Prevalence and Potential Genetic Determinants of Sensorineural Deafness in

*KCNQ1* Homozygosity and Compound Heterozygosity

**Running title:** Giudicessi et al.; Bi-Allelic *KCNQ1* Mutations and Deafness

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**Journal Subject Codes:** [89] Genetics of cardiovascular disease and Ion channels/membrane transport [152]
Abstract:

**Background** - Homozygous or compound heterozygous mutations in KCNQ1 cause Jervell and Lange-Nielsen syndrome (JLNS), a rare, autosomal recessive form of long QT syndrome (LQTS) characterized by deafness, marked QT prolongation, and a high risk of sudden death. However, it is not understood why some individuals with mutations on both KCNQ1 alleles present without deafness. Here, we sought to determine the prevalence and genetic determinants of this phenomenon in a large referral population of LQTS patients.

**Methods and Results** - Retrospective analysis of all LQTS patients evaluated from July 1998 to April 2012 was used to identify those with ≥1 KCNQ1 mutation. Of the 249 KCNQ1-positive patients identified, 15 patients (6.0%) harbored a rare putative pathogenic mutation on both KCNQ1 alleles. Surprisingly, 11 (73%) of these patients presented without the sensorineural deafness associated with JLNS. The degree of QT interval prolongation and number of breakthrough cardiac events were similar between cases with and without deafness. Interestingly, truncating mutations were more prevalent in JLNS (79%) than non-deaf cases (36%, p<0.001) derived from this study and those in the literature.

**Conclusions** - Here, we provide evidence that the “recessive” inheritance of a severe LQT1 phenotype in the absence of an auditory phenotype may represent a more common pattern of LQTS inheritance than previously anticipated and that these cases should be treated as a higher-risk LQTS subset similar to their JLNS counterparts. Furthermore, mutation type may serve as a genetic determinant of deafness, but not cardiac expressivity, in individuals harboring ≥1 KCNQ1 mutation on each allele.

**Keywords:** long QT syndrome, genetics, ion channels, pediatrics, sudden cardiac death.
Background

Congenital long QT syndrome (LQTS) is characterized by a prolonged heart rate-corrected QT interval (QTc) on electrocardiogram (ECG) and an increased risk of syncope and sudden death secondary to polymorphic ventricular arrhythmias.\(^1\) Loss-of-function mutations in the \(KCNQ1\)-encoded Kv7.1 potassium channel, which conducts the slowly activating delayed rectifier outward K+ current (\(I_{\text{Ks}}\)) in the heart\(^2\) and inner ear\(^3\), cause type 1 LQTS (LQT1)\(^4\) the most common genetic subtype of LQTS.\(^5,6\) Classically, LQTS assumes two clinically recognized forms: autosomal dominant Romano-Ward syndrome (RWS) which affects between 1:2000 and 1:5000 individuals and presents with only a cardiac phenotype\(^7\) and the extremely rare (< 1 per 4 million), autosomal recessive Jervell and Lange-Nielsen syndrome (JLNS) that presents with a malignant cardiac phenotype and congenital bilateral sensorineural deafness.\(^8,9\)

Although individuals homozygous or compound heterozygous for \(KCNQ1\) disease-causative mutations typically present with JLNS, over the past decade isolated reports of homozygous or compound heterozygous individuals presenting with only cardiac manifestations in the absence of deafness (so called “autosomal recessive” RWS/LQT1 or AR LQT1) have surfaced in the literature.\(^10-14\) It has been postulated that hearing preservation in these \(KCNQ1\) homozygotes/compound heterozygotes stems from the presence of “milder” mutations that fail to completely abolish Kv7.1 function resulting in enough residual \(I_{\text{Ks}}\) current to maintain normal K+ cycling in the inner ear, but not the normal electrical activity of the heart.\(^10,11,15\) However, aside from a single individual with intact hearing who was found to harbor a homozygous splice-site mutation (c.387-5 T>A) in exon 2 of \(KCNQ1\) that results in incomplete exon skipping\(^14\), few insights into the overall prevalence of \(KCNQ1\) homozygosity/compound heterozygosity without sensorineural deafness and the genetic determinants underlying hearing preservation in these
individuals exists.

As such, we performed a retrospective analysis of LQTS patients evaluated at the Mayo Clinic to determine: 1) the overall prevalence, degree of cardiac expressivity, and spectrum of auditory phenotypes associated with individuals harboring a mutation on both KCNQ1 alleles and 2) if mutation type or topological location of mutations in the Kv7.1 channel represents a genetic determinant of sensorineural deafness in KCNQ1 homozygotes/compound heterozygotes.

Methods

Study population

In this Mayo Clinic IRB-approved study, a retrospective review of all patients seen in the LQTS Clinic from July 1998 to April 2012 was used to identify all patients with ≥ 1 LQT1-associated mutation(s) in the KCNQ1-encoded Kv7.1 potassium channel. Of the 249 KCNQ1-positive patients (average age at evaluation 21 ± 16 years and average QTc 466 ± 42 msec), those patients harboring either i) a single KCNQ1 mutation, ii) mutation(s) observed in > 0.5% of ostensibly healthy individuals in either the National Heart Lung and Blood Institute (NHLBI) exome sequencing project (ESP) or 1000 genomes public datasets, iii) multiple KCNQ1 mutations on the same allele, or iv) additional mutations in other channelopathgenic genes were excluded from the analysis. Furthermore, individuals with acquired cardiac diseases, electrolyte abnormalities, or receiving QT prolonging medications were also excluded.

The following parameters were obtained from the electronic medical records of each family member: age, sex, proband status, family history of sudden death, incidence of TdP, documented VF, syncopal episodes, β-blocker status, ICD status, pertinent surgical interventions such as left cardiac sympathetic denervation (LCSD) and right cardiac sympathetic denervation (RCSD), and type of KCNQ1 mutation(s). The researcher (JG) who obtained the clinical
parameters and analyzed ECGs was blinded initially with respect to the mutation type and auditory phenotype of each patient.

**ECG analysis**

Twelve-lead electrocardiograms were analyzed manually and the QT duration (lead II or V5) was corrected for heart rate using Bazett’s formula (QTc = QT/√RR). The QTc value for each individual represents the mean value of five consecutive beats and is reported in milliseconds.

**Genetic analysis**

The identification of LQT1-associated mutations in *KCNQ1* was accomplished using either commercial genetic testing or through the use of laboratory-based genetic testing using mutation detection protocols described previously.\(^\text{16}\)

**Genotype-phenotype correlation analysis**

Given the rare nature of bi-allelic inheritance of two *KCNQ1* mutations, for the purposes of identifying potential genotype-phenotype correlations the results of the present study were combined with several large JLNS cases series\(^\text{17,18}\) and AR LQT1 case reports\(^\text{10,11,13,14}\) in the literature where full genotypic information was available. A list of the literature-derived unrelated JLNS and AR LQT1 cases used in this analysis are detailed in Table S1 of the supplemental appendix.

**Statistical methods**

Univariate analysis was employed to compare groups identified on the basis of clinical (e.g. sensorineural deafness) or molecular (e.g. truncating mutations) characteristics. All continuous variables are presented as mean ± standard deviation. Fisher’s exact test was used to compare categorical variables and Wilcoxon Rank Sum/Mann-Whitney U test was employed to compare continuous variables. For both tests a p value ≤ 0.05 was considered statistically significant.
Ethical statement

Both authors had full access to and take full responsibility for the integrity of the data. Both authors have read and agree to the manuscript as written.

Results

Prevalence and clinical evaluation of KCNQ1 homozygotes/compound heterozygotes referred to the Mayo Clinic

Out of the 249 KCNQ1-positive patients evaluated at Mayo Clinic’s Long QT Syndrome Clinic between July 1998 and April 2012, 15 patients (6.0%) harbored rare, potentially pathogenic mutations on both KCNQ1 alleles. Surprisingly, 11 (73%) of these double KCNQ1-positive individuals presented without the sensorineural deafness/hearing loss typically associated with autosomal recessive JLNS1 and thus are best defined as “recessive” LQT1 (AR LQT1) cases. Pertinent clinical information on cardiac expressivity and auditory phenotype of each KCNQ1 homozygote/compound heterozygote is summarized in Table 1. Pedigree structures and genotypic information of AR LQT1 and JLNS1 families are detailed in Figure 1 and Figure 2, respectively. Brief clinical/family histories for the 14 cases not previously described in the literature are provided in the supplement (see supplemental text).

Clinical characteristics of patients homozygous or compound heterozygous for mutations in the KCNQ1-encoded Kv7.1 potassium channel

The clinical characteristics of the 15 individuals homozygous or compound heterozygous for mutations in KCNQ1 are summarized in Table 2. Interestingly, those cases defined as AR LQT1 (i.e. intact hearing) were significantly more likely to have a positive family of SUD or LQTS (91%) in comparison to JLNS cases (25%, p ≤ 0.05). Indicators of the severity of the cardiac phenotype such as previously suffering a cardiac event (defined as syncope, documented VF/VT,
or cardiac arrest) and the degree of QT interval prolongation were statistically similar between JLNS and AR LQT1 cases (Table 2). Furthermore, AR LQT1 cases trended towards a higher likelihood of suffering from at least one syncopal episode (100%) in comparison to their JLNS counterparts (50%, p = 0.06; Table 2). However, this observation may reflect the small sample size.

Clinical characteristics of the parents of KCNQ1 homozygotes/compound heterozygotes

Complete clinical demographics were available on 21 out of 28 AR LQT1/JLNS parents (Table 3). Unfortunately, limited clinical information was not available on 7 AR LQT1/JLNS parents who either died of non-cardiac causes prior to their child’s LQTS diagnosis (3) or who declined further participation (4) in this study. Nevertheless, only 25% of the parents with available clinical information, who by definition are obligate positive for 1 KCNQ1 mutation, displayed phenotypic manifestations suggestive of LQTS (e.g. symptoms or a resting QTc ≥ 470 in males or ≥ 480 in females; Figure 3). There was no statistical difference in the percentage of parents of JLNS compound heterozygotes or parents of non-deaf compound heterozygotes that displayed objective phenotypic manifestations of LQTS (Figure 3). Furthermore, no statistically significant differences in the average QTc, percentage of symptomatic parents or percentage of parents requiring clinical management of their LQT1 genetic substrate was observed between parents of JLNS and non-deaf compound heterozygotes (Table 3).

Potential genetic determinants of auditory/deafness phenotype in KCNQ1 homozygosity/compound heterozygosity

In order to strengthen the identification of potential AR LQT1/JLNS genotype-phenotype correlations, the cases described in the current study were combined and analyzed with JLNS and AR LQT1 cases derived from case series17,18 or cases reports10,11,13,14 in the literature. A
breakdown of KCNQ1 mutations in this combined analysis by mutation type is summarized in Figure 4a. To allow for further statistical comparison, mutations were classified subsequently as either non-truncating (e.g. missense or in-frame deletion) or truncating (e.g. nonsense, frame-shift, or splice-site) mutations to reflect shared effects on protein structure. Interestingly, JLNS cases were significantly more likely to harbor truncating mutations (79%) than AR LQT1 cases (36%, p < 0.001; Figure 4b). No statistical difference in the localization of AR LQT1- or JLNS1-causative mutations to specific regions of the Kv7.1 channel topology was observed (Figure 4c).

Discussion

Prevalence and inheritance patterns of KCNQ1 homozygosity/compound heterozygosity

The observation that marked variable penetrance and expressivity is a hallmark of LQTS has led some to hypothesize that widespread genetic testing in the general population may result in the identification of a surprisingly high number of low-frequency “reduced penetrance” mutations that manifest clinically only when other genetic (e.g. presence of a similar “reduced penetrance” mutation on the opposite allele) or environmental factors (e.g. QT prolonging drugs) are present.10, 21, 22

Indeed, the release of large-scale exome sequencing data from the NHLBI GO Exome Sequencing Project (ESP) revealed that 1:31 individuals (3%) harbor a rare genetic variant of one of the 13 established LQTS-susceptibility genes.23 While the vast majority of established LQTS-associated mutations (94.8%), including all but the KCNQ1-R518X mutation described in the present study, are absent from the NHLBI ESP, nine rare missense or nonsense variants, previously associated with LQT1, were identified in KCNQ1 alone.23 This would place the prevalence of a heterozygous LQT1 genotype between 1:600 and 1:1080 in the general
population, far greater than the estimated LQT1 disease prevalence of ~1:7500 (1:2500 estimate for LQTS of which approximately one-third is attributed to LQT1.24

While many of the rare LQTS-associated variants identified in ESP individuals are likely to be innocuous bystanders that slipped through the cracks, the discordance between the prevalence of functional/co-segregating \textit{KCNQ1} variants and overall LQTS disease prevalence may suggest that a subset of \textit{KCNQ1} variants, with defined pathogenic influence, are at best infrequent causes of monogenic disease in isolation. Furthermore, this observation suggests that the number of individuals who are compound heterozygous (or less likely homozygous) for rare potentially pathogenic \textit{KCNQ1} mutations exceeds the estimated prevalence of 1 in 4 million to 1 in 25 million derived from overall LQTS disease prevalence.

Given the severe clinical course experienced by 12 out of 14 (86%) unrelated individuals who have a rare variant on each \textit{KCNQ1} allele (e.g. QTc >500 msec with documented cardiac events) and the concealed phenotype observed in the majority of their heterozygous parents/family members assessed, it is not surprising that the pedigree structures of at least 11 out of the 14 (79%) families in this study display a probable autosomal recessive (AR) pattern of inheritance. While two of the remaining pedigrees (AR LQT1g and AR LQT1j) had insufficient information to clearly determine the pattern of inheritance, one pedigree (AR LQT1f) clearly represents classic autosomal dominant LQT1 as P320S-positive individuals display significant QT prolongation regardless of the P448L status on their opposite allele. Thus, given the relatively high prevalence of “private” innocuous \textit{KCNQ1} variants in the general population, it should not be assumed that the identification of a rare \textit{KCNQ1} mutation on both alleles directly correlates to an AR pattern of inheritance.
Spectrum of auditory/deafness phenotype and degree of cardiac expressivity in \textit{KCNQ1} compound heterozygotes

Over a decade ago, Priori et al provided the first clinical and molecular evidence that homozygous or compound heterozygous mutations in \textit{KCNQ1} do not invariably lead to JLNS.\textsuperscript{10} While several additional case reports confirmed that AR LQT1 is not an isolated phenomenon\textsuperscript{11-14} and previous studies have assessed the prevalence and phenotypic severity of a compound/digenic heterozygosity involving the three major LQTS-susceptibility genes\textsuperscript{5,25,26}, the prevalence of sensorineural hearing loss and degree of cardiac expressivity in individuals with mutations on both \textit{KCNQ1} alleles remains undefined.

Surprisingly, the present study suggests that the majority of unrelated \textit{KCNQ1} compound heterozygotes with a probable AR pattern of inheritance (7/11; 64\%) present without sensorineural hearing loss. To our knowledge, even when cases with an uncertain pattern of inheritance are excluded, this study still more than doubles (from 4 to 11) the number of individuals with intact hearing despite homozygous or compound heterozygous mutations in \textit{KCNQ1} that have been described in the literature. As such, this report provides further evidence that the two traditional patterns of LQTS inheritance, autosomal dominant RWS with cardiac phenotype only and autosomal recessive JLNS with cardiac phenotype and sensorineural deafness, inadequately describe the full spectrum of inheritance patterns observed in LQTS cases.

In addition to providing evidence that the existing patterns of LQTS inheritance should be expanded to include instances where the LQTS cardiac phenotype is inherited in a “recessive” manner without a discernible auditory phenotype culminating in what is best described as recessive RWS/LQT1, this study also provides additional evidence that JLNS and recessive
RWS/LQT1 compound heterozygotes represent equally high-risk LQTS subsets that are both prone to suffering breakthrough cardiac events. Given that JLNS1 and AR LQT1 individuals share similarly severe clinical courses, the early initiation of surgical options, such as prophylactic LCSD or ICD implantation for secondary prevention, in addition to β-blockers merits serious consideration as a means of further reducing the risk of sudden death in these higher-risk LQTS populations.

**Genetic determinants of sensorineural hearing loss in KCNQ1 compound heterozygosity**

While most LQT1-causative mutations are non-truncating, missense mutations capable of exerting a dominant-negative effect on channel function\(^5\), most JLNS1-causative mutations are truncating nonsense or frameshift mutations that likely abolish the ability of mutant α-subunits to post-translationally co-assemble thereby resulting in a non-functioning channel when expressed in isolation and haploinsufficiency when co-expressed with a wild type subunit.\(^{21,27}\) Not surprisingly, 79% of JLNS mutations identified in the cases analyzed for this study were truncating, consistent with previous observations.\(^{17,21,28}\) However, this observation did not extend to the 14 newly and previously described unrelated AR LQT1 cases were only 36% of individuals harbored truncating mutations expected to result in \(KCNQ1\) haploinsufficiency.

As such, this study provides preliminary evidence that \(KCNQ1\) mutation type represents a major differentiating factor between JLNS and AR LQT1 and thus may play a role in determining the presence or absence of an auditory phenotype. Furthermore, this study suggests that the residual \(KCNQ1\) function needed to maintain the normal secretion of K\(^+\) into the endolymphatic compartment partially responsible for generating the endocochlear potential in the inner ear must be fairly low. Interestingly, through the study of a patient homozygous for the incomplete exon skipping c.387 -5 T>A splice-site mutation, Bhuiyan and colleagues were able
to demonstrate that the degree of residual KCNQ1 function required for hearing preservation is roughly 10%. While the current study cannot improve upon the numerical KCNQ1 “threshold” required for hearing preservation, it is clear from this study and others that the complete cessation of KCNQ1-mediated K+ secretion in the inner ear linked to the bi-allelic inheritance of two truncating/haploinsufficient mutations is the primary mechanism that disrupts cochlear fluid homeostasis resulting in the collapse of endolymphatic compartment and sensorineural deafness in JLNS patients and murine JLNS models.29,30 As such, current evidence places the threshold for hearing preservation in KCNQ1 homozygosity/compound heterozygosity at > 0%, but ≤ 10% residual KCNQ1 function. Functional investigation of unique or unexpected AR LQT1 and JLNS mutation combinations, perhaps by employing patient-specific induced pluripotent stem cell (iPS) models that more accurately recapitulate a endocochlear/cardiac environment, may shed more light on this interesting phenomena and help precisely define the degree of residual KCNQ1 function required for hearing preservation in KCNQ1 homozygosity/compound heterozygosity.

Limitations

As a result of the rarity of KCNQ1 homozygosity/compound heterozygosity and the single center nature of this study, only 15 patients from 14 unrelated families were enrolled in this study. However, to our knowledge, this study represents the only attempt in the literature to assess the overall prevalence and phenotypic spectrum of all KCNQ1 compound heterozygotes, not just JLNS, evaluated at a single referral center. While every attempt was made to gather clinical information and genetic material on as many family members as possible, due to death, or declining further participation, clinical information and DNA were not available on all parents and extended family members. As a result, we were unable to fully assess the inheritance
patterns, clinical characteristics, and potential genetic determinants of cardiac/auditory phenotype in a few of the pedigrees included in this study.

Additionally, emerging evidence in the literature suggests that KCNQ1 homozygosity/compound heterozygosity resulting in JLNS may also be accompanied by additional hematologic and gastrointestinal manifestations.\textsuperscript{31,32} Unfortunately, clinical data such as serum gastrin levels pertinent to these additional phenotypic manifestations were not available for the patients enrolled in this study. Thus, it remains to be seen if AR LQT1 patients are susceptible to similar hematologic and gastrointestinal pathologies as those described previously for JLNS.

Given the referral nature of our LQTS Clinic, it is also possible that the observed 6% frequency of bi-allelic KCNQ1 mutations is an overestimate of the actual frequency/burden of multiple hit KCNQ1-mediated disease. Patients with LQT1 and recurrent symptoms despite beta-blocker therapy have been referred increasingly over the years for LCSD therapy and thus may be over-represented in this cohort, which could inflate the apparent frequency of compound mutation LQT1.

Lastly, the vast majority of KCNQ1 mutations identified in this study have not been characterized functionally. Without an electrophysiological phenotype, it is difficult to assess the mechanism (e.g. dominant-negative vs. haploinsufficiency) and the relative strength of each mutation’s electrophysiological phenotype. It is certainly possible that both mutation mechanism and electrophysiological phenotype could shed even more light on the potential genetic mechanisms and determinants underlying the phenotypic presentation of KCNQ1 compound heterozygotes identified in this study. However, even without an electrophysiological phenotype on each of the 22 mutations identified, we were still able to glean new observations in regards to
the genetic determinants that may partially define the severity of the cardiac/auditory phenotype in *KCNQ1* compound heterozygosity.

**Conclusions**

By increasing the number of recessive LQT1 cases reported in the literature, this study provides compelling evidence that the “recessive” inheritance of a severe LQTS cardiac phenotype in the absence of an auditory phenotype may represent a more common pattern of LQTS inheritance than previously anticipated. Furthermore, given the severe clinical course and high rate of breakthrough cardiac events observed in recessive LQTS cases, this study suggests that these individuals should be treated as a higher-risk LQTS subgroup similar to their JLNS counterparts. In other words, normal hearing in a patient with multiple mutations in LQT1 should not result in a better cardiac prognosis than for a deaf patient with LQT1 (JLNS1). Lastly, this study provides preliminary evidence that *KCNQ1* mutation type functions as a genetic determinant of sensorineural deafness, but not cardiac expressivity, in *KCNQ1* homozygosity/compound heterozygosity.

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**Conflict of Interest Disclosures:** MJA is a consultant for Transgenomic. Intellectual property derived from MJA’s research program resulted in license agreements in 2004 between Mayo Clinic Health Solutions (formerly Mayo Medical Ventures) and PGxHealth (formerly Genaissance Pharmaceuticals and now Transgenomic).
References:


Table 1. *KCNQ1* homozygotes/compound heterozygotes referred to the Mayo Clinic for evaluation

<table>
<thead>
<tr>
<th>Family ID</th>
<th>Sex</th>
<th>Auditory Phenotype</th>
<th>Syncopal episodes</th>
<th>Documented VF/TdP</th>
<th>OHC A</th>
<th>QTc (ms)</th>
<th>β-blocker</th>
<th>ICD</th>
<th>Sympathetic Denervation</th>
<th>KCNQ1 Allele #1</th>
<th>KCNQ1 Allele #2</th>
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<td>0</td>
<td>648</td>
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<td>Yes</td>
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<td>1</td>
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<td>No</td>
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*Pedigrees previously published through international LQTS registry.19, 20* Abbreviations: OHCA, out-of-hospital cardiac arrest; QTc, heart-rate corrected QT interval; TdP, torsades de pointes; VF, ventricular fibrillation.
### Table 2. Clinical characteristics of KCNQ1 homozygotes/compound heterozygotes referred to Mayo Clinic for evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cases</th>
<th>“Recessive” LQT1</th>
<th>JLNS</th>
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<td><strong>Clinical demographics and family history</strong></td>
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<td>Patients, n (%)</td>
<td>15 (100)</td>
<td>11 (73)</td>
<td>4 (27)</td>
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<td>Male/female, n</td>
<td>7/8</td>
<td>6/5</td>
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<td>Age at diagnosis, years</td>
<td>7.0 ± 9.5</td>
<td>8.8 ± 11.0</td>
<td>2.0 ± 2.7</td>
</tr>
<tr>
<td>Family history of LQTS/sudden death, n (%)</td>
<td>11 (73)</td>
<td>10 (91)*</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Bilateral sensorineural deafness, n (%)</td>
<td>4 (27)</td>
<td>0 (0)</td>
<td>4 (100)</td>
</tr>
<tr>
<td><strong>Symptomatology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiac event (%)</td>
<td>13 (87)</td>
<td>11 (100)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>13 (87)</td>
<td>11 (100)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Documented TdP/VF, n (%)</td>
<td>5 (39)</td>
<td>4 (36)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Out of hospital cardiac arrest, n (%)</td>
<td>2 (15)</td>
<td>3 (27)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>557 ± 60</td>
<td>560 ± 69</td>
<td>549 ± 29</td>
</tr>
<tr>
<td><strong>Clinical management</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>15 (100)</td>
<td>11 (100)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator, n (%)</td>
<td>8 (53)</td>
<td>6 (55)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Left cardiac sympathetic denervation, n (%)</td>
<td>11 (73)</td>
<td>7 (64)</td>
<td>4 (100)</td>
</tr>
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</table>

Clinical characteristic and management values are expressed as number of patients (percentage of total) or as mean ± standard deviation. All ECG parameters represent mean ± standard deviation. *P ≤ 0.05 compared to JLNS cases. **P ≤ 0.05 compared to AR LQT1 cases. Abbreviations: JLNS, Jervell and Lange-Nielsen syndrome; LQT1, type 1 long QT syndrome; TdP, torsades de pointes; VF, ventricular fibrillation.

### Table 3. Clinical characteristics of obligate LQT1-mutation carrying biological parents of KCNQ1 homozygotes/compound heterozygotes

<table>
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<tr>
<th>Variable</th>
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<th>“Recessive” LQT1 parents*</th>
<th>JLNS parents</th>
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<tbody>
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<td><strong>Clinical characteristics</strong></td>
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<tr>
<td>Patients, n (%)</td>
<td>21 (100)</td>
<td>13 (63)</td>
<td>8 (37)</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>10/11</td>
<td>6/7</td>
<td>4/4</td>
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<td>Family history of LQTS/sudden death, n (%)</td>
<td>6 (29)</td>
<td>5 (38)</td>
<td>1 (13)</td>
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<td>Bilateral sensorineural deafness, n (%)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>1 (5)</td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Documented TdP/VF, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Out of hospital cardiac arrest, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>446 ± 29</td>
<td>450 ± 29</td>
<td>440 ± 31</td>
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<td><strong>Clinical management</strong></td>
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<td></td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>4 (19)</td>
<td>4 (31)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Left cardiac sympathetic denervation, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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</tbody>
</table>

Clinical characteristic and management values are expressed as number of patients (percentage of total) or as mean ± standard deviation. *Limited clinical information was available on seven parents of KCNQ1 homozygotes/compound heterozygotes with intact hearing who either died of non-cardiac causes prior to their child’s LQTS diagnosis (3) or declined further participation (4). Abbreviations: JLNS, Jervell and Lange-Nielsen syndrome; LQT1, type 1 long QT syndrome; TdP, torsades de pointes; VF, ventricular fibrillation.
Figure Legends:

Figure 1. Pedigree structure and genotypic information for families of KCNQ1 homozygotes/compound heterozygotes with intact hearing. Genotype-positive individuals indicated by gray (single KCNQ1 mutation) or black (two KCNQ1 mutations) squares (male) and circles (female). Genotype-negative individuals indicated by open symbols; index cases by black arrows; and deceased individuals by slashes. Lastly, squares or circles containing “NT” (not tested) indicate individuals who have yet to undergo or have refused genetic testing. QTc intervals and genotypes are displayed beneath each symbol. a. Family AR LQT1a. This three-generation pedigree is notable for the index case with severe QT prolongation that suffered from breakthrough syncopal episodes prior to undergoing a LCSD (III.1). b. Family AR LQT1b. This three-generation pedigree is notable for the index case with severe QT prolongation and a history of breakthrough cardiac events (III.1). c. Family AR LQT1c. This three-generation pedigree is notable for the index case with severe QT prolongation and a history of breakthrough cardiac events including an out-of-hospital cardiac arrest (III.1) and her brother who also has severe QT prolongation and has suffered multiple breakthrough cardiac events including an ICD storm (III.4). d. Family AR LQT1d. This two-generation pedigree is notable only for the index case that displays extreme QT prolongation and suffered multiple breakthrough cardiac events prior to succumbing to his malignant LQTS phenotype at the age of 3 (II.1). e. Family AR LQT1e. This four-generation pedigree is notable for the index case with QT prolongation that suffered numerous exertional syncopal episodes during childhood (III.4). f. Family AR LQT1f. This three-generation pedigree is notable for the index case who features a prolonged QT interval but has remained asymptomatic for the last 25 years (III.9) and the sudden unexplained deaths of her
siblings at the age of 13 and 3, respectively (III.7 and III.10). g. Family AR LQT1g. A two-generation pedigree notable for the index case with QT prolongation (III.1) and the swimming-triggered sudden unexplained death of the index case’s 13-year old sister (III.3). h. Family AR LQT1h. A two-generation pedigree notable for the index case who has severe QT prolongation and suffered several breakthrough ICD shocks prior to undergoing a LCSD (III.2). i. Family AR LQT1i. This two-generation pedigree is notable for the index case who has QT prolongation and suffered several breakthrough cardiac events including an out-of-hospital cardiac arrest (III.5). j. Family AR LQT1j. This two-generation pedigree is notable for the symptomatic index case that has QT prolongation (III.2).

**Figure 2.** Pedigree structure and genotypic information for families of *KCNQ1* homozygotes/compound heterozygotes with bilateral sensorineural hearing loss. a. Family JLNS1a. This three-generation pedigree is only significant for the index case with severe QT prolongation and suffered from numerous breakthrough syncopal events during childhood including several appropriate VF-terminating ICD shocks (III.3). b. Family JLNS1b. This two-generation pedigree is only significant for the index case who features QT prolongation but is otherwise asymptomatic (III.1). Genotype-positive individuals indicated by gray (single *KCNQ1* mutation) or black (two *KCNQ1* mutations) squares (male) and circles (female). Genotype-negative individuals indicated by open symbols; index cases by black arrows; and deceased individuals by slashes. Lastly, squares or circles containing “NT” indicate individuals who have yet to undergo or have refused genetic testing. QTc intervals and genotypes are displayed beneath each symbol.
Figure 3. Electrocardiographic phenotype KCNQ1 compound heterozygote parents. Bar graph of the electrocardiographic phenotype of the parents of JLNS and non-deaf KCNQ1 compound heterozygotes. A normal-to-borderline QT interval was defined as a QTc < 470 in males and a QTc < 480 in females.

Figure 4. Potential genetic determinants of auditory phenotype in patients harboring mutations on both KCNQ1 alleles identified in the current study and previously in the literature. a. Comparison of mutation types identified in “recessive” type 1 long QT syndrome with intact hearing and Jervell and Lange-Nielsen syndrome cases. b. Percentage of truncating (e.g. nonsense, frameshift, etc.) and non-truncating (e.g. missense, in-frame deletion, etc.) mutations identified in “recessive” type 1 long QT syndrome with intact hearing and Jervell and Lange-Nielsen syndrome case, respectively. c. Location of putative “recessive” type 1 long QT syndrome with intact hearing- and Jervell and Lange-Nielsen syndrome-causative mutations in the Kv7.1 channel topology. Dark gray bars indicate “recessive” type 1 long QT syndrome cases, light gray bars indicate Jervell and Lange-Nielsen syndrome cases, and white circles indicate mutations seen in both “recessive” LQT1 and Jervell and Lange-Nielsen syndrome.
a.

QTc (msec)
KCNQ1-C122Y
KCNQ1-P448fs/13

II

1

400
-/-
+-/

2

424
?/?
+/-

3

NT

4

NT

III

1

?/

2

?/

3

561
+/-

4

?/

b.

QTc (msec)
KCNQ1-M159sp
KCNQ1-Y171X

II

1

NT

2

NT

III

1

421
?/

440
?/

2

?/

3

524
+/-

Genotype-positive (single KCNQ1 mutation)
Genotype-negative
Genotype-positive (two KCNQ1 mutations)
Prevalence and Potential Genetic Determinants of Sensorineural Deafness in KCNQ1 Homozygosity and Compound Heterozygosity
John R. Giudicessi and Michael J. Ackerman

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SUPPLEMENTAL MATERIAL

Clinical and Family Histories of \textit{KCNQ1} homozygotes/compound heterozygotes

\textit{Family AR LQT1a}

The index case (III.1, Fig. 1a), a 4-year-old male with intact hearing, was diagnosed with LQTS after an exertional syncopal episode prompted his primary care physician to order an ECG that revealed dramatic QT prolongation. Commercial genetic testing was initiated and the index case was found to harbor a maternally derived missense mutation (G179S) and a paternally derived nonsense mutation (Q530X) in \textit{KCNQ1}. The index case’s younger brother (II.2, Fig. 1a) only inherited the paternally derived Q530X mutation. The maternal family history is positive for the sudden unexplained death of a distant relative (nephew of the maternal grandfather) at the age of 20, no family history of sudden death was present in the paternal family history. At present, the only additional family member known to carry one of the index case’s \textit{KCNQ1} mutations is the maternal grandfather (I.3, Fig. 1a) who has displayed no clinical or electrocardiographic hallmarks of LQTS. The index case has suffered no breakthrough cardiac events since his left cardiac sympathetic denervation (LCSD) surgery, the remainder the index case’s clinical history is summarized in Table 1 of the manuscript.

\textit{Family rLQT1b}

The index case (III:1, Fig. 1b), a 5-year-old female with intact hearing, was diagnosed with LQTS following a sentinel syncopal/seizure episode at the age of 3. A subsequent swimming-triggered syncopal episode while on β-blockers and a QTc consistently >500 msec prompted the index case to undergo a left cardiac sympathetic denervation (LCSD) and she has not experienced any breakthrough events. The paternal
family history is positive for the sudden death of the index case’s paternal grandfather who died suddenly and unexpectedly at the age of 48 (I.2, Fig. 1b) and a paternal uncle (II.1, Fig. 1b) suffered from seizures as a child. Commercial genetic testing revealed that the index case harbors both a maternally derived missense mutation (G568R) and a paternally derived in-frame deletion (H614del) in KCNQ1. While the index case’s younger sister (III.2, Fig. 1b) tested negative for both mutations, a maternal cousin (III.4, Fig. 1b) with a prolonged QT interval tested positive for the maternal G568R mutation.

*Family AR LQT1c*

The index case (III.1, Fig. 1c), a now 23-year old female with intact hearing, was diagnosed with LQTS at 5 weeks following several cyanotic episodes. Despite taking a β-blocker since infancy, the index case suffered several breakthrough cardiac events including three syncopal episodes, an out-of-hospital cardiac arrest, and several appropriate VF-terminating shocks after an ICD was implanted following her cardiac arrest. The patient has been asymptomatic the past 11 years. Her paternal family history is positive for LQTS-related sudden death of a distant relative (great uncle’s granddaughter). The index case’s youngest brother (III.4, Fig. 1c) was diagnosed with LQTS at the age of 1 following several syncopal/seizure episodes and has been on a β-blocker since he was a toddler. Like the index case, her youngest brother has also suffered several breakthrough cardiac events including multiple exertional syncopal episodes and an ICD storm. Following the ICD storm, he had an LCSD, but continued to receive appropriate VF-terminating ICD shocks prompting him to undergo right
sympathetic denervation surgery. Since the bilateral denervation, the index case’s youngest brother has not experienced any additional breakthrough events.

Commercial genetic testing revealed that the index case (III.1, Fig. 1c) and her youngest brother (III.4, Fig. 1c) harbor both a maternally derived frameshift mutation (L191fs/90) and a paternally derived missense mutation (V524G) in KCNQ1. In addition, the index case’s younger sister (III.2, Fig. 1c) and youngest sister (III.5, Fig. 1c) tested positive for the paternal V524G mutation, whereas her younger brother (III.2, Fig. 1c) tested positive for the maternal L191fs/90 mutation. Prior to his death of non-cardiac causes, the index case’s paternal grandfather (I.1, Fig. 1c) tested positive for the V524G mutation, all remaining family members have elected to not submit samples for genetic testing.

Family AR LQT1d

The index case (III.1, Fig. 1i), a 2-year-old male with intact hearing referred to the Mayo Clinic for further management of his extreme genetically proven LQT1 phenotype, was diagnosed with LQTS as a newborn and immediately placed on β-blockers. Following a breakthrough aborted SCA at 20 months; the index case had an ICD implanted as secondary prevention and several months later underwent an LCSD after suffering a significant number of VF terminating ICD shocks while maximally β-blocked. Unfortunately, in the months following his LCSD the index case continued to carry a high VT/VF burden and eventually succumb to his malignant LQTS substrate when his ICD failed to consistently capture following a symptomatic episode of VT.

Previous commercial based genetic testing revealed that the index case was homozygous for KCNQ1-R174C. While it appears that the index case inherited the same
mutation from both parents, confirmation was not possible as the index case’s biological father and paternal relatives declined further participation. The index case is an only child and aside from a maternal great uncle with epilepsy (not shown), the remainder of the maternal family history is unremarkable.

*Family AR LQT1e*

The index case (**III.4, Fig. 1e**), a now 42-year-old male was diagnosed with LQTS at the age of 12 after presenting with multiple exertional syncopal episodes, including several swimming-triggered faints/near drownings, during childhood. The index case was placed on a stiff β-blocker regime (nadolol 120 mg/daily) and has remained event-free for the past 30 years. There is no family history of sudden death. Commercial genetic testing revealed that the index case harbors both a maternally derived missense mutation (K362R) and a paternally derived nonsense mutation (R518X) in *KCNQ1*. Two maternal aunts (**II.6 and II.7, Fig. 1e**) and the index case’s teenage son (**IV.1, Fig. 1e**) have tested positive for the maternal K362R mutation, whereas one brother (**III.3, Fig. 1e**) has tested positive for the paternal R518X mutation. At present, the index case remains the only symptomatic individual within the family, although several family members display evidence of QT prolongation on ECG (**Figure 1e**).

*Family AR LQT1f*

The index case (**III:9, Fig. 1f**), a 31-year-old female with intact hearing, was referred to the Mayo Clinic for a second opinion regarding prophylactic ICD implantation given her significant family history of sudden unexplained death which includes an older sister (**III.7, Fig. 1f**) who died while swimming at age 13 and a younger brother (**III.10, Fig. 1f**) who died suddenly at age 3. Aside from a single childhood syncopal episode the
index case has remained asymptomatic for the last 25 years. Commercial based genetic testing identified a maternally derived missense mutation (P320S) and a second missense mutation (P448L) in KCNQ1 of either paternal or sporadic origin in the index case. The index case’s two oldest daughters (III.4 and III.5, Fig. 1f) and youngest twin daughters (III.8 and III.9, Fig. 1f) inherited the P448L mutation and all have an asymptomatic clinical course with normal QT intervals suggesting that P448L is an extremely low penetrance LQT1 mutation or innocuous background variant. The index case’s only son (III.7, Fig. 1f) inherited the P320S mutation and displays a clearly prolonged QT interval. The P320S mutation was also identified in the index case’s mother (I.2, Fig. 1f), a nephew (III.1, Fig. 1f), and a niece (III.3, Fig. 1f) who all reportedly carry a diagnosis of LQTS (ECGs not available). The index case’s father (II.1, Fig. 1f) died at the age of 41 of non-cardiac causes. Remaining family members could not be reached or declined participation and thus their genotypes and clinical phenotypes are unknown.

**Family AR LQTIg**

The index case (II:1, Fig. 1g), a now 35-year-old female with intact hearing, came to clinical attention as a result of electrocardiographic screening triggered by the death of her 13-year-old sister (II:3, Fig. 1g) while swimming and the detection of prolonged QT interval in her 11-year-old sister (II:4, Fig. 1g) who suffered from multiple syncopal episodes during the late 1980’s. Aside from a single syncopal episode during middle school, the patient has had an asymptomatic clinical course. Over a decade later, laboratory-based genetic testing revealed the presence of two KCNQ1 mutations (R259L and V524G) in the index case, whereas her brother (II.2, Fig. 1g) was found to harbor a single KCNQ1 mutation (R259L). Tragically, as a result of a double murder/suicide, no
genetic material and limited clinical information was available for both parents and the index case’s symptomatic youngest sister.

*Family AR LQT1h*

The index case (II:2, Fig. 1h and Table 1), a 7 year-old-male with intact hearing, was diagnosed with LQTS following two suspicious syncopal episodes. Given the proband’s symptomatic clinical course and extreme degree of QT prolongation an ICD was implanted as secondary prevention. Following several appropriate VF-terminating ICD shocks while on β-blockers, the index case underwent LCSD surgery to provide further protection and aside from a single appropriate VF-terminating ICD shock in the setting of β-blocker non-compliance, he has not experienced any additional breakthrough events. No apparent history of sudden unexplained death or LQTS was elicited from either the maternal or paternal side. Subsequent commercial genetic testing revealed that the index case harbors both a maternally derived nonsense mutation (R518X) and a paternally derived missense mutation (K362R) in *KCNQ1*. The index case’s sister (II.1, Fig. 1h) was found to harbor the R518X nonsense mutation but not the K362R missense mutation. At present, no additional family members have tested positive for either the R518X or K362R mutations.

*Family AR LQT1i*

The index case (II.5, Fig. 1i), a now 3 year-old-male was diagnosed with LQTS following multiple seizure-like spells and an out-of-hospital cardiac arrest at the age of 2. The index case has suffered numerous breakthrough cardiac events including several syncopal episodes while on β-blockers and a second out-of-hospital cardiac arrest while on β-blockers and post-LCSD surgery. The paternal family history is positive for a
paternal cousin with a history of emotion-triggered syncope/seizures. Commercial-based genetic testing revealed the presence of a maternally-derived nonsense mutation (W392X) and a paternally-derived missense mutation (V215M) in KCNQ1. The index case has three half siblings (II.2 to II.4, Fig. 1i) with normal QT intervals. At present genetic testing results are not available for the index case’s three half siblings or any additional extended family members.

Family AR LQT1j

The index case (II.2, Fig. 1d), a now 35-year-old female with intact hearing, came to clinical attention following a swimming-induced syncopal event at the age of 34. Due to profound β-blocker intolerance, the index case elected to undergo LCSD surgery in hopes of improving her quality of life and has remained event free in the 6 months following the procedure on a reduced β-blocker dose (nadolol 20 mg/daily). There is a positive family history of sudden death involving the index case’s otherwise healthy paternal grandmother who died suddenly in her 50’s while sitting in a chair. There is no maternal history of sudden death. Commercial genetic testing of the index case and her mother indicated that the index case harbors a maternally derived missense variant of unknown significance (V576I) and a second missense mutation (R594P) of unknown origin. The index case’s brother who displays a borderline-prolonged QT interval (II.1, Fig. 1d) declined genetic testing and her father, who is estranged from the family, could not be contacted for this study. As a result, it is unknown whether the R594P mutation was inherited from her father or arose sporadically in the index case.
Family JLN

The index case (III.3, Fig. 2a), a now 10-year-old male with bilateral sensorineural deafness, was diagnosed with LQTS at birth when a screening ECG prompted by the presence of fetal bradycardia revealed a significantly prolonged QT interval. Despite taking β-blockers from birth, the index case suffered from numerous break-through syncopal episodes during early childhood and at the age of 6 had both an LCSD and an ICD implanted. In the 4+ years since these procedures, the index case has had 2 appropriate VF-terminating ICD shocks. Both the maternal and paternal family histories are negative for SUD and LQTS. Laboratory-based genetic testing was initiated on the immediate family and revealed that the index case harbors both a maternally derived missense mutation (C122Y) and a paternally derived frameshift mutation (P448fs/13) in KCNQ1. The only additional family member to test positive for either of these mutations is the maternal grandmother (I.2, Fig. 2b), notably all 3 of the index siblings were found to be negative for both KCNQ1 mutations. As depicted in Figure 2b, both parents are asymptomatic and do not display any clinical or electrocardiographic hallmarks of LQTS.

Family JLNSb

The index case (III.1, Fig. 2b), a now 3-year-old female with bilateral sensorineural deafness, was diagnosed with LQTS at 10 months when a prolonged QT interval was noticed during post-operative monitoring following a cochlear implant procedure. The patient was immediately started on β-blockers and once the diagnosis of JLNS was firmly established underwent a prophylactic LCSD at 15 months. At present, the index case remains asymptomatic. Both the maternal and paternal family histories are
negative for SUD or LQTS. Commercial genetic testing on the immediate family was initiated and the index case has both a maternally derived nonsense mutation (Y171X) and a paternally derived splice-site mutation (IVS2+5 G>A, also known as M159sp) in \textit{KCNQ1}. The index case is an only child and both sets of grandparents are living but have yet to undergo genetic testing. As depicted in Figure 2b, both parents are asymptomatic and do not display any clinical or electrocardiographic hallmarks of LQTS.

While the index cases of families JLNS1c and JLNS1d both sought care at the Mayo Clinic, their respective pedigrees and clinical histories were published previously through the international LQTS registry.\(^{(1, 2)}\)
## SUPPLEMENTAL TABLES

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<td>c.1686 -1 G &gt; A</td>
<td>c.1686 -1 G &gt; A</td>
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Abbreviations: AR LQT1, autosomal recessive type 1 long QT syndrome and JLNS, Jervell and Lange-Nielsen syndrome.
SUPPLEMENTAL REFERENCES


