Short Report

Identification of a novel \( KCNQ1 \) mutation in a large Saudi family with long QT syndrome: clinical consequences and preventive implications


Congenital long QT syndrome (LQTS) is an inherited potentially fatal arrhythmogenic disorder that is characterized by prolonged corrected QT (QTc) interval (1). The clinical course of LQTS is variable, whereby affected individuals may have a lifelong asymptomatic course (2). To date, 13 genes have been implicated in LQTS (3). However, mutations in three genes (\( KCNQ1 \), \( KCNH2 \), and \( SCN5A \)) account for approximately 70% to 75% of the cases (4). The syndrome can be inherited either as an autosomal dominant disorder known as Romano-Ward syndrome (OMIM # 192500) or as an autosomal recessive disorder, associated with congenital deafness, known as Jervell and Lange-Nielsen syndrome (JLNS, OMIM # 220400). The clinical diagnosis

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Conflict of interest

Nothing to declare.

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Fig. 1. Three-generation pedigree of the family of the proband (indicated by the arrow) showing the results of screening for KCNQ1 mutation H258P. Filled symbols indicate genetically affected individuals.

of LQTS can be challenging; therefore, a scoring system known as Schwartz criteria is often used for the diagnosis of LQTS (1, 5).

In addition to avoidance of QT-prolonging drugs and competitive athletics, beta-blockade is the mainstay of therapy for patients with LQTS. Implantable cardioverter-defibrillator (ICD) therapy is reserved to patients that remain symptomatic while on therapy and survivors of aborted cardiac arrest (6). Left cardiac sympathetic denervation has also been shown to control the symptoms of LQTS in selected cases (7).

In this work, we describe the clinical and molecular analysis in a large Saudi family with LQTS, which was identified to segregate a novel KCNQ1 mutation. The relevant therapeutic and preventive implications of the extended clinical and genetic screening that was conducted in this family are discussed.

Materials and methods

Clinical evaluation

The proband (Individual II-6, Fig. 1) was a 25-year-old female who presented to the Cardiovascular Genetics Program at King Faisal Specialist Hospital & Research Center (KFSH&RC), Riyadh, with a history of syncope. She was found to have a prolonged QTc interval of 550 ms. Her family history indicated that her brother (individual II-4) had repeated syncope, which necessitated the implantation of a cardioverter-defibrillator. There is no history of sudden death in the family. The proband’s relatives (n = 24) underwent clinical assessment, electrocardiogram (ECG), and molecular testing. The QTc intervals were measured separately by two cardiologists who were blinded to the mutation result. The longest QTc interval was recorded. This study was approved by the Research Advisory Council at KFSH&RC. The participants were recruited in the study after obtaining an informed consent.

KCNQ1, KCNH2 and SCN5A gene sequencing

Genomic DNA was extracted from whole blood using Puregene Blood Core Kit C (QIAGEN Sciences, Valencia, CA) and amplified by polymerase chain reaction (PCR) using intronic primers that were designed to flank 50–100 bp of the coding exons of three LQTS-susceptibility genes: KCNQ1 (NM_000238), KCNH2 (NM_198056) and SCN5A (NM_000335). All the three genes were amplified using QIAGEN PCR Reagent kit (QIAGEN GMBH, Hilden, Germany). Purified PCR amplicons were directly sequenced using the dideoxy chain-termination method with an ABI Prism Big Dye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) following the manufacturer’s instructions and processed on a MegaBACE 1000 DNA Analysis System (Molecular Dynamics, Sunnyvale, CA). Sequence analysis was performed using the SeqMan 6.1 module of the Lasergene (DNA Star Inc., Madison, WI) software package and compared to the reference GenBank sequences.

NOS1AP and KCNE1 variants screening

All family members were screened for two NOS1AP variants (rs4657139 and rs16847548) and for the D85N variant in KCNE1 gene. PCR primers were designed to flank the variants, and the amplicons were sequenced and analyzed using the same methods stated in the previous section.

Results

Clinical evaluation

Twenty-six family members (16 males and 10 females; age 2–84 years) were evaluated (Table 1). QTc interval was ≥480 ms in 11 individuals (8 males and 3 females; age 6–67 years), between 450–480 ms in 5 individuals (3 males and 2 females, age 5–84 years), and <450 ms in 10 individuals (5 males and 5 females, age 2–50 years). Of the 26 individuals, only 2 were found to be symptomatic (individuals II-4 and II-6). Their QTc intervals were 590 and 550 ms, respectively. However, of the 12 mutation carriers, 7 were children and all of them have been asymptomatic. Both symptomatic individuals were treated with beta-blockers, which controlled the manifestations in individual II-6, but individual II-4 continued to have episodes of syncope and therefore an ICD was implanted.

KCNQ1 mutation detection and modifiers screening

Direct sequencing of the KCNQ1 gene in both the forward and reverse directions in the proband
revealed the presence of a novel heterozygous c.773 A>C mutation resulting in the substitution of histidine with proline at position 258. This mutation was identified in the proband’s mother, daughter and 9 other relatives (Fig. 1). This novel mutation was not found in 100 chromosomes from ethnically matched normal controls. Protein sequence alignment of KCNQ1 orthologs showed that the histidine residue is highly conserved down to Xenopus tropicalis (UCSC Genome Browser Vertebrate Multiz Alignment and Conservation Tool; http://genome.ucsc.edu/). In addition, both SIFT (http://sift.jcvi.org) and Polyphen (http://genetics.bwh.harvard.edu/pph/) programs predicted the variant to be probably ‘intolerant’ and ‘probably damaging’, respectively. Sequence analysis of KCNH2 and SCN5A did not reveal any difference from the reference sequence. Screening for the NOS1AP variants (rs4657139 and rs16847548) and KCNE1-D85N polymorphism did not reveal a correlation with the cardiac symptoms or with the QTc intervals.

Discussion

In this study, we identified a novel heterozygous mutation (c.773 A>C, p.H258P) in the KCNQ1 gene in a large Saudi family with LQTS. Screening the entire coding regions of the other two genes KCNH2 and SCN5A revealed no change. Several clues are in support of this novel mutation being causative. There was a clear cosegregation of the mutation with the clinical and/or electrocardiographic findings. All of the proband’s first-degree relatives who were negative for the mutation were asymptomatic and had normal QTc interval. The mutant allele, which changes a polar amino acid with a non-polar one, was not detected in ethnically matched controls. In addition, this change was predicted to be pathogenic by SIFT and Polyphen programs.

The KCNQ1 subunit has six membrane spanning segments (S1–S6) with intracellular amino- and carboxy-termini. The transmembrane domains are partitioned into distinct functional modules: a voltage-sensing module (S1–S4) and an ion-conducting module (S5–S6) (8). Histidine at 258, which is conserved down to X. tropicalis, is located in the S4–S5 linker, and its replacement with asparagine or arginine has been previously reported in association with LQTS (9), which suggests that histidine at position 258 has an important role in maintaining the properties of the KCNQ1 subunit. Moreover, other mutations in the S4–S5 linker have been shown to alter gating properties and significantly produce smaller current (10, 11).

Our work in this study illustrates several genetic concepts. First, the clinical, electrocardiographic and
molecular analysis of the 26 members across the three generations of our family revealed that the c.773 A>C allele has incomplete penetrance. Of the 12 mutation carriers, only 2 were clinically symptomatic. However, 7 were children and all of them have been asymptomatic. Nevertheless, they will remain at risk of developing symptoms later. With the exception of 1 child (individual III-15) who had a QTc of 470 ms, all identified carriers had prolonged QTc intervals of ≥480 ms. In addition, the electrocardiographic and molecular screening in our family showed a clear intrafamilial variability from being asymptomatic to episodes of syncope that require ICD, as well as from normal ECG to a prolonged QTc interval of 590 ms. The proband’s sibling (individual II-4) had a prolonged QTc of 590 ms and episodes of syncope that necessitated an ICD implantation, whereas his mother was asymptomatic. Of note though, our evaluation identified infant carriers who may show clinical symptoms and/or electrocardiographic abnormalities in the future. Incomplete penetrance in LQTS has been well described in literature, with about 10–35% of LQTS patients presenting with a normal QTc (12). The clinical consequence of this finding is that patients who are found to be carriers of the mutation are at risk of developing symptoms that might be life threatening. However, aggressive medical intervention, such as device implantation or sympathetic denervation, may not be needed in all affected individuals as beta-blocker therapy is generally effective for those with KCNQ1 mutations. Furthermore, the presymptomatic identification of mutation carriers would help in counseling affected individuals about the importance of initiating and compliance to prophylactic beta-blocker therapy as well as avoidance of the use of a QT-prolonging drugs (13).

It has been shown that the risk of a cardiac event among carriers of a KCNQ1 mutation is strongly dependent on the duration of QTc (14). A QTc of ≥500 ms with a mutation at KCNQ1 carries a high risk of events. The clinical and molecular analysis in our family can be utilized in risk stratification for identified carriers. Seven carriers had a QTc of ≥500 ms and are at high risk of a cardiac event. Of note, the two symptomatic patients had QTc of 590 and 550 ms, respectively. All of the carriers who had a QTc of <500 ms (n = 5) were asymptomatic and, by adopting this risk stratification model, are at low risk. The implication of this stratification in our family is that prophylactic treatment might be more warranted in the high-risk group of carriers. It is noteworthy, however, that the risk of life-threatening events in patients with LQTS and normal QTc intervals has been shown to be significantly higher than in the unaffected family members (15).

The NOS1AP (rs4657139 and rs16847548) and KCNE1-D85N variants have been shown to be significantly associated with LQTS (16, 17). In our family, screening for these three variants did not explain the differences in the cardiac symptoms or in the QTc intervals. This finding suggests that probably other gene(s) variants may have been implicated in modifying the expression of the mutant allele identified in our family.

The extended clinical and molecular analysis conducted in our family illustrates the importance of cascade screening and allows for offering preventive interventions (18). In addition to at-risk carrier screening, preimplantation genetic diagnosis can also be offered. Taking into account the tradition of cousin marriages in our population, identifying carriers would help in counseling such families about the possibility of transmitting the mutation to children who would be at risk of being homozygous and, consequently, of developing a severe phenotype that might be lethal in utero (19) or of presenting with congenital deafness as JLNS, the recessive form of the LQTS (20).

In conclusion, we have identified a novel KCNQ1 mutation in a large Saudi family with LQTS. The extended clinical and molecular screening in this family has relevant implications in terms of therapeutic and preventive interventions and would help in offering an appropriate counseling, taking into consideration the customary consanguineous marriage in our population.
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