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KCNQ1 mutations in patients with a family history of lethal cardiac arrhythmias and sudden death

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Abstract

Long QT syndrome (LQTS) is the prototype of the cardiac ion channelopathies which cause syncope and sudden death. LQT1, due to mutations of *KCNQ1* (*KVLQT1*), is the most common form. This study describes the genotype–phenotype characteristics in 10 families with mutations of *KCNQ1*, including 5 novel mutations. One hundred and two families with a history of lethal cardiac events, 55 LQTS, 9 Brugada syndrome, 18 idiopathic ventricular fibrillation (IVF), and 20 acquired LQTS, were studied by single-strand conformational polymorphism (SSCP) and DNA sequence analyzes. Families found to have *KCNQ1* mutations were phenotyped using ECG parameters and cardiac event history, and genotype–phenotype correlation was performed. No mutations were found in Brugada syndrome, IVF, or acquired LQTS families. Ten out of 55 LQTS families had *KCNQ1* mutations and 62 carriers were identified. Mutations included G269S in domain S5; W305X, G314C, Y315C, and D317N in the pore region; A341E and Q357R in domain S6; and 1338insC, G568A and T587M mutations in the C-terminus. W305X, G314C, Q357R, 1338insC, and G568A, appeared to be novel mutations. Gene carriers were 26 ± 19 years (32 females). Baseline QTc was 0.47 ± 0.03 s (range 0.40–0.57 s) and 40% had normal to borderline QTc (≤ 0.46 s). Typical LQT1 T wave patterns were present in at least one affected member of each family, and in 73% of all affected members. A history of cardiac events was present in 19/62 (31%), 18 with syncope, 2 with aborted cardiac arrest (ACA) and six with sudden death (SD). Two out of 6 SDs (33%) occurred as the first symptom. No difference in phenotype was evident in pore vs. non-pore mutations. *KCNQ1* mutations were limited to LQTS families. All five novel mutations produced a typical LQT1 phenotype. Findings emphasize (1) reduced penetrance of QTc and symptoms, resulting in diagnostic challenges, (2) the problem of sudden death as the first symptom (33% of those who died), and (3) genetic testing is important for

identification of gene carriers with reduced penetrance, in order to provide treatment and to prevent lethal cardiac arrhythmias and sudden death.

Keywords

arrhythmias; ECG; *KVLQT1/KCNQ1*; long QT syndrome; mutations; sudden death

Long QT syndrome (LQTS) is a cardiac ion channel disorder with genotypic-specific ST-T ECG patterns and variable clinical expression. Patients are susceptible to *torsade de pointes* and ventricular fibrillation, leading to syncope episodes and sudden death (1–3). It is the prototype of the expanding list of cardiac ion channelopathies.

In the past decade significant advances from molecular genetic studies have dramatically improved our understanding of LQTS. To date, mutations have been identified in five genes: *KCNQ1*, previously called *KVLQT1*, on chromosome 11p15.1 (LQT1), *KCNH2* or *HERG* on 7q35–36 (LQT2), *SCN5A* on 3p21 (LQT3), *KCNE1* (LQT5) and *KCNE2* (LQT6) on 21q22. *KCNQ1* was the first LQTS gene cloned. It spans approximately 400 kb, and encodes a novel cardiac potassium channel (4). *KCNQ1* is the α -subunit for a functional potassium channel in the heart and has a conserved potassium-selective pore-signature sequence flanked by six membrane-spanning segments. *KCNQ1* protein normally functions by interacting with MinK (encoded by *KCNE1*), a short potassium channel β -subunit with a mere 130 amino acids and only one transmembrane-spanning segment (5,6). The physical interaction between *KCNQ1* and MinK forms the functional channel that produces the slow delayed rectifier potassium current (I_{Ks}) in cardiac myocytes. Moreover, MiRP1 (encoded by *KCNE2*), a homolog of MinK, also has interaction with the *KCNQ1* subunit resulting in a drastic change of *KCNQ1* current amplitude and gating properties (7).

Individuals who are heterozygous for mutations in *KCNQ1/KCNE1* are associated with autosomal dominant LQTS (Romano–Ward syndrome). Those with homozygous mutations in *KCNQ1* or compound heterozygous *KCNQ1* or *KCNQ1/KCNE1* mutations have a more severe clinical outcome, and are associated with autosomal recessive LQTS (Jervell–Lange–Nielsen syndrome) (8).

Mutations in *KCNQ1* are the most common cause of LQTS and over 100 mutations have been reported. In addition to the genetic heterogeneity, there is prominent phenotypic heterogeneity with reduced penetrance and variable expression, causing challenges for accurate diagnosis of some patients (9). Therefore, to identify additional mutations and further expand the genotype–phenotype correlations in LQT1 we screened 102 families for mutations in *KCNQ1* and correlated mutation findings with clinical features in mutation carriers.

Methods

Identification of LQTS patients

One hundred and two families with cardiac ion channelopathy phenotype or acquired LQTS were referred to the Q. Wang laboratory for genotyping from medical clinics in North America, South America and Europe. Included were 55 with suspected LQTS, 9 Brugada syndrome, 18 idiopathic ventricular fibrillation (IVF) and 20 acquired LQTS. Informed consent was obtained from all participants or their guardians, in accordance with standards established by local institutional review boards.

Isolation of genomic DNA

Genomic DNA was prepared from whole blood using the DNA Isolation Kit for Mammalian Blood (Roche Diagnostic Co., Indianapolis, IN).

SSCP analysis

Single-strand conformational polymorphism (SSCP) analysis was carried out as described previously (4,10). The coding region and the intron splice sites of the *KCNQ1* gene were screened by SSCP analysis for mutations in the probands. PCR primers for SSCP were described previously (4,11).

Sequence analysis of SSCP conformers

The aberrant SSCP conformers were excised directly from dried gels and rehydrated in 100 μ l of distilled water with shaking overnight at 55 °C. The eluted DNA (10 μ l) was used as the template for a second round of PCR with the original primer pair. Amplified products were purified through a QIAquick PCR Purification Kit (QIAGEN Inc., Valencia, CA) and sequenced with forward and reverse primers using an ABI3100 Genetic Analyzer (Applied Biosystems, Foster City, CA).

Phenotyping of families with *KCNQ1* mutations

Phenotyping was performed on those families who had *KCNQ1* mutations, blinded to genotype results.

ECG—The initial resting 12-lead ECG was examined on all subjects except three SD patients who had no ECG records. QT interval was manually measured by one of two investigators (LZ or GMV) from the lead with the longest QT interval (usually lead II or V5). The end of the T wave was taken as the point of maximal change in slope as T wave merged with the baseline, as previously described (9). QTc was calculated using Bazett's formula for heart rate correction (12). The U wave, if present, was excluded from the QT measurement. In the presence of sinus arrhythmia, the average cycle length was determined and QTc was calculated from a beat with average cycle length (13). T wave morphology was evaluated for characteristic LQTS patterns (14) by one investigator (LZ) blinded to genotype results.

History—History of cardiac events including syncope, aborted cardiac arrest (ACA) and sudden cardiac death (SD) was obtained from patient records or by contact with patients, family members or guardians as needed. Therapeutic information including β -blockers, pacemakers and implantable cardiac defibrillators (ICD) was obtained.

Genotype–phenotype correlations

For simplicity, kindreds are identified by the Wang laboratory kindred number rather than by the kindred number of the referring physicians. Phenotypic features by genotype were compared between genotypes and probands and other affected family members using the Kruskal–Wallis test. A p-value of 0.05 or less was used to denote statistical significance.

Results

No mutations of *KCNQ1* were found in families with the Brugada syndrome, IVF or acquired LQTS phenotypes. Ten out of 55 (18%) LQTS phenotype families had *KCNQ1* mutations. Five of the mutations were novel. We identified 62 gene carriers (age: 26 ± 19 years; 32 females) from these 10 families; 46 were genotyped and 16 were obligate gene carriers. A summary of the genotype–phenotype results in these 62 carriers is shown in Table 1. The pedigrees and SSCP/DNA sequence analysis results are shown in Figs 1–4. *KCNQ1* mutations

were clustered in transmembrane domain S5 (one mutation), the pore region (four mutations), domain S6 (two mutations), and the C-terminus (three mutations). None of the mutations reported here were detected in DNA samples from 200 unrelated control individuals (data not shown). No mutations were identified in the N-terminus or domains S1 to S4. Family history and phenotype findings are described in the following paragraphs, arranged by mutation location and mutation type.

Domain S5 mutation

G269S mutation in kindred 167—Figure 1 shows the pedigree and SSCP results for this kindred. Mean QTc was 0.47 ± 0.02 s, and 36% (4/11) showed QTc ≤ 0.46 s. The proband had a history of frequent syncope while playing basketball, but was not recognized as LQTS until he experienced an ACA while swimming at the age of 14 years. ECG at that time showed a QTc of 0.50 s with broad-based T waves. He has been asymptomatic on β -blockers. Ten other affected family members were asymptomatic, two on β -blockers.

Pore region mutations

Four mutations in the pore region were identified: the pedigrees and SSCP results are shown in Fig. 2.

Nonsense mutation W305X in kindred 960—The proband died suddenly, hours after playing basketball, at the age of 16 years. ECG was not available. Mean QTc in eight other affected members was 0.46 ± 0.2 s. Seventy-five percent (6/8) of the affected members showed resting QTc ≤ 0.46 s, including two who had syncopal episodes before β -blocker therapy.

Missense mutation G314C in kindred 846—The proband had experienced several episodes of syncope during exercise in her teenage years, but was not recognized as LQTS until she had an ACA just after swimming at the age of 33 years. QTc on baseline ECG was 0.57 s. A slow heart rate (<50 bpm) was noted, and an ICD was implanted. At the age of 37 years, she had another syncopal episode while skiing, off β -blockers because of fatigue side-effect. The ECG from ICD interrogation revealed *torsade de pointes* degenerating into ventricular fibrillation, which was converted to sinus rhythm by the ICD. Five other affected family members were asymptomatic, QTc 0.51, 0.50, 0.47, 0.46 and 0.45 s. Three were on β -blockers.

Missense mutation Y315C was identified in two members of kindred muj—The proband experienced syncope while engaged in a game of basketball at the age of 11 years. Her QTc was 0.55 s. She is asymptomatic on β -blockers. A 9-year-old brother was asymptomatic at diagnosis, QTc 0.47 s, and has continued asymptomatic on β -blocker therapy.

Missense mutation D317N in kindred 862—The proband had multiple episodes of syncope associated with exercise prior to sudden death at the age of 32 years. No ECG was available. The two siblings of the proband were found to be mutation carriers. A 30-year-old sister with a QTc of 0.50 s had a history of syncopal episodes during exercise. Another sister was asymptomatic at the age of 28 years, QTc 0.48 s. Both are now on β -blocker therapy.

Domain S6 mutations

Two mutations in domain S6 were identified. The SSCP and sequence analyzes are shown in Fig. 3.

Missense mutation A341E in kindred 1339—This kindred had 10 clinically affected members. Their mean QTc was 0.47 ± 0.1 s, and 88% showed typical LQT1 T wave patterns.

Only one was genotyped and she had a QTc of 0.49 s and was asymptomatic when diagnosed at the age of 35 years. Two affected members had experienced syncope in the absence of β -blockers. A grandfather of the proband had died suddenly around 1930 at the age of 30 years, with no clear cause. A341 appears to be a mutation hotspot, with A341E found in three families ((4) and this study) and A341V found in four families (4).

Missense mutation Q357R in kindred 588—The 40-year-old female patient with mutation Q357R had reported a syncopal event. She also reported recurrent chest discomfort and palpitations, said to be due to supraventricular tachycardia at 170 bpm, and ‘polymorphous ventricular tachycardia’ at the age of 39 years. LQTS was diagnosed at age 40, QTc was 0.43 s. She has been asymptomatic on β -blocker therapy.

C-terminus mutations

Three mutations were identified in the C-terminus. The pedigrees and the SSCP and sequence analyzes are shown in Fig. 4a–c.

Insertion frameshift mutation 1338insC in kindred 457—This mutation inserts a single nucleotide C between nucleotide position 1338 and 1339. This insertion causes a frameshift, leading to a premature stop codon and truncation of the KCNQ1 C-terminus. The proband (Fig. 4a) had syncopal episodes at the age of 7 years, but was not recognized as LQTS. He died suddenly while swimming at the age of 11 years. His ECG had a QTc of 0.48 s. His mother subsequently had an episode of syncope on an airplane flight immediately after departure and afterwards had an ICD implanted. Eleven other family members were identified as mutation carriers, all asymptomatic at ages 8–70 years, mean QTc 0.46 s, including two with a QTc of 0.52 and 0.51 s, respectively, and four with a QTc of 0.40 to 0.44 s and normal T waves.

Missense mutation G568A in kindred 187—This mutation was identified in the proband and his mother (Fig. 4b). The proband had syncopal episodes during emotion and swimming, and had received a pacemaker and had been prescribed Atenolol at 4 mg/kg. He died suddenly at the age of 15 years during excitement. His mother had had numerous auditory stimuli-induced syncopal attacks (e.g. fire alarms in school, thunder) and had an ICD implanted. She subsequently had several appropriate ICD discharges delivered during similar circumstances, in the absence of β -blocker therapy. The *HERG* gene was examined during her genotyping and no mutation was identified.

Missense mutation T587M in kindred 933—The proband was diagnosed as LQTS after syncope during exercise and emotion as a child. He had been on β -blockers for 10 years and asymptomatic for some time. At age 14 he experienced sudden death during intense emotional distress. He was reportedly on 80 mg of propranolol LA at the time of death. His father indicated he was quite compliant with his medication, but it was noted he sometimes missed doses. QTc was 0.50 s. Three other affected family members included the proband’s asymptomatic mother at age 47, QTc 0.48 s, his 12-year-old brother who had syncopal episodes during emotion and swimming before β -blocker medication, and his asymptomatic grandfather, age 75, QTc 0.46 s.

ECG and clinical correlations

ECGs were available on 58/62 patients. No ECG was available on four patients, including three SD victims. The mean QTc was 0.47 ± 0.03 s (range 0.40–0.57 s), 19% (11/58) had a normal QTc (≤ 0.44 s), 40% (23/58) a normal to borderline QTc (≤ 0.46 s) on initial resting ECG.

A history of cardiac events was present in 31%, 19/62, including 18 with syncope, 2 with ACA and 6 with SD. In patients with QTc ≤ 0.46 s, 22% (5/23) had a history of syncope, and there were no ACA or SD. The sudden death victims were all males, mean age 19 ± 10 years; five were obligate gene carriers, and two (33%) had SD as the first symptom. Four SDs occurred prior to the diagnosis of LQTS and five occurred in the absence of β -blocker or other therapy. One 14-year-old SD victim had been prescribed β -blocker medication, Atenolol at 4 mg/kg, and had received a pacemaker several years prior to SD. It is not known with certainty whether he was taking the prescribed β -blocker at the time of death. In the 14/18 patients in whom a specific cardiac event trigger was identifiable, it was exercise in 11 (7 swimming), emotional stress in 2, and startle/auditory stimuli in 2 patients. Typical LQT1 T wave patterns (14) were found in at least one affected member of each family, and in 73% of all affected members. The four typical patterns, infantile T wave, normal appearing T wave, broad-based T wave and late onset of normal appearing T were seen in 6%, 36%, 23% and 8% of the patients, respectively. 13% had non-specific T waves or abnormal T waves due to other cardiac conditions. Fourteen percent had both a normal T wave and normal QTc interval.

There were no significant differences detected in clinical manifestations between mutations in the pore region and the other locations (Table 1). Mean QTc in patients with pore region mutations was 0.48 ± 0.04 s, and in non-pore mutation patients was 0.47 ± 0.03 s, $p = \text{NS}$. Comparing symptoms, 10% (2/21) of pore mutation patients and 10% (4/41) of non-pore mutations patients experienced sudden death. ACA occurred in 5% (1/21) and 2% (1/41), respectively. Differences in QTc and clinical outcome between probands and other affected family members are shown in Table 2.

Discussion

Ten mutations of the *KCNQ1* gene were identified in 10 out of 55 (18%) families with the LQTS phenotype. LQT1 is the most common LQTS genotype, thus, finding only 18% with LQT1 was surprising but is probably just coincidental, related to the small number of families involved. Five out of the 10 mutations, W305X, G314C, Q357R, I338insC, and G568A, have not been previously reported and appear to be novel mutations. Therefore, the results expand the spectrum of *KCNQ1* mutations causing LQTS. The novel mutations produced a typical LQT1 phenotype.

Compared with the results of prior studies (15), the majority (70%) of mutations identified in this study were located in the pore region and transmembrane domains S5 and S6 that are immediately adjacent to the pore, and 30% were in the C-terminus. In the report by Splawski et al. (15) just 23% of 75 *KCNQ1* mutations were in S5 or S6 domains or pore region. In a recent report on clinical expression of different *KCNH2* (*HERG*) mutations (16), pore region mutations appeared to result in a more severe phenotype than other mutations. We did not observe any significant difference in QTc or frequency/type of cardiac events between pore and other mutational sites in these *KCNQ1* mutations (Table 1).

Reduced penetrance

Our findings emphasize previous observations regarding the reduced penetrance of the QT and symptoms phenotypes in LQTS and the resultant difficulty in diagnosis by QTc interval alone. Schwartz first suggested in 1980 (17) that some LQTS patients might have a normal QT interval. This was confirmed by Vincent et al. in 1992 (9) in the first genotype–phenotype study of LQTS, in which 6% of 83 gene carriers had a normal (≤ 0.44 s) QTc on baseline ECG. An additional 25% had QTc values of 0.45 or 0.46 s such that 31% of gene carriers had a QTc ≤ 0.46 s, values which overlapped those of normals, and were, thus, non-diagnostic for LQTS. The range of QTc intervals in gene carriers was 0.41 to 0.59 s. A QTc ≥ 0.48 s in females and ≥ 0.47 s in males was 100% diagnostic in the absence of other diseases (heart, neurologic) or

QT prolonging drugs. A QTc ≤ 0.40 s made LQTS highly unlikely. More recent data (18) on 201 gene carriers demonstrated that 12% of all gene carriers (12% LQT1, 17% LQT2 and 5% LQT3) had a normal QTc of 0.41 to 0.44 s on baseline ECG. Thirty-one percent, similar to the 1992 report, had a QTc ≤ 0.46 s, and QTc sensitivity and specificity were also similar to the earlier report. Priori et al. (19) and others have added additional insights into the issue of phenotypic heterogeneity and reduced penetrance. In the present study, 40% of the mutation carriers had QTc intervals of between 0.40–0.46 s on resting ECG. Three of the families with novel mutations had enough gene carriers to at least make a comment on frequency of normal-borderline QTc intervals in the novel mutation families: W305X in the pore region 67% (6/9), 1338 ins in the C terminus 46% (6/13) and G314C in the pore region 43% (3/7). These percentages are higher than the average 31% in LQT1, suggesting that these novel mutations may cause a lower QTc than other mutations. Also, the frequency of cardiac events in families with these mutations is lower than other mutations (Table 1). However, the number of patients involved is probably too small to make any definitive conclusions regarding these points. The percent of patients in each of the 10 genotypes who experienced cardiac events is shown in Table 1. While the numbers are small for meaningful conclusions, the wide range of event frequency is consistent with many prior studies on heterogeneity of symptoms in LQTS families.

This degree of reduced penetrance, and our finding that 14% of gene carriers had both a normal QTc and T wave morphology, highlights the importance of genetic testing in patients and families suspected of LQTS. Genetic testing is of particular importance in those family members with these overlapping, normal to borderline QT intervals. Correct diagnosis allows preventive measures, including β -blockade, reduction of physical and emotional stress, avoidance of QT prolonging drugs, and ICD or pacemaker therapy to be instituted. Correct diagnosis also enables non-gene carriers to be reassured that they do not have the risk of their affected relatives for life-threatening arrhythmias, syncope, and sudden death, allowing them to lead normal and secure lives.

Variability of symptoms

Considerable variability in the frequency of cardiac events occurs in members of single families, between families with the same genotype and between genotypes. At least one out of three and probably more of gene carriers never have symptoms (9). Among those with symptoms, some have hundreds of events without ever experiencing ACA or SCD, while others have SCD as their first episode. A comparison of probands with other affected family members is illustrative. Probands are, of course, those with the most prominent phenotype, which is why they are the easiest and the first to be identified. Table 2 shows that the probands in this series had the expected longer QTc values and higher rate of cardiac events than the other affected family members who were identified by family screening rather than obviously prolonged QT or presence of symptoms. These results are similar to the findings from the International LQTS Registry (20). Why certain patients have a higher risk of lethal events than other patients, even in the same family, is unknown and a topic of vigorous research at present. Modifier and regulatory genes, presence and location of SNPs affecting gene function, the autonomic system (21), environmental or other unknown factors may be involved in the variable expression and initiation of cardiac events.

Cardiac event triggers differ by genotype, and the triggers in 90% of LQT1 cases are exercise and emotion (22). Consistent with that large study, 8 out of 10 families, including 4 out of 5 with novel mutations, had events triggered by physical activity or emotional stress (Table 2). Auditory stimuli, recognized in LQT1 but more associated with LQT2, were prominent triggers in one patient. Different triggers may be present in different members of the same family, and sometimes in the same patient, for example, the G568A mutation carrier with both auditory

stimuli and emotional stress triggers. In two families the cardiac events occurred without clear triggers.

Our study was not designed to examine therapeutic issues. Just 18 out of 62 gene carriers had a history of symptoms so the numbers are too small for meaningful conclusions. Five SD patients were untreated at the time of death, four occurring prior to diagnosis; the sixth patient experienced SD after having a pacemaker inserted and β -blockers prescribed, though compliance with the medication at the time of death could not be verified. Moss et al. have reported on the effectiveness and limitations of β -blockers in LQTS (23) and a preliminary report in LQT1 alone demonstrated a very high degree of efficacy when patients were counseled and followed to assure compliance with the medication, and appropriate dose increments during growth in children were made (24). The role of ICD therapy in LQTS patients is not well defined (25,26). Three patients in this study received ICDs, one after an ACA. Two had appropriate and successful shocks delivered subsequently, all in the absence of β -blocker therapy.

Typical LQT1 ECG patterns were observed in 73% of mutation carriers, including 100% of probands, confirming that ECG patterns may be used to predict the genotype in most families and subjects (14). This approach is very helpful for directing genotype screening by indicating which gene should be screened first, reducing time and cost. Some gene carriers have a normal phenotype with normal QTc and T wave morphology and mutation screening is the only approach for diagnosis in these individuals.

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Fig. 1.

KCNQ1 mutation G269S in domain S5. (a) Pedigree structure of kindred QW167. Males are denoted by squares and females are indicated by circles. Affected individuals are shown as filled symbols, and normal individuals are in empty symbols. The individuals with uncertain diagnosis of LQTS are indicated by gray symbols. The proband is indicated by an arrow. The results of SSCP analysis are shown below the pedigree. (b) Sequence analysis of the abnormal SSCP conformer revealed a G to A change at nucleotide position 805 (805G>A), leading to substitution of a glycine residue by a serine residue at codon 269 (G269S) in the S5 domain.

Fig. 2.

KCNQ1 mutations associated with LQTS in the pore region. (a) Pedigree structures of kindreds QW960, QW846, QWmuj, QW862 are shown above the results of SSCP analysis. For kindred QW846, only two out of six family members are shown. (b) Sequence analysis of abnormal SSCP bands in (a) revealed the stop codon mutation W305X in kindred QW960 due to the nucleotide change 914G>A, the G314C mutation in kindred QW846 (nucleotide change, 940G>T), the Y315C mutation in kindred QWmuj (nucleotide change, 944 A>G), and the D317N mutation in kindred QW862 (nucleotide change, 949G>A).

Fig. 3.

KCNQ1 mutations associated with LQTS in domain S6. (a) The results of SSCP analyzes are shown in a patient in kindred QW1339 and in QW588, along with unrelated normals. Family pedigree analysis revealed nine additional affected members in QW1339 and two additional patients in QW588. (b) Sequence analysis of abnormal SSCP bands revealed the A341E mutation in kindred QW1339 and the Q357R mutation in kindred QW588.

Fig. 4.

KCNQ1 mutations associated with LQTS in the C-terminus. (a) Identification of the *KCNQ1* mutation 1338 insC in kindred QW457. Pedigree structure of kindred QW457 is shown at the left. The result of SSCP analysis is shown below the pedigree (only 4 out of the 13 family members are shown). Sequence analysis identified that a C insertion between nucleotides 1338 and 1339, which results in a frameshift mutation and a premature stop codon X, leading to truncation of *KCNQ1* protein. (b) Identification of *KCNQ1* mutation G568A in kindred QW187. Pedigree structure of kindred QW187 is shown at the left. The result of SSCP analysis is shown below the pedigree. Sequence analysis identified a G to C change at nucleotide position 1703 (1703 G>C). It leads to substitution of a glycine residue by an alanine residue at codon 568 in the C-terminal region distal to S6. (c) Identification of *KCNQ1* mutation T587M in kindred QW933. Pedigree structure of kindred QW933 is shown at the left. The result of SSCP analysis is shown below the pedigree. Sequence analysis identified a C to T

change at nucleotide position 1760 (1760C>T), leading to substitution of a threonine residue by a methionine residue at codon 587 in the C-terminal region distal to S6.

Genotype-phenotype characteristics in 10 families with *KCNQ1* mutations

Kindred no.	Nucleotide change	Mutation	Coding effect	Region	QTc Mean, SD	Affected members (% with CE)	SCD/ syncope/ ACA	Trigger factor	Prior identification
167	805 G>A	G269S	Missense	S5	0.47 ± 0.02	11 (9%)	0/0/1	Swimming	(27)
960	914 G>A	W305X	Nonsense	Pore	0.46 ± 0.01	9 (33%)	1/3/0	Basketball/running	Novel
846	940 G>T	G314C	Missense	Pore	0.49 ± 0.04	6 (30%)	0/2/1	Swimming/skiing	Novel
mutj	944 A>G	Y315C	Missense	Pore	0.51 ± 0.06	3 (33%)	0/1/0	Basketball	(11)
862	949 G>A	D317N	Missense	Pore	0.49 ± 0.01	3 (33%)	1/1/0	Exercise	(28)
1339	1022 C>A	A341E	Missense	S6	0.47 ± 0.01	10 (30%)	1/2/0	None	(4)
588	1070 A>G	Q357R	Missense	S6	0.43	1 (100%)	0/1/0	None	Novel
457	1338insC	—	Insertion frameshift	C-terminal region distal to S6	0.46 ± 0.04	13 (15%)	1/2/0	Swimming	Novel
187	1703 G>C	G568A	Missense	C-terminal region distal to S6	0.50	2 (100%)	1/2/0	Auditory stimuli, excitement, emotional stress, physical stress	Novel
933	1760 C>T	T587M	Missense	C-terminal region distal to S6	0.48 ± 0.02	4(50%)	1/1/0	Emotional stress	(29)

Table 2
Differences in phenotype and cardiac event rate between probands and other affected members

Age	(years)	QTc Sex ^a	LQT1 T ms	wave patterns ^a	Syncope ^b	ACA ^b	SD ^b
Probands n = 10	20 ± 11	M = 7	0.49 ± 0.39	100%	90%	20%	50%
Affected members n = 52	29 ± 20	M = 23	0.47 ± 0.26	68%	23%	0	2%

^a p < 0.05 and

^b p < 0.005 probands vs. affected members by Kruskal–Wallis test.