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Deleterious Protein-altering Mutations in the *SCN10A* Voltage-gated Sodium Channel Gene are Associated with Prolonged QT

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Abstract

Long QT syndrome (LQT) is a pro-arrhythmogenic condition with life threatening complications. Fifteen genes have been associated with congenital LQT however, the genetic causes remain unknown in more than 20% of cases.

Eighteen patients with history of palpitations, presyncope, syncope and prolonged QT were referred to the Yale Cardiovascular Genetics Program. All subjects underwent whole exome sequencing (WES) followed by confirmatory Sanger sequencing. Mutation burden analysis was carried out using WES data from sixteen subjects with no identifiable cause of LQT.

Deleterious and novel *SCN10A* mutations were identified in three of the sixteen patients (19%) with idiopathic LQT. These included two frameshifts and one missense variants (p.G810fs, p.R1259Q, and p.P1877fs). Further analysis identified two damaging *SCN10A* mutations with allele frequencies of ~0.2% (p.R14L, p.R1268Q) in two independent cases. None of the *SCN10A* mutation carriers had mutations in known arrhythmia genes. Damaging *SCN10A* mutations (p.R209H, p.R485C) were also identified in the two subjects on QT prolonging medications.

Our findings implicate *SCN10A* in LQT. The presence of frameshift mutations suggests loss of function as the underlying disease mechanism. The common association with AF suggests a unique mechanism of disease for this LQT gene.

Graphical Abstract

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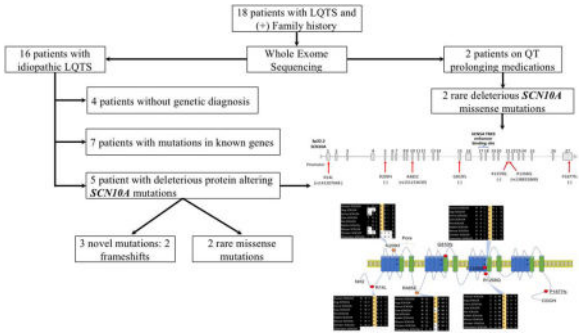

1. Introduction

Long QT syndrome (LQT) is a pro-arrhythmogenic condition that increases the risk of a unique life threatening polymorphic ventricular tachycardia known as “torsades de pointes”, and sudden cardiac death (SCD). Congenital LQTs are inherited disorders caused by mutations in cardiac conduction channels or associated proteins, and are estimated to affect 0.005% to 0.05% of the general population (1). LQT is also accounted for by QT prolonging drugs, electrolyte abnormalities (2), ischemic heart disease (3) or structural heart disease; a condition that is often referred to as acquired LQT. With the advent of genome sequencing it is evident that genetic variants with small effects also account for some, if not all, subclinical acquired LQTs that manifest themselves in the presence of additional precipitating factors (4, 5). It has also been estimated that 10 to 36% of patients with LQT genotypes are silent mutation carriers (6, 7).

To this date fifteen different types of congenital LQT have been characterized and account for about 80% of inherited long QT cases. These correspond to mutations in genes encoding potassium channels (8–13), calcium channels (14), calcium signaling proteins (15–17), anchoring proteins (18, 19), transport proteins (20, 21), and voltage gated sodium channels (22, 23). Most of these genes have been established as casual genes for LQT based on linkage or segregation analysis, or in the case of *KCNE2*, *CAV3*, *SNTA1* and *CALM2* genes by association studies. The genetic cause of congenital LQT remains unknown in at least 20% of cases (24).

The *SCN10A* gene encodes the alpha subunit of a voltage-gated sodium channel ($Na_v1.8$), which is expressed in the peripheral nervous system but also has low expression in atrial and ventricular cardiomyocytes and neurons of the heart (25–28). Genome wide association studies implicated the *SCN10A* gene in cardiac conduction (29–31). In addition, mutations in the *SCN10A* gene have been linked to cardiac arrhythmias such as Brugada syndrome (32–36), atrial fibrillation (37–40) and sudden cardiac death (41).

SCN10A influences cardiac conduction via three proposed mechanisms based on a multitude of in-vitro and in-vivo studies (42). Given the expression of $Na_v1.8$ in cardiac myocytes, it can have direct effects on cellular physiology (25, 26, 30). Alternatively, indirect effects could be mediated via modifying the expression of *SCN5A* gene, located immediately downstream of its 3′ end. The presence of an enhancer binding domain of

SCN5A within the *SCN10A* gene, encompassing exons 17 and 18, supports this concept (43–45). Lastly, *SCN10A*, which has robust expression in the cholinergic vagal neurons and dorsal root ganglia, has been associated with modulation of cardio-vagal input from the peripheral nervous system (27, 46, 47).

No prior studies attributed QT prolongation to mutations in *SCN10A*. In this study, we report a series of patients who were referred to our cardiovascular genetics clinic for genetic screening for prolonged QT associated with either syncope, pre-syncope, SCD, or AF and were found by whole exome sequencing (WES) to have damaging mutations in the *SCN10A* gene.

2. Materials and Methods

Study Subjects

Patients were referred to the Yale Cardiovascular Genetics team for genetic screening of SCD and/or cardiac arrhythmias. The protocols were approved by the institutional review board at Yale University School of Medicine. Written consent to participate in the study and to undergo genetic sequencing was obtained from all patients. Detailed clinical information, including laboratory data and clinical imaging were collected. Potential non-genetic causes for prolonged QT were excluded. Out of the eighteen patients referred for prolonged QT, palpitation and syncope/presyncope, two were on QT prolonging medications and hence were excluded from the initial mutation burden analysis. Five out of the sixteen patients had already undergone targeted panel genotyping for LQT in previous years with negative results.

Genomic DNA was extracted from peripheral blood leukocytes and sent for exome sequencing. Family history was obtained from the index cases, and pedigrees were constructed based on self-reported phenotypes. Family members were not available for segregation analysis. Thus, we proceeded with a mutation burden analysis.

Whole Exome Sequencing and Targeted Sequence Capture

Genomic DNA was captured on exomes at the W.M. Keck Facility at Yale University using Roche NimbleGen 2.1M Human Exome Array, as described earlier (48). In brief, DNA libraries were prepared and sequenced on the Illumina Genome Analyzer, followed by image analysis and base calling. Sequences were aligned against human reference genome (UCSC Genome Browser hg19) and processed using MAQ program SAMtools. SAMtools was also used for the single-nucleotide variant detection and filtering against the reference genome as described earlier. Filters were applied against published databases. A computer script was designed for variants annotation based on the novelty, conservation, tissue expression and their effect on protein function. They were considered nonconservative if the substituted amino acid was conserved in all species. Polyphen, SIFT and CADD scoring were used for in silico prediction of pathogenicity of the mutations (49). Genetic intolerance score was calculated using RVIS (Residual Variation Intolerance Score) (50).

We first screened for all variants in known LQT-associated genes with allele frequencies < 1% in the ExAC database. Based on the prevalence of congenital long QT syndrome

(1:2,000 to 1:20,000) (1) and percentage of unknown genes (20%) we used a stringent filtering for discovery of novel variants. All variants with allele frequencies greater than 1:100,000 in the ExAC database, or variants considered benign either by by PolyPhen or SIFT prediction software were filtered out. Once the disease associated variant(s) were identified we screened the database for presence of variants with allele frequencies of less 1% in EXAC database in the same gene(s). In addition, we screened for variants in genes encoding cardiac voltage gated calcium, sodium, or potassium channels, with allele frequencies less than 1%.

The 1,000 Genomes Project and an exome database of 2,000 healthy white subjects were also used as reference. Confirmatory Sanger sequencing was carried out for all variants of interest.

Literature and Database Review

We queried existing genetic databases (EXAC) for mutation burden analysis in the *SCN10A* gene. EXAC contained 121,412 alleles in 60,706 subjects with available SCN10A sequences. We filtered the database for rare damaging mutations that have allele frequency less than 0.001%. The number of mutation carriers was calculated using the Hardy-Weinberg equilibrium model. Assuming low prevalence of prolonged QT in the general population, we used the EXAC database as a control and examined the association between rare deleterious *SCN10A* mutations and long QT. The odds ratio, standard error and 95% confidence interval were calculated (51) and the p-value was calculated using a two-tailed Chi-Squared test with Yates' correction. We also performed a literature review on all reported *SCN10A* mutations. All the reported cases, disease associations and corresponding ECG parameters were summarized.

3. Results

SCN10A Mutations Among Patients with QT Prolongation Referred for Genetic Testing

Of the 18 patients referred for QT prolongation, 16 were not on any QT-prolonging medications and did not have any other identifiable cause for prolonged QT. Mutations in known arrhythmia genes were identified in 7 out of the 16 patients with idiopathic LQT. Five of those patients had pathogenic variants in known LQT genes; AKAP9 (p.Q3520H), ANK2 (p.V3632I), ANK2 (p.E1449G), CAV3 (p.T78M), and KCNQ1 (p.L266P). One had mutations in RBM20 (p.D996Y) and TTN (c.32562-insAGA) that are associated with arrhythmias and dilated cardiomyopathy (52, 53). Another patient had a mutation in CTNNA3 (p.H727R), a gene associated with arrhythmogenic right ventricular cardiomyopathy (54).

The mutation burden analysis of WES using all variants with allele frequencies <1:100,000 revealed 3 independent novel heterozygous deleterious mutations in *SCN10A* gene in 3 subjects without mutations in known LQT genes with a P-value<0.0001 and an odds ratio of 90.9 (95% confidence interval of 31.4 to 263.2; supplemental table 1). No other mutations were found in the same gene in more than 2 subjects.

Two patients had completely novel frameshift mutations (p.G810fs and p.P1877fs). The subject with p.G810fs variant was a 53 years old patient with palpitations, pre-syncope, paroxysmal AF, and a biphasic T-wave on ECG. His corrected QT (QTc) was prolonged at 466 msec. The proband with the p.P1877fs variant presented at 33 years of age due to palpitations and a QTc of 519 msec. He had shortening of his QTc during an exercise stress test, and did not have AF. In this subject, genetic variants in *AKAP-9* (p.R3704Q) and *ANK-2* (p.D955G) were also identified. The variant in *AKAP-9* was predicted to be benign, whereas the *ANK-2* variant falls in the non-canonical transcript of the protein. A third completely novel variant was identified in a patient with pre-syncope and palpitations. The mutation, which results in p.R1259Q substitution was predicted to be damaging by PolyPhen and SIFT (table 1). None of the *SCN10A* mutations carriers had neuropathy. Of the five patients that had previously undergone panel genotyping, only one had an *SCN10A* mutation, while the disease gene for the other four remains unidentifiable at this point.

Given that nonsynonymous *SCN10A* mutations with allele frequencies as high as 1% have been associated with Brugada syndrome and AF, we screened the remaining subjects for *SCN10A* mutations using a less stringent frequency of <1%. The analysis revealed 2 additional missense mutations. One mutation leading to p.R14L amino acid substitution in *SCN10A* was identified in a 48 years old woman who presented with syncope and LQT and had no identifiable mutation in known LQT genes. The p.R14L variant, which based on PolyPhen and SIFT is predicted to be damaging (table 1) has an allele frequency of 0.19% in EXAC database and has been previously associated with AF and Brugada but not long QT (table 2). The second missense mutation in *SCN10A* resulted in p.R1268Q substitution and was identified in a subject with familial AF, long QT, pre-syncope and palpitations of no identifiable cause, who also had no identifiable mutation in known LQT genes. The p.R1268Q variant has an allele frequency of 0.18% in EXAC database (table 1), but its disease association was not known. The variant was predicted to be damaging by SIFT only.

Conservation analysis showed that all of the substituted amino-acids are evolutionarily highly conserved (figure 1b). There was no clustering of the mutations observed, hence a genotype phenotype correlation could not be established (figure 1b). For instance, the p.R1268Q variant is located in the cytoplasmic portion of the protein, while the p.R1259Q variant is in the transmembrane portion between the voltage sensing domain and the channel pore domain. Interestingly, none of the above mutations were near the enhancer-binding domain of the *SCN10A* gene (figure 1a). There was strong family history of arrhythmias and LQT among *SCN10A* mutation carriers (figure 2). Careful review of the pedigree suggests pleotropic effect of these mutations, resulting in trait that range from atrial fibrillation to supraventricular tachycardia, long QT and syncope with an inheritance that is consistent with an autosomal dominant pattern. First degree relatives were not available for genetic testing.

SCN10A Mutations Among Patients on QT Prolonging Medications

Two patients, who were taking QT prolonging medications also underwent exome sequencing. The first patient was a 59 years old man with a complex medical history including hypertrophic cardiomyopathy (HCM), on metoclopramide who had QT

prolongation, and was found to have a genetic variant in the *SCN10A* gene leading to p.R485C substitution. Interestingly, he later developed persistent AF. He had also a non-conservative *MYBPC3* mutation as the underlying cause of his HCM. The *SCN10A* p.R485C is a rare variant with an allele frequency of 7.0×10^{-4} in the EXAC database, which is also predicted to be damaging. The second patient was a 57 years old woman, who presented with persistent AF and had been placed on Sotalol. Her QTc on this drug ranged from 459 to 615 msecs. Given the strong family history of arrhythmia and AF she underwent WES, which revealed a missense mutation in *SCN10A* gene leading to p.R209H substitution. There were no other mutations identified in known arrhythmia genes. The p.R209H is a rare variant with an allele frequency of 3.3×10^{-5} in the EXAC database and is predicted to be damaging. Both substituted amino-acids were highly conserved (figure 1a) and none was located near the enhancer-binding domain of the *SCN10A* gene (figure 1b). Moreover, the CADD scores for p.R485C and p.R209H were 34 and 33, respectively which suggest a very high likelihood of pathogenicity.

Review of Rare Damaging *SCN10A* Mutations in EXAC and Mutation Burden Analysis

We queried the EXAC database for rare damaging mutations in the *SCN10A* gene. Out of the 60,706 total subjects, there were 303 damaging mutations at an allele frequency of less <1:100,000 (figure 3).

Mutation burden analysis (supplementary table 1) using the EXAC database as control showed an odds ratio of 90.9 for having prolonged QT if the patient harbors a rare and deleterious *SCN10A* mutation (95% confidence interval of 31.4 to 263.2, P-value < 0.0001).

In a second analysis using an allele frequency of <1:100 two more variants in the *SCN10A* gene were identified in our patient cohort. Additionally, out of the 60,706 total subjects in the EXAC database, there were 574 damaging mutations at an allele frequency <1:100. These included missense (n=501), non-sense (n=32), splice (n=17), frameshift (n=15), deletion (n=8), and insertion (n=1). Mutation burden analysis at this allele frequency showed an odds ratio of 4.9 for having prolonged QT if the patient harbors a deleterious *SCN10A* mutation (95% confidence interval of 1.7 to 14.2, P-value = 0.0047; supplemental table 1). Interestingly, *SCN10A*'s RVIS score of −1.32 places this gene among the 4.74% most intolerant genes. Taken together, our analyses provide strong statistical evidence for association between *SCN10A* mutations and long QT trait.

Systematic Literature Review of All Reported *SCN10A* Mutations and Available ECG Characteristics

In our review of the published literature we found 46 different *SCN10A* reported mutations. The available clinical and ECG data are summarized in table 2. Interestingly, heterozygous *SCN10A* mutations causing p.F385C, p.I1225T, p.N1328K, p.N1715T amino acid substitutions were detected in four independent patients with QT prolongation. All four variants had been reported in independent publications, hence they lacked the power to establish association between *SCN10A* mutations and QT prolongation.

The subject with the deleterious p.F385C *SCN10A* variant is reported as a 65-year-old man with a history of sudden cardiac death, Brugada syndrome, and a QTc of 464 msec (table 2).

One of the two subjects with symptomatic Brugada syndrome and p.I1225T variants had been reported to have a prolonged QTc of 525 msec (table 2).

The third deleterious *SCN10A* mutation had been reported in a 68-year-old man with syncope and a prolonged QTc of 450 msec. He had a novel missense mutation in *SCN10A* that substituted a highly conserved amino acid (p.N1328K).

The fourth reported deleterious *SCN10A* mutation substitutes a highly conserved amino acid (p.N1715T) with a rare allele frequency of 8.1×10^{-4} in the EXAC database. This mutation had been identified in a 65-year-old man with presyncope and palpitations, inducible ventricular tachycardia, and ventricular fibrillation, diagnosis of Brugada syndrome and a QTc of 463 msec.

In addition, there has been report of 6 different SCN10A mutations in 6 subjects with borderline prolonged QTc, resulting in p.R14L, p.W189R, p.R844H, p.S1337T, p.G1406D, and p.G1662S amino acid substitutions (table 2). All of these mutations substituted highly conserved amino acids and were predicted to be damaging. Of note, there have been 6 patients with the p.R14L variant, 4 patients with the p.G1662S variant and 2 patients with the p.R844H variant reported and only one from each group has had borderline prolonged QTc (table 2).

4. Discussion

Voltage gated sodium channels (Na_v) conduct inward sodium currents that are regulated by the transmembrane potential. These channels are composed of the pore forming or α-subunit, and a β regulatory subunit. The α-subunit possesses a voltage sensing domain, a pore domain with a filter selective for sodium ions, an activation gate, and an inactivation gate (55). There are nine different Na_vs identified in humans with different tissue distribution and functionality based on the α-subunit (55). The α-subunits of $Na_v1.1$ to $Na_v1.9$ are encoded by nine different genes.

Gain of function mutations in *SCN5A* have been previously implicated in congenital LQT type 3 (56). The *SCN5A* gene encodes $Na_v1.5$, which is the most abundant voltage gated sodium channel in cardiac tissue. $Na_v1.5$ is responsible for the depolarization phase of the cardiac action potential, characterized by rapid inward sodium current that is quickly inactivated by the inactivation gate (57). Congenital LQT type 3 mutations cause a gain of function in $Na_v1.5$ due to failure of the inactivation gate to terminate the influx of sodium at the appropriate time. Hence, sodium entry slowly continues during the subsequent phases of the action potential and results in prolonged repolarization (58). This is in contrast to Brugada associated mutations in *SCN5A* that cause loss of function via premature closure of $Na_v1.5$ channel without effect on the QT interval (59). An overlap syndrome of long QT and Brugada has also been described as some *SCN5A* genotypes can cause features of both syndromes (60).

In parallel, *SCN10A* mutations have been strongly associated with Brugada syndrome and other cardiac conduction abnormalities in humans. In fact, up to 10% of Brugada cases are attributed to *SCN10A* mutations (34).

A recent fine-mapping study implicated the *SCN5A-SCN10A* locus in QT prolongation (61). In-vitro studies have shown that the $Na_v1.8$ contributes to late cardiac sodium current and displays marked differences in gating compared to $Na_v1.5$ (26). While the enhancer hypothesis offered a mechanism whereby polymorphisms in *SCN10A* could contribute to *SCN5A* expression levels (45), the majority of the arrhythmia associated *SCN10A* mutations fall far from the enhancer-binding domain. However, a direct effect through the sympathetic nervous system is another plausible mechanism. Although Nav1.8 has low expression in cardiomyocytes, its expression levels are high in intra-cardiac ganglia and neurons (27, 62). Loss of Nav1.8 current had low effect on cardiomyocyte conduction (27, 62). However, Nav1.8 blockade significantly reduces the sodium current and firing frequency of intra-cardiac neurons (27). Similarly, Nav1.8 channel blockade in cardiac ganglionated plexi has been shown to suppress cardiac conduction and atrial fibrillation inducibility (46). Accordingly, left cardiac sympathetic neuron denervation (LCSD) has been successfully used to treat LQT syndrome (63, 64).

In our study, we observed a remarkably high prevalence of deleterious *SCN10A* mutations in patients with prolonged QT, an association that hasn't been made before. All the observed mutations affected the amino-acid sequence of Nav1.8, either through deleterious amino-acid substitutions at conserved sites or frameshift mutations. None of the observed mutations resides near the enhancer-binding domain, which means that they are less likely to disturb cardiac conduction via indirect effects on *SCN5A* expression levels. Although, one cannot exclude an allosteric effect of these mutations on the enhancer-binding domain. More likely these mutations affect Nav1.8 function in regulation of cardiac sodium current and repolarization. The amino acid substitutions involve the voltage sensing domain (p.R209, p.R1259Q and p.R1268Q), channel modulation domain (p.R485C), and N-terminal domain (p.R14L).

While the three deleterious and entirely novel variants (p.G810fs, p.R1259Q, and p.P1877fs) in *SCN10A* provided a strong signal of association with LQT, the subsequent mutations were present at higher allele frequencies. For instance, the p.R1268Q variant was present at an allele frequency of 0.18% that is high compared to the prevalence of LQT. However, the same mutation had been associated with Brugada syndrome (34, 36), which is also a rare disease (65). Similarly, the p.R14L variant with an allele frequency of 0.19% had been previously associated with Brugada syndrome (34, 38, 39). We speculate that these are disease-contributing variants that are not sufficient to independently cause disease, which explains their pleotropic effects and incomplete penetrance. The two variants (p.R209H, p.R485C) identified in the two patients who were on QT prolonging medications are also most likely not sufficient to cause LQT and require the contribution of environmental factors such as QT prolonging drugs. Although mutations in known LQT genes account for about 80% of LQT cases, our study was enriched for patients who had previously undergone targeted genotyping panels (5 out of 16 patients) with negative results for LQT gene mutations. This has resulted in the lower yield for mutations in known LQT genes in our WES and likely higher *SCN10A* mutation rate compared to the general population.

Of interest is the prior association between *SCN10A* mutations and unexplained nocturnal sudden cardiac death (41). Although the SCD had been attributed to a possible underlying

Brugada syndrome, the current findings suggest that LQT induced torsades could be another mechanism of SCD in patients harboring *SCN10A* mutations. Overall, these findings are of great significance to the study of cardiac electrophysiology and prevention of fatal arrhythmias in at-risk subjects.

5. Conclusion and Future Prospects

To this date there is no definitive therapy available for LQT, therefore, screening and early detection of prolonged QT remains a central approach for risk stratification and primary prevention against fatal arrhythmias in affected subjects and their extended families. Hence, it is imperative to identify all genetic culprits in abnormal cardiac repolarization and long QT. Strikingly, the genetic cause in congenital LQT remains elusive in about 20% of inherited cases, while many of the acquired LQTs are also accounted for by predisposing genetic mutations.

Our study implicates *SCN10A* mutations as an underlying cause of LQT, adding to the list of genes that should be screened for in patients with prolonged QT. The presence of frameshift mutations, which result in premature stop codon and potentially non-sense mediated decay, suggest that the disease mechanism is due to loss of function of the encoded protein. In addition, the common association with AF suggests that *SCN10A* may represent a unique subtype of LQT genes.

Our findings advance the identification of genetic causes of LQT and improve the capability of screening in individuals at risk. Further investigations into genotype-phenotype correlation may improve our ability to predict the development of isolated atrial fibrillation, Brugada syndrome, LQT or combination thereof in *SCN10A* mutation carriers. In addition, future investigations are necessary to examine the co-expression and interaction of *SCN10A* with *SCN5A* in regulation of sodium current in cardiomyocytes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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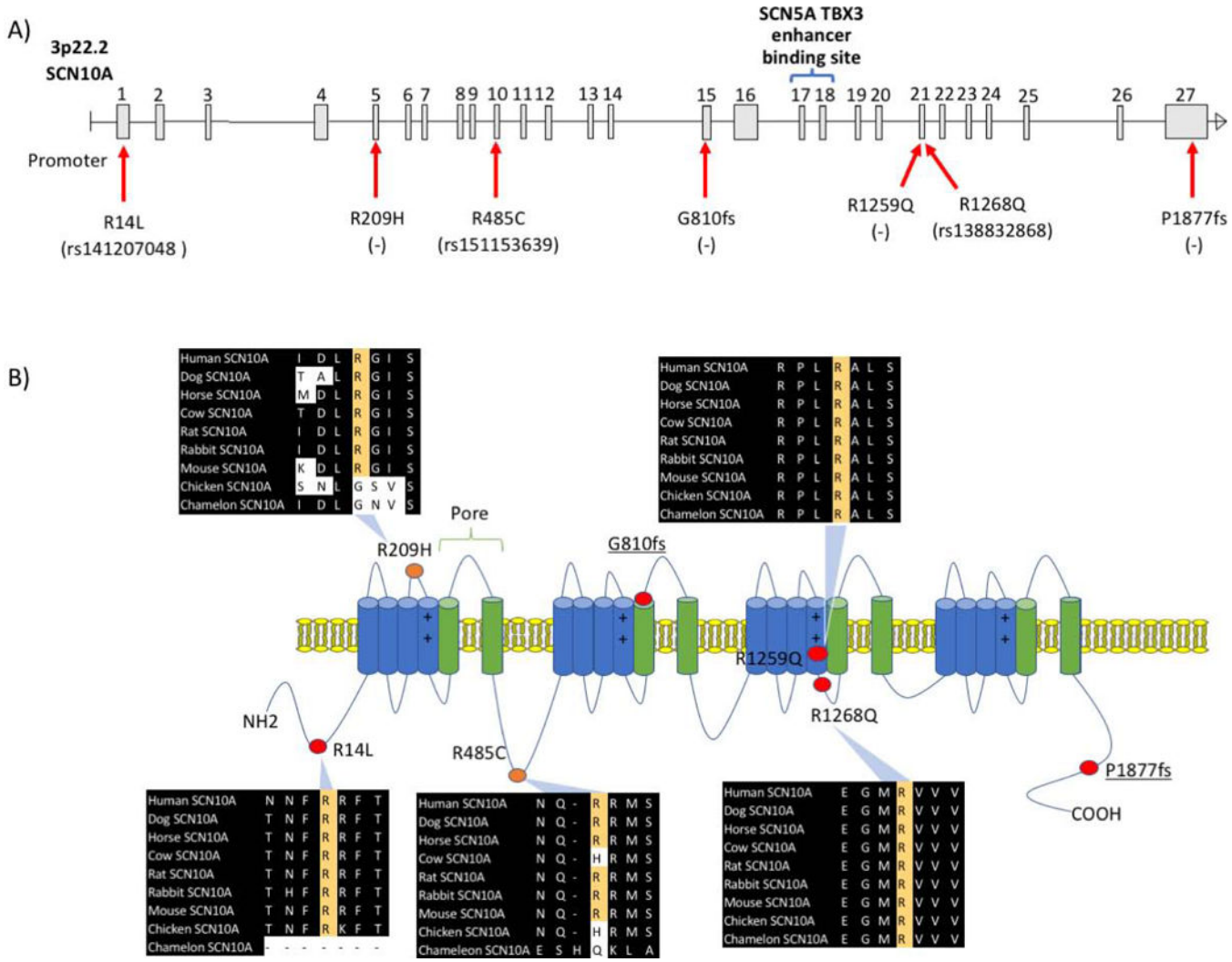

Figure 1.

Nav1.8 voltage gated sodium channel encoding *SCN10A* gene domains, long QT associated mutations and conservation analysis. (A) *SCN10A* gene is comprised of 27 exons located on the short arm of chromosome 3. The enhancer-binding domain encompasses exons 17, 18 and the intronic region in between. The mutations are labelled along the gene with the corresponding dbSNP (rs) number when available. (B) Several of the mutations fall within the transmembrane alpha helical domains (G810fs, R1259Q, and R1268Q), the R14L is in the N-terminal domain, and the P1877fs is in the C-terminal domain. The two mutations in the patients who were on QT prolonging medications are labelled in orange, the R209H in proximity to the voltage sensing domain and R485C within the channel modulation domain. All the mutation occurred at evolutionarily conserved site.

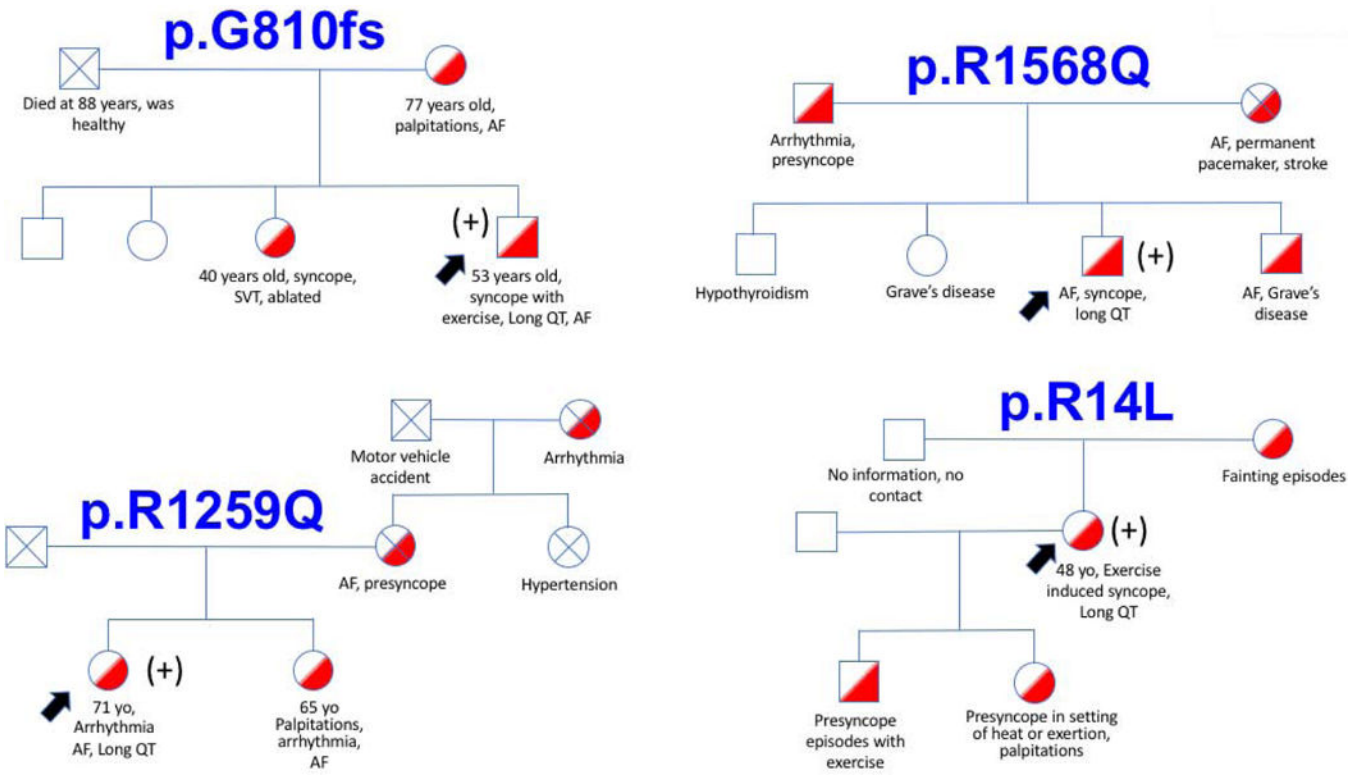

Figure 2.

Family pedigrees of index cases with *SCN10A* mutations. There was strong family history among *SCN10A* mutation carriers concerning for arrhythmias and underlying long QT syndrome (labelled in red). The black arrows show index cases. The (+) sign indicates that the subject is heterozygous for an *SCN10A* mutation.

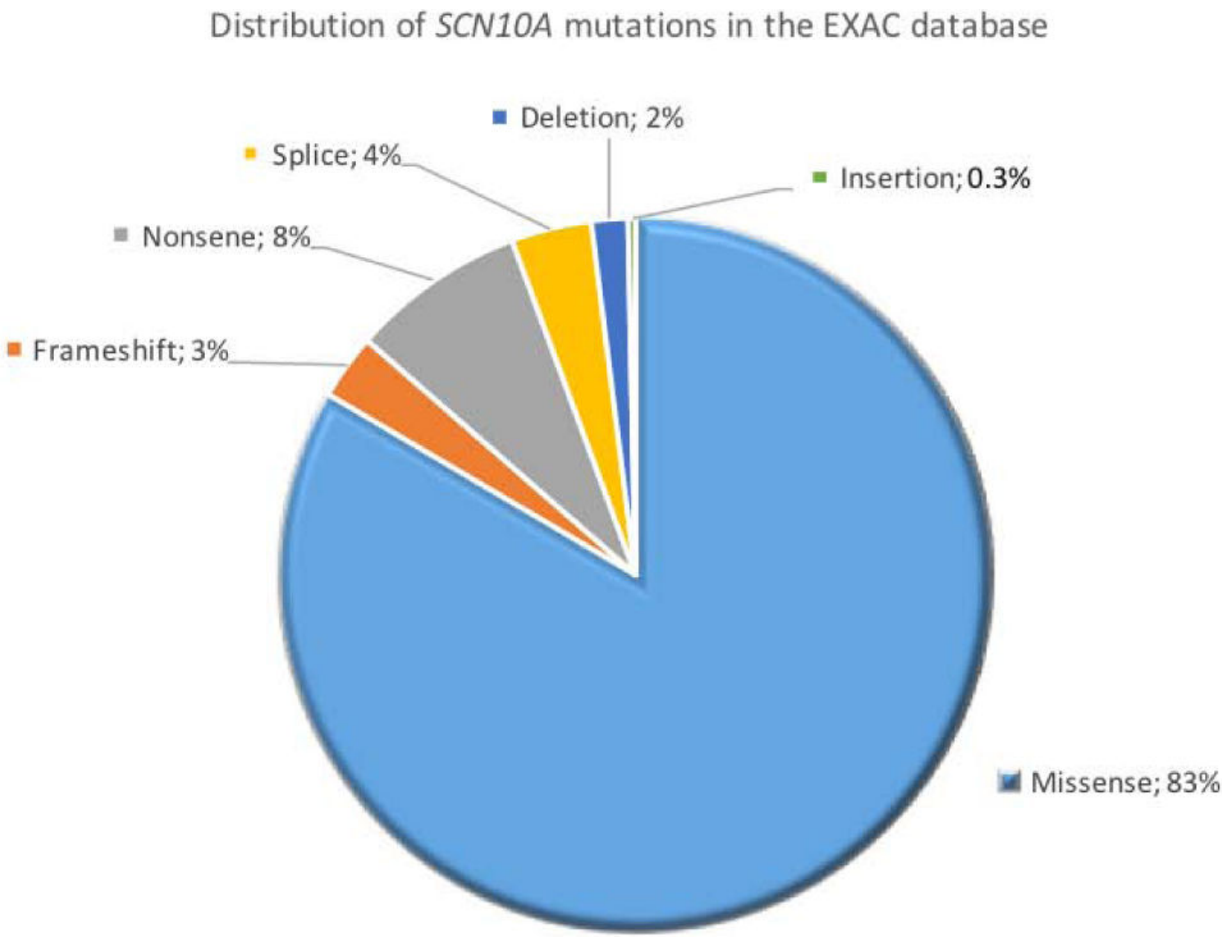

Figure 3.

Distribution of *SCN10A* mutations exomes of 60,706 subjects in EXAC database. Overall there were 303 rare (minor allele frequency< 0.001%) and damaging mutations. The majority of the mutations were miss-sense (n= 253, 83%), followed by 24 non-sense (8%), 11 splice site (4%), and 9 frameshift (3%) mutations, 5 were deletion (2%) and 1 was an insertion mutation (0.3%).

Table 1

Population characteristics of *SCN10A* mutation carriers. Clinical data, ECG parameters along with the genetic variants in the studied patients with idiopathic QT prolongation.

Protein Variant	Incidence in EXAC	Age[1]	Sex	Fam hx[2]	Afib[3]	Symptoms[4]	ECG characteristics[5]							PolyP[8]	SIFT[9]	CADD[10]
							HR	PR	QRS	QT	QTc	TdP[6]	T-wave[7]			
R14L	0.001928	48	F	Yes	No	Syncope	81	168	102	444	516	No	Normal	D	D	27
G810fs	Novel	53	M	Yes	Yes	Pre-syncope	60	200	98	460	466	No	Biphasic	D	D	–
R1259Q	Novel	71	F	Yes	Yes	Pre-syncope, palpitations	73	N/A	106	488	535	No	Normal	D	D	35
R1268Q	0.001765	48	M	Yes	Yes	Pre-syncope, palpitations	59	78	104	444	437	No	Normal	B	D	28
P1877fs	Novel	33	M	No	No	Palpitations	84	158	102	460	519	No	Notched	D	D	–

[1] Age at the time of diagnosis is reported in years.

[2] Family history of syncope, long QT syndrome, or sudden cardiac death.

[3] Presence of atrial fibrillation (Afib).

[4] Symptoms experienced by the patient without stress. Stress tests were performed in all patients except R1268Q. QTc lengthening was observed only with R14L with the stress test.

[5] All ECG intervals are reported in msecs.

[6] TdP refers to torsades de pointes.

[7] T-wave morphology, checked for T-wave alternans, and notched T-waves.

[8] PolyP: Polyphen in silico prediction software, D= damaging, B= benign.

[9] SIFT in silico prediction software, D= damaging

[10] CADD score, a score of more than 15 is considered pathogenic.

Table 2

Summary of reported *SCN10A* mutations with known clinical significance

All reported cases are summarized along with electrocardiographic characteristics when available.

							ECG characteristics[7]							
Mutation (dbSNP)[1]	**Ref[2]**	**n[3]**	**G[4]**	**Age[5]**	**Phenotype**	**Family Hx[6]**	**HR**	**PR**	**QRS**	**QTc**	**SIFT**	**Polyphen**	**Conservation**	**MAF[8]**
R14L (rs141207048)	1	1	M	20	Persistent AF	–	–	–	–	–	Damaging	Probably-damaging	Conserved	1.93E-03
	3	1	–	31	AVNRT, paroxysmal AF	–	112	206	98	434	Damaging	Probably Damaging	Conserved	1.93E-03
	4	1	F	50	BrS, dizziness/palpitations	Yes	73	234	112	443	Damaging	Probably Damaging	Conserved	2.00E-03
	4	1	M	19	BrS	No	66	185	113	416	Damaging	Probably Damaging	Conserved	2.00E-03
	4	1	M	65	BrS, SCD, syncope	Yes	54	194	94	378	Damaging	Probably Damaging	Conserved	2.00E-03
	4	1	M	49	BrS, dizziness/palpitations	N/A	88	130	110	411	Damaging	Probably Damaging	Conserved	2.00E-03
V94G (rs202143516)	3	1	–	28	Paroxysmal AF	PPM in dad and sister	57	144	102	414	Damaging	Probably Damaging	Conserved	8.11E-04
	3	1	–	31	Paroxysmal AF, non-hemorrhagic stroke	–	64	132	84	396	Damaging	Probably Damaging	Conserved	8.11E-04
T137M (rs148663098)	4	1	M	37	BrS	No	59	205	72	348	Tolerated	Benign	Conserved	7.70E-05
Y158D (rs202192818)	1, 8	1	F	48	Paroxysmal AF	–	–	–	–	NP	Damaging	Probably Damaging	Conserved	2.64E-04
	1, 8	1	M	52	Persistent AF	–	–	–	–	NP	Damaging	Probably Damaging	Conserved	2.64E-04
	3	1	–	32	Persistent AF	–	103	186	86	418	Damaging	Probably Damaging	Conserved	2.64E-04
W189R (−)	7	1	F	63	–	no	77	180	60	453	Damaging	Damaging	Conserved	0.00E+00
A200V (−)	5	–	–	–	BrS association	–	–	–	–	–	damaging	Probably Damaging	conserved	1.08E-04
I206M (rs74717885)	4	1	M	39	BrS, syncope	No	78	168	80	388	Damaging	Benign	Not conserved	1.16E-02
	4	1	M	58	BrS, syncope	No	84	210	100	408	Damaging	Benign	Not conserved	1.16E-02
S242T (rs140288103)	4	1	M	20	BrS, SCD, syncope	No	67	170	105	396	Damaging	Probably Damaging	Conserved	2.31E-04
E285K (rs146151670)	1	1	F	48	Paroxysmal AF	–	–	–	–	–	Tolerated	Benign	Not conserved	3.71E-04
F386C (rs78555408)	4	1	M	65	BrS, SCD	No	55	200	116	464	Damaging	Probably Damaging	Conserved	2.00E-03
L388P (rs199734710)	4	1	M	56	BrS, dizziness/palpitations	N/A	86	180	112	418	Damaging	Probably Damaging	Conserved	2.31E-04
417delK (−)	1	1	M	29	Permanent AF, SVR	–	–	–	–	–	–	–	–	–
H506N (−)	1	1	M	60	Paroxysmal AF	–	–	–	–	–	Tolerated	Benign	Conserved	8.40E-06
c.599+1 (rs75991777)	3	1	–	35	Paroxysmal AF, aflutter, inducible VT and ICD, normal coronary angiography	SCD and AF	63	162	116	421	–	–	–	–
V620I (rs151303346)	4	1	F	46	BrS, SCD	No	53	280	84	406	Damaging	Probably Damaging	Conserved	3.84E-04
I671V (−)	5	–	–	–	BrS association	–	–	–	–	–	N/A	Benign	conserved	0.00E+00
F719S (−)	1	1	M	25	Persistent AF	–	–	–	–	–	Damaging	Possibly-damaging	Conserved	4.13E-05

Mutation (dbSNP)[1]	Ref[2]	n[3]	G[4]	Age[5]	Phenotype	Family Hx[6]	ECG characteristics[7]				SIFT	Polyphen	Conservation	MAF[8]
							HR	PR	QRS	QTc				
G810W (rs145712124)	1	1	M	51	Paroxysmal AF	–	–	–	–	–	Damaging	probably-damaging	Conserved	1.89E-04
R814H (rs139861061)	1, 8	1	F	48	Paroxysmal AF	–	–	–	–	NP	Damaging	Possibly-damaging	Not conserved	3.13E-04
	1, 8	1	M	52	Persistent AF	–	–	–	–	NP	Damaging	Possibly-damaging	Not conserved	3.13E-04
	3	1	–	32	persist AF	–	103	186	86	418	Damaging	Possibly Damaging	Not Conserved	3.13E-04
E825D (rs146028829)	3	1	–	18	Paroxysmal AF, AVNRT	–	84	172	72	423	Tolerated	Benign	Not Conserved	7.66E-04
R844H (−)	7	1	M	35	SCD	SCD	60	144	72	336	Damaging	Damaging	Conserved	1.65E-05
	7	1	M	56	–	No	77	160	80	430	Damaging	Damaging	Conserved	1.65E-05
F938YFSX12 (−)	4	1	F	42	BrS, syncope, dizziness/palpitations	No	68	160	120	426	–	–	–	–
I999L (−)	3	1	–	35	Paroxysmal AF, IRBBB	Mother with SVPCs	61	160	100	412	Tolerated	Benign	Conserved	0.00E+00
P1045T (rs73062575)	6	1	F	25	AVNRT, concealed BrS, chest pain, migraines	–	–	–	–	–	Tolerated	Benign	Not conserved	5.00E-01
A1073V (rs6795970)	2	743	–	–	PR interval duration in all patients, and heart rate response in Afib patients.	–	–	–	–	–	benign	Benign	Not conserved	3.41E-01
	5	–	–	–	BrS association	–	–	–	–	–	benign	Benign	Not conserved	3.41E-01
V1078A (−)	6	1	M	44	BrS, AVNRT, PVC, VT, syncope	–	–	–	–	–	Tolerated	Benign	Not conserved	0.00E+00
D1080N (−)	4	1	M	28	BrS	No	71	240	158	409	Tolerated	Probably Damaging	Conserved	7.70E-05
F1115L (−)	1	1	M	58	Persistent AF	–	–	–	–	–	Damaging	Probably Damaging	Conserved	0.00E+00
W1135R (−)	1	1	F	34	Persistent AF	–	–	–	–	–	Damaging	Probably Damaging	Conserved	0.00E+00
I1225T (rs139638446)	4	1	M	44	BrS, dizziness/palpitations	N/A	80	180	110	404	Damaging	Probably Damaging	Conserved	4.61E-04
	4	1	M	44	BrS, syncope	No	3	200	116	525	Damaging	Probably Damaging	Conserved	4.61E-04
R1268Q (rs138832868)	1	1	M	16	Paroxysmal AF	–	–	–	–	–	Damaging	Benign	Conserved	1.77E-03
	1	1	M	46	Paroxysmal AF	–	–	–	–	–	Damaging	Benign	Conserved	1.77E-03
	3	1	–	30	Paroxysmal AF, IRBBB	–	59	152	94	394	Damaging	Probably Damaging	Conserved	1.77E-03
	3	1	–	23	AF, Aflutter	–	96	–	–	–	Damaging	Probably Damaging	Conserved	1.77E-03
	4	1	F	49	BrS, syncope, dizziness/palpitations	Yes	79	170–200	102	436	Damaging	Probably Damaging	Conserved	2.08E-03
	6	1	F	28	AVNRT, suspected BrS	–	–	–	–	–	Damaging	Benign	Conserved	1.00E-01
V1287I (rs145032037)	1	1	M	31	Persistent AF	–	–	–	–	–	Damaging	Probably Damaging	Conserved	5.03E-04
	1	1	M	52	Persistent AF	–	–	–	–	–	Damaging	Probably Damaging	Conserved	5.03E-04
G1299A (−)	5	–	–	–	BrS association	–	–	–	–	–	damaging	Probably Damaging	conserved	0.00E+00
N1328K (−)	7	1	M	68	Syncope	no	76	140	160	450	Damaging	Damaging	Conserved	0.00E+00
S1337T (rs11711062)	4	1	M	46	BrS, syncope, dizziness/palpitations	No	69	148	105	448	Damaging	Benign	Not conserved	4.54E-03

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Mutation (dbSNP)[1]	Ref[2]	n[3]	G[4]	Age[5]	Phenotype	Family Hx[6]	ECG characteristics[7]				SIFT	Polyphen	Conservation	MAF[8]
							HR	PR	QRS	QTc				
R1380Q (rs149155352)	1	1	M	60	Paroxysmal AF	–	–	–	–	–	Damaging	Probably Damaging	Conserved	9.08E-05
	7	1	M	50	VF	Seizure, syncope, SCD	59	200	60	388	Damaging	Damaging	Conserved	9.08E-05
G1406D (−)	4	1	M	36	BrS, dizziness/palpitations	No	73	150	110	442	Damaging	Probably Damaging	Conserved	8.26E-06
C1523Y (rs142217269)	1	1	M	47	Persistent AF	–	–	–	–	–	Damaging	Probably Damaging	Conserved	1.11E-03
	3	1	–	30	pAF	AF	54	154	96	398	Damaging	Probably Damaging	Conserved	1.11E-03
V1548F (−)	1	1	M	28	Paroxysmal AF, SVR	–	–	–	–	–	Damaging	Benign	Not conserved	0.00E+00
R1588Q (−)	3	1	–	28	Paroxysmal AF, AVNRT	–	55	156	96	419	Damaging	Probably Damaging	Conserved	1.65E-05
G1662S (rs151090729)	1	1	M	46	Persistent AF	–	–	–	–	–	Damaging	Probably Damaging	Conserved	1.57E-03
	4	1	M	44	BrS, syncope	No	79	190	120	436	Damaging	Probably Damaging	Conserved	1.31E-03
	4	1	M	19	BrS, SCD, syncope, dizziness/palpitations	Yes	44	200	120	352	Damaging	Probably Damaging	Conserved	1.31E-03
	4	1	M	27	BrS, SCD	No	120	220	120	387	Damaging	Probably Damaging	Conserved	1.31E-03
V1697I (rs77804526)	4	1	M	39	BrS, syncope	No	78	168	80	388	Tolerated	Benign	Conserved	1.01E-02
	4	1	M	31	BrS	Yes	75	200	120	403	Tolerated	Benign	Conserved	1.01E-02
	4	1	M	58	BrS, syncope	No	84	210	100	408	Tolerated	Benign	Conserved	1.01E-02
	6	1	M	60	AVNRT, suspected BrS	–	–	–	–	–	Tolerated	Benign	Conserved	4.10E-01
	6	1	F	41	AVNRT, concealed BrS, chest pain	–	–	–	–	–	Tolerated	Benign	Conserved	4.10E-01
N1715T (−)	4	1	M	65	BrS, induced VT/VF, dizziness/palpitations	No	71	220	72	463	Damaging	Probably Damaging	Conserved	8.24E-06
R1863Q (rs191869263)	7	1	M	51	Syncope	no	57	190	70	351	Damaging	Damaging	Conserved	1.65E-05
R1869C (rs141648641)	1	1	M	25	Persistent AF	–	–	–	–	–	Damaging	Probably-damaging	Conserved	8.07E-04
	4	1	M	43	BrS, SCD, dizziness/palpitations	No	64	192	84	385	Damaging	Probably Damaging	Conserved	9.23E-04
	4	1	F	47	BrS, dizziness/palpitations	No	56	180	88	408	Damaging	Probably Damaging	Conserved	9.23E-04
A1886V (rs142653846)	1, 8	1	M	17	Paroxysmal AF, SVR	–	–	–	–	NP	Tolerated	Benign	Not conserved	1.18E-03

[1]Mutation; designated amino-acid changes and corresponding dbSNP annotation when available. Of note, none of these mutations with QT prolongation fell in the enhancer region.

[2]References; 1: (Savio-Galimberti, et al., 2014), 2: (Delaney, et al., 2014), 3: (Jabbari, et al., 2015), 4: (Hu, et al., 2014), 5: (Behr, et al., 2015), 6: (Hasdemir, et al., 2015), 7: (Fukuyama, et al., 2016), 8: (Bezzina, et al., 2013).

[3]n; number of patients.

[4]G; gender, M: male and F: female.

[5]Age; age in years

[6] Family Hx; family history.

[7] ECG characteristics; HR: heart rate in beats per minute, PR: PR interval in milliseconds, QRS: QRS interval in milliseconds, QTc: corrected QT interval in milliseconds, borderline elevated QTc interval is highlighted in grey and high QTc interval is highlighted in yellow.

[8] MAF; minor allele frequency based on the EXAC database.