28	rs12720457	0.002	0.9912	T	G	KCNQ1	missense_variant	NP_000209.2:p.Lys393Asn,NP_861463.1:p.Lys266Asn	T	G	NM_000218.3(KCNQ1): c.1179G>T (p.Lys393Asn)	Conflicting_interpretations_of_pathogenicity
chr11	2588804	0.59165	-0.069	-1.7457	chr11:2588804:SG	-8.12	4.63	rs12720449	0.041	0.99476	G	A	KCNQ1	missense_variant	NP_000209.2:p.Pro448Arg,NP_861463.1:p.Pro321Arg	C	G	NM_000218.3(KCNQ1): c.1343C>G (p.Pro448Arg)	Benign/Likely_benign
chr3	38562467	0.61547	-0.078	-1.9734	chr3:38562467:SG	-9.67	5.73	rs199473603	0.035	0.99742	G	A	SCN5A	missense_variant	NP_000326.2:p.Thr1303Met,NP_001092874.1:p.Thr1304Met,NP_001092875.1:p.Thr1304Met,NP_001153632.1:p.Thr1303Met,NP_001153633.1:p.Thr1250Met,NP_001341630.1:p.Thr1303Met,NP_932173.1:p.Thr1304Met	C	T	NM_000335.5(SCN5A): c.3908C>T (p.Thr1303Met)	Conflicting_interpretations_of_pathogenicity
chr3	38581266	0.62401	0.399	10.0947	chr3:38581266:SG	-30.27	50.46	rs199473180	0.002	1	A	G	SCN5A	missense_variant	NP_000326.2:p.Arg965Cys,NP_001092874.1:p.Arg965Cys,NP_001092875.1:p.Arg965Cys,NP_001153632.1:p.Arg965Cys,NP_001153633.1:p.Arg965Cys,NP_001341630.1:p.Arg965Cys,NP_932173.1:p.Arg965Cys	G	A	NM_198056.2(SCN5A): c.2893C>T (p.Arg965Cys)	Conflicting_interpretations_of_pathogenicity
chr7	150952642	0.64277	-0.508	-12.8524	chr7:150952642:SG	-67.16	41.46	.	0.001	0.97766	C	T	KCNH2	missense_variant	NP_000229.1:p.Tyr447Cys,NP_001191727.1:p.Tyr107Cys,NP_742053.1:p.Tyr447Cys,NP_742054.1:p.Tyr107Cys				
chr3	38554303	0.67582	0.265	6.7045	chr3:38554303:SG	-24.72	38.13	rs199473279	0.003	0.99964	T	C	SCN5A	missense_variant	NP_000326.2:p.Val1596Met,NP_001092874.1:p.Val1597Met,NP_001092875.1:p.Val1579Met,NP_001153633.1:p.Val1543Met,NP_001341630.1:p.Val1578Met,NP_932173.1:p.Val1597Met	C	T	NM_001160160.2(SCN5A):c.4714+72G>A	Uncertain_significance
chr7	150947789	0.67797	-0.222	-5.6166	chr7:150947789:SG	-32.13	20.89	.	0.003	0.95237	G	C	KCNH2	missense_variant	NP_000229.1:p.Gly928Arg,NP_742054.1:p.Gly588Arg				
chr3	38550629	0.68302	0.04	1.012	chr3:38550629:SG	-3.85	5.87	rs762462124	0.087	0.99849	A	G	SCN5A	missense_variant	NP_000326.2:p.His1914Tyr,NP_001092874.1:p.His1915Tyr,NP_001092875.1:p.His1897Tyr,NP_001153632.1:p.His1882Tyr,NP_001153633.1:p.His1861Tyr,NP_001341630.1:p.His1896Tyr,NP_932173.1:p.His1915Tyr	C	A	NM_000335.5(SCN5A): c.5740C>T (p.His1914Tyr)	Uncertain_significance

chr	pos				variant			rsID			ref	alt	gene	consequence	protein (NP)			HGVS (NM)	ClinVar
chr3	38576782	0.69228	0.235	5.9455	chr3:38576782:SG	-23.5	35.39	.	0.003	0.92384	G	C	SCN5A	splice_acceptor_variant	NM_000335.5:c.3388-1G>C,NM_001099404.1:c.3391-1G>C,NM_001099405.1:c.3391-1G>C,NM_001160160.2:c.3388-1G>C,NM_001160161.1:c.3229-1G>C,NM_001354701.2:c.3388-1G>C,NM_198056.2:c.3391-1G>C				
chr7	150949934	0.70341	0.083	2.0999	chr7:150949934:SG	-8.71	12.91	rs370393086	0.02	0.9925	A	G	KCNH2	missense_variant	NP_001191727.1:p.Arg538Cys, NP_742053.1:p.Arg878Cys	G	A	NM_172056.2(KCNH2): c.2632C>T (p.Arg878Cys)	Likely_benign
chr3	38566531	0.71348	0.177	4.4781	chr3:38566531:SG	-19.43	28.38	rs199473211	0.002	0.9928	G	C	SCN5A	missense_variant	NP_000326.2:p.Glu1239Gln,NP_001092874.1:p.Glu1240Gln,NP_001092875.1:p.Glu1240Gln,NP_001153632.1:p.Glu1239Gln,NP_001153633.1:p.Glu1186Gln,NP_001341630.1:p.Glu1239Gln,NP_932173.1:p.Glu1240Gln	G		NM_198056.2(SCN5A): c.3718G>C (p.Glu1240Gln)	Uncertain_significance
chr7	150952441	0.74603	-0.174	-4.4022	chr7:150952441:SG	-31.04	22.24	.	0.002	0.94507	T	C	KCNH2	missense_variant	NP_000229.1:p.Gly514Asp,NP_001191727.1:p.Gly174Asp,NP_742053.1:p.Gly514Asp,NP_742054.1:p.Gly174Asp				
chr3	38613787	0.76194	0.083	2.0999	chr3:38613787:SG	-11.49	15.69	rs45620037	0.014	0.96467	A	G	SCN5A	missense_variant	NP_000326.2:p.Thr220Ile,NP_932173.1:p.Thr220Ile	G	A	NM_000335.5(SCN5A): c.659C>T (p.Thr220Ile)	Conflicting_interpretations_of_pathogenicity
chr3	38550562	0.76746	-0.162	-4.0986	chr3:38550562:SG	-31.27	23.07	.	0.002	0.99787	C	G	SCN5A	missense_variant	NP_000326.2:p.Ser1936Cys,NP_001092874.1:p.Ser1937Cys,NP_001092875.1:p.Ser1919Cys,NP_001153632.1:p.Ser1904Cys,NP_001153633.1:p.Ser1883Cys,NP_001341630.1:p.Ser1918Cys,NP_932173.1:p.Ser1937Cys				
chr3	38579416	0.77612	0.081	2.0493	chr3:38579416:SG:	-12.07	16.17	rs7626962	0.01	1	T	!	SCN5A	missense_variant	NP_000326.2:p.Ser1102Tyr,NP_001092874.1:p.Ser1103Tyr,NP_001092875.1:p.Ser1103Tyr,NP_001153632.1:p.Ser1102Tyr,NP_001341630.1:p.Ser1102Tyr,NP_932173.1:p.Ser1103Tyr	T		NM_000335.5(SCN5A): c.3305C>A (p.Ser1102Tyr)	Benign/Likely_benign,_risk_factor
chr11	2527999	0.78977	0.293	7.4129	chr11:2527999:SG	-47.08	61.91	rs143709408	0.001	0.96869	T	C	KCNQ1	missense_variant	NP_000209.2:p.Thr153Met,NP_861463.1:p.Thr26Met	T		NM_000218.3(KCNQ1): c.458C>T (p.Thr153Met)	Conflicting_interpretations_of_pathogenicity
chr7	150945459	0.80551	0.116	2.9348	chr7:150945459:IG	-20.43	26.3	.	0.004	0.98439	T	TG	KCNH2	frameshift_variant	NP_000229.1:p.Gln1129LysfsTer126,NP_742054.1:p.Gln789LysfsTer126				
chr3	38550604	0.8094	-0.05	-1.265	chr3:38550604:SG	-11.54	9.01	rs777302118	0.019	0.99935	C	T	SCN5A	missense_variant	NP_000326.2:p.His1922Arg,NP_001092874.1:p.His1923Arg,NP_001092875.1:p.His1905Arg,NP_001153632.1:p.His1890Arg,NP_001153633.1:p.His1869Arg,NP_001341630.1:p.His1904Arg,NP_932173.1:p.His1923Arg				
chr3	38575385	0.83521	-0.015	-0.3795	chr3:38575385:SG	-3.96	3.2	rs41261344	0.153	0.99927	T	C	SCN5A	missense_variant	NP_000326.2:p.Arg1192Gln,NP_001092874.1:p.Arg1193Gln,NP_001092875.1:p.Arg1193Gln,NP_001153632.1:p.Arg1192Gln,NP_001153633.1:p.Arg1139Gln,NP_001341630.1:p.Arg1192Gln,NP_932173.1:p.Arg1193Gln	C	T	NM_000335.5(SCN5A): c.3575G>A (p.Arg1192Gln)	Benign/Likely_benign
chr3	38550521	0.84783	-0.025	-0.6325	chr3:38550521:SG	-7.09	5.83	rs41315493	0.044	1	A	C	SCN5A	missense_variant	NP_000326.2:p.Val1950Leu,NP_001092874.1:p.Val1951Leu,NP_001092875.1:p.Val1933Leu,NP_001153632.1:p.Val1918Leu,NP_001153633.1:p.Val1897Leu,NP_001341630.1:p.Val1932Leu,NP_932173.1:p.Val1951Leu	A	T	NM_000335.5(SCN5A): c.5848G>T (p.Val1950Leu)	Benign/Likely_benign
chr7	150948462	0.89859	0.14	3.542	chr7:150948462:SG	-50.93	58.02	rs201627778	0.001	1	A	G	KCNH2	missense_variant	NP_000229.1:p.Arg892Cys,NP_742054.1:p.Arg552Cys	A		NM_000238.4(KCNH2): c.2674C>T (p.Arg892Cys)	Conflicting_interpretations_of_pathogenicity
chr11	2570742	0.90539	-0.038	-0.9614	chr11:2570742:SG	-16.82	14.89	rs199472700	0.011	0.99318	G	A	KCNQ1	missense_variant	NP_000209.2:p.Ile198Val,NP_861463.1:p.Ile71Val	A	G	NM_181798.1(KCNQ1): c.211A>G (p.Ile71Val)	Pathogenic
chr7	150952745	0.90539	-0.023	-0.5819	chr7:150952745:SG	-10.18	9.01	.	0.017	0.98788	A	G	KCNH2	missense_variant	NP_000229.1:p.Leu413Phe,NP_001191727.1:p.Leu73Phe,NP_742053.1:p.Leu413Phe,NP_742054.1:p.Leu73Phe				
chr3	38551354	0.90956	-0.06	-1.518	chr3:38551354:SG	-27.71	24.67	.	0.003	0.99695	T	A	SCN5A	missense_variant	NP_000326.2:p.Ile1672Asn,NP_001092874.1:p.Ile1673Asn,NP_001092875.1:p.Ile1655Asn,NP_001153632.1:p.Ile1640Asn,NP_001153633.1:p.Ile1619Asn,NP_001341630.1:p.Ile1654Asn,NP_932173.1:p.Ile1673Asn				
chr3	38550362	0.92438	-0.005	-0.1265	chr3:38550362:SG:	-2.74	2.49	rs41311117	0.271	0.99965	G	!	SCN5A	missense_variant	NP_000326.2:p.Phe2003Leu,NP_001092874.1:p.Phe2004Leu,NP_001092875.1:p.Phe1986Leu,NP_001153632.1:p.Phe1971Leu,NP_001153633.1:p.Phe1950Leu,NP_001341630.1:p.Phe1985Leu,NP_932173.1:p.Phe2004Leu	G		NM_000335.5(SCN5A): c.6007T>C (p.Phe2003Leu)	Conflicting_interpretations_of_pathogenicity
chr3	38603836	0.9388	-0.04	-1.012	chr3:38603836:SG	-26.85	24.82	.	0.003	0.89336	T	C	SCN5A	missense_variant	NP_000326.2:p.Gly589Asp,NP_001092874.1:p.Gly589Asp,NP_001092875.1:p.Gly589Asp,NP_001153632.1:p.Gly589Asp,NP_001153633.1:p.Gly589Asp,NP_001341630.1:p.Gly589Asp,NP_932173.1:p.Gly589Asp				

chr	pos				variant			rsID			ref	alt	gene	consequence	protein			HGVS	clinical significance
chr3	38575439	0.95169	-0.007	-0.1771	chr3:38575439:SG	-5.91	5.55	rs374314562	0.051	0.99982	T	C	SCN5A	missense_variant	NP_000326.2:p.Arg1174His,NP_001092874.1:p.Arg1175His,NP_001092875.1:p.Arg1175His,NP_001153632.1:p.Arg1174His,NP_001153633.1:p.Arg1121His,NP_001341630.1:p.Arg1174His,NP_932173.1:p.Arg1175His	C	T	NM_198056.2(SCN5A):c.3524G>A (p.Arg1175His)	Uncertain_significance
chr3	38603900	0.95549	0.035	0.8855	chr3:38603900:SG	-30.21	31.98	.	0.002	0.97157	C	G	SCN5A	missense_variant	NP_000326.2:p.Arg568Gly,NP_001092874.1:p.Arg568Gly,NP_001092875.1:p.Arg568Gly,NP_001153632.1:p.Arg568Gly,NP_001153633.1:p.Arg568Gly,NP_001341630.1:p.Arg568Gly,NP_932173.1:p.Arg568Gly				
chr7	150958203	0.96635	0.007	0.1771	chr7:150958203:SG	-8.05	8.41	rs773928705	0.024	0.9809	A	G	KCNH2	missense_variant	NP_000229.1:p.Pro258Ser,NP_742053.1:p.Pro258Ser		A	NM_000238.4(KCNH2):c.772C>T (p.Pro258Ser)	Uncertain_significance
chr3	38550356	0.97939	0.002	0.0506	chr3:38550356:SG	-3.79	3.89	rs45489199	0.167	0.99668	C	G	SCN5A	missense_variant	NP_000326.2:p.Pro2005Ala,NP_001092874.1:p.Pro2006Ala,NP_001092875.1:p.Pro1988Ala,NP_001153632.1:p.Pro1973Ala,NP_001153633.1:p.Pro1952Ala,NP_001341630.1:p.Pro1987Ala,NP_932173.1:p.Pro2006Ala	G	C	NM_000335.5(SCN5A):c.6013C>G (p.Pro2005Ala)	Conflicting_interpretations_of_pathogenicity
chr3	38562500	0.99158	-0.011	-0.2783	chr3:38562500:SG	-51.97	51.41	rs41311127	0	1	G	A	SCN5A	missense_variant	NP_000326.2:p.Phe1292Ser,NP_001092874.1:p.Phe1293Ser,NP_001092875.1:p.Phe1293Ser,NP_001153632.1:p.Phe1292Ser,NP_001153633.1:p.Phe1239Ser,NP_001341630.1:p.Phe1292Ser,NP_932173.1:p.Phe1293Ser	G	C	NM_000335.5(SCN5A):c.3875T>C (p.Phe1292Ser)	Conflicting_interpretations_of_pathogenicity
chr7	150947630	0.99158	-0.003	-0.0759	chr7:150947630:SG	-14.17	14.02	rs76649554	0.006	0.98837	C	T	KCNH2	missense_variant	NP_000229.1:p.Ser981Gly,NP_742054.1:p.Ser641Gly		C	NM_000238.4(KCNH2):c.2941A>G (p.Ser981Gly)	Conflicting_interpretations_of_pathogenicity

Table S3. ACMG classification

Chr	Pos (hg38)	rs #	Amin	Amaj	Gene	Coding effect	Coding change	ACMG classification
chr5	129112870	rs372435	C	A	*ISOC1*	missense	NP_057132.2: p.Gly256Arg	Uncertain significance
chr11	2571363	rs172154	A	G	*KCNQ1*	missense	NP_000209.2: p.Val215Met	Uncertain significance (PM1, PM2 moderate, PP3 supporting)
chr11	2572882	rs120074	T	C	*KCNQ1*	missense	NP_000209.2: p.Leu273Phe	Pathogenic (PM1, PP5 strong, PM2 moderate, PP3 supporting)
chr11	2583457	rs744623	G	A	*KCNQ1*	missense	NP_000209.2: p.Tyr315Cys	Pathogenic (PS1 strong, PM1,PM2,PP5 moderate, PP3 supporting)
chr11	47346372	rs397516	T	C	*MYBPC3*	splice	NM_000256.3: c.927-2A>G	Pathogenic (PVS1: null variant, PS4,PP5 strong, PM2 moderate)
chr8	2144739	rs201108	C	T	*MYOM2*	stop	NP_003961.3: p.Gln1386Ter	Uncertain significance
chr11	2778023	rs794728	T	C	*KCNQ1*	Stop	NP_000209.2: p.Arg594Ter	Pathogenic (PVS1: null variant, PM2, PP5 moderate, PP3 supportive)
chr12	32802499	rs759179	GGGTGT	G	*PKP2*	frameshif	NP_001005242.2: p.His689ProfsTer8	Pathogenic (PVS1: null variant, PS4 strong, PM2,PP5 moderate)
chr7	150947670	rs7862041	CG	C	*KCNH2*	frameshift	NP_000229.1: p.Pro968AlafsTer151	Pathogenic (PVS1: null variant, PP5 strong, PM2 moderate)
chr11	2572852	.	A	AT	*KCNQ1*	frameshift	NP_000209.2: p.Ile263LysfsTer26	Likely pathogenic (PVS1: null variant, PM2 moderate)
chr7	150952748	.	G	A	*KCNH2*	missense	NP_000229.1: p.Trp412Arg	Uncertain significance (PM2 moderate)
chr7	150974821	.	G	C	*KCNH2*	missense	NP_000229.1: p.Cys66Ser	Likely pathogenic (PM1,PM2,PM5 moderate)

PVS1: null variant (nonsense, frameshift, canonical +- 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease

PM1: Located in a mutational hot spot and/or critical and well-established functional domain (e.g., active site of an enzyme) without benign variation

PM2: (Absent from controls) in in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium

PP5: Reputable source recently reports variant as pathogenic

PP3: Multiple lines of computational evidence support a deleterious effect on the gene or gene product

PS4: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in control

PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before

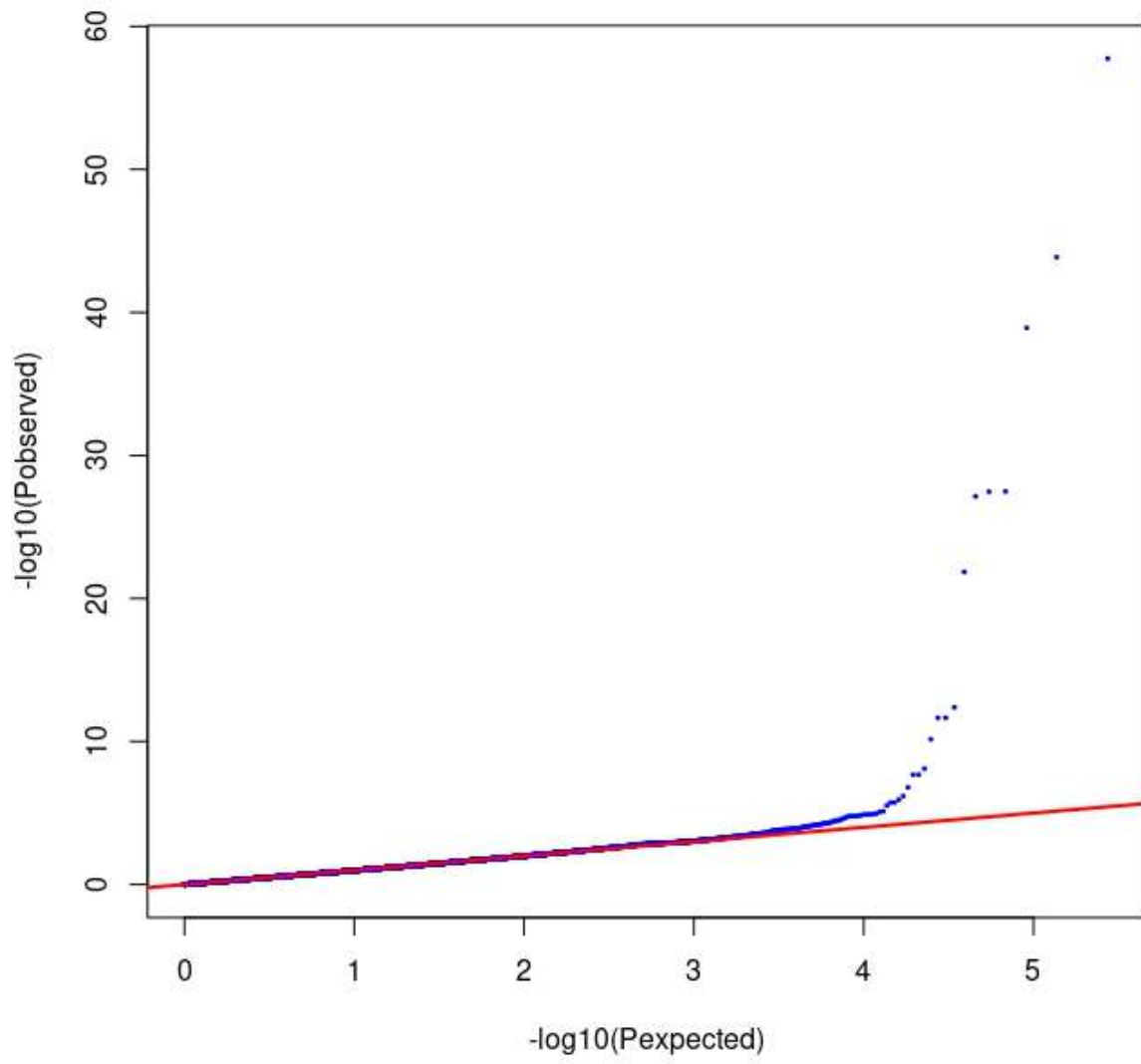**Figure S1.** QQ-plot for the EWAS of rare variants.

Figure S2. QTc interval plotted by age bins (left). Histogram of QTc values by sex (right). The LSH cohort is shown on top and the HERA cohort below.
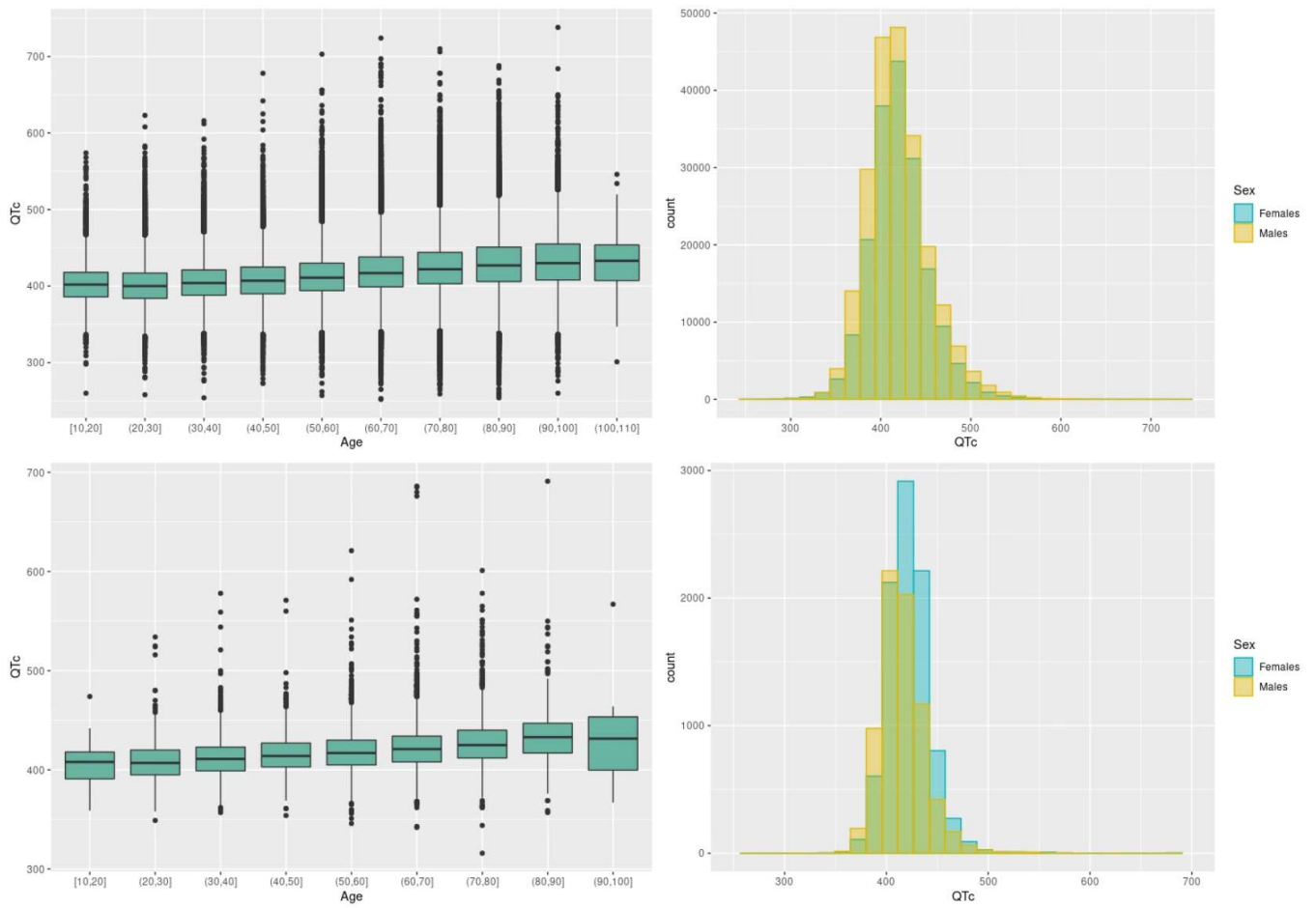
Figure S3. Locus plot showing association signal with coding variants in *ISOC1* and *MYOM2*. The *ISOC1* variant is correlated ($r^2 > 0.8$) with intronic variants in *FBN2, SLC27A6* and *LINC01183*