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Genetic variants for long QT syndrome among infants and children from a statewide newborn hearing screening program cohort

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Abstract

Objectives—Autosomal recessive long QT syndrome (LQTS), or Jervell and Lange-Nielsen syndrome (JLNS), can be associated with sensorineural hearing loss (SNHL). We aimed to explore newborn hearing screening combined with ECGs for early JLNS detection.

Study design—We conducted California statewide, prospective ECG screening of children 6 years of age with unilateral or bilateral, severe or profound, sensorineural or mixed hearing loss. Families were identified through newborn hearing screening and interviewed about medical and family histories. Twelve-lead ECGs were obtained. Those with positive histories or QTc intervals 450 ms had repeat ECGs. DNA sequencing of 12 LQTS genes was performed for repeat QTc intervals 450 ms.

Results—We screened 707 subjects by ECGs (number screened/number of responses = 91%; number of responses/number of families who were mailed invitations = 54%). Of these, 73 had repeat ECGs, and 19 underwent gene testing. No subject had homozygous or compound heterozygous LQTS mutations, as in JLNS. However, 3 individuals (with QTc intervals of 472, 457, and 456 ms, respectively) were heterozygous for variants that cause truncation or missplicing: 2 in KCNQ1 (c.1343dupC or p.Glu449Argfs*14; c.1590+1G>A or p.Glu530sp) and 1 in SCN5A (c.5872C>T or p.Arg1958*).

Conclusions—In contrast to reports of JLNS in up to 4% of children with SNHL, we found no examples of JLNS. Because the 3 variants identified were unrelated to hearing, they likely represent the prevalence of potential LQTS mutations in the general population. Further studies are needed to define consequences of such mutations and assess the overall prevalence.

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Keywords

Electrocardiography; epidemiology; hearing loss; KCNQ1 mutations; SCN5A mutations; sudden infant death syndrome

The congenital long QT syndromes (LQTS) are an important cause of sudden death in children and adolescents.¹ Individuals with homozygous or compound heterozygous LQTS mutations (in the *KCNQ1* or *KCNE1* genes) may have the Jervell and Lange-Nielsen syndrome (JLNS), a rare condition that also produces bilateral sensorineural hearing loss (SNHL).^{2–6} The hearing loss is due to absence of functional KCNQ1-KCNE1 pores in the cochlea. The JLNS prevalence in Norway is 1 in 200,000, but the prevalence in other populations is unknown. Among individuals with SNHL, it has been estimated that up to 4% may have prolonged QT intervals (QTc).^{7–10}

The more common, heterozygous forms of LQTS, previously known as Romano-Ward syndrome,^{11, 12} are not associated with hearing loss. The prevalence of heterozygous LQTS is estimated to be 1 in 2,500, on the basis of a newborn screening study in Italy.¹³ Molecular testing for LQTS is now widely used,¹⁴ and neonatal treatment can be lifesaving.¹⁵

Most infants with SNHL are identified by 6 months of age, through universal newborn hearing screening programs established since the mid-2000s in most of the United States.^{16, 17} The prevalence of SNHL is roughly 1 in 1,000 (for bilateral SNHL of 40 dB).¹⁸ Universal newborn hearing screening may provide an opportunity for early detection of LQTS associated with SNHL. We conducted prospective cardiac screening of infants and children with severe or profound SNHL found by newborn screening, as an approach to early detection of JLNS in California.

METHODS

The California Newborn Hearing Screening Program (NHSP) began in 2000 and expanded in 2006 to all general hospitals with licensed perinatal services. The screening rate was 93% in 2008 and 99% in 2010. With NHSP assistance, we identified potentially eligible children on the basis of birth dates and initial hearing diagnoses. Invitations to participate (up to 3 letters) were mailed to parents of 1,442 potentially eligible children. We also asked audiology centers and schools that provide early intervention services to distribute study information to parents.

We recruited infants and young children with SNHL statewide over 2 years (December, 2009, to December, 2011). Eligible children were (1) California residents born between August, 2005, and December, 2011, who (2) had severe, severe-to-profound, or profound hearing loss (>70 dB) in one or both ears, due to sensorineural or mixed (sensorineural and conductive) hearing loss. Subjects with unilateral hearing loss were considered eligible, in order to include children for whom the hearing test could not be performed in one of the ears, or hearing loss in one of the ears could not be excluded in the early stages of screening. Children with mild or moderate hearing loss, or hearing loss solely due to conductive causes or auditory neuropathy, were excluded.

Institutional Review Boards at Harbor-UCLA Medical Center, Santa Clara Valley Medical Center, and the California Health and Human Services Agency approved the study. Parents signed consent for release of medical records, which allowed review of audiology reports by a pediatric audiologist to verify diagnoses.

Cardiac screening

Cardiac screening consisted of detailed family and personal histories and 12-lead ECGs. In structured face-to-face interviews, parents were asked if the child was diagnosed with a genetic disorder, defined syndrome, or chromosomal abnormalities, and if the infant had symptoms such as fainting, seizures, episodes of unresponsiveness, any “apparently frightening event” (requiring a 911 call), any hospitalizations, or medication use. Family histories inquired about: long QT syndrome, deafness, syncope, unexplained fainting or seizures, sudden infant death syndrome, sudden unexpected deaths in first-degree relatives <30 years of age, arrhythmias, death due to accident (eg, drowning or motor vehicle accidents), and known genetic disorders. Names of medications used at the time of screening were recorded.

Standard 12-lead ECGs were performed digitally (MidMark IQecg™, Versailles, OH). The ECG sampling rate was set at 1000 Hz. Recordings were repeated until up to 5 good quality recordings of a 10-second standard 12-lead ECG were obtained. Personal and family histories and electronic ECGs were uploaded immediately to a secure server. Data were reviewed within 48 hours, including manual QTc measurements.

QTc measurements

Two pediatric cardiologists made independent ECG interpretations and QT interval measurements. Interpretations followed “Guidelines for the interpretation of the neonatal electrocardiogram” of the European Society of Cardiology¹⁹ and the 2009 guidelines from the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society.²⁰ QT intervals from ECG recordings of the best quality from lead II or V₅ were used. If neither lead II nor V₅ was of sufficient quality or amplitude, the nearest adequate precordial or limb lead was used. QTc intervals were calculated by the Bazett formula (QT interval divided by the square root of the preceding RR interval). Three consecutive intervals were measured from 2 recordings, and the mean QTc was reported. When the difference in QTc measurements between the 2 ECG interpreters was ≥20 ms, or if one interpreter measured the QTc as ≥450 ms and the other as <450 ms, the ECG was independently reviewed by a pediatric electrophysiologist for adjudication.

Subjects with QTc intervals ≥450 ms or positive histories were selected for a repeat ECG. Examples of positive histories included symptoms of syncope, seizures, arrhythmias, or a family history of LQTS or sudden unexplained death in the young. Genetic testing was offered, if the repeat ECG confirmed a QTc ≥450 ms. QTc intervals of 450 ms were used as a threshold, to reduce false-negative screening results -- not as a diagnostic criterion for LQTS.

Genetic testing

Genetic tests were performed by DNA sequencing on the 12–13 genes most commonly associated with LQTS^{21–23} (*KCNQ1*, *KCNH2*, *SCN5A*, *ANK2* exons 38–40 and 42–49, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1* exons 8–9, *CAV3*, *SCN4B*, *AKAP9* exon 18, *SNTA1*, *KCNJ5*; Transgenomics, Inc.; Omaha, NE).

RESULTS

A total of 779 responses were received from 1,442 families. Among respondents, 710 were considered eligible, on the basis of hearing diagnoses reported by parents. Audiogram verification of hearing diagnoses was not available until after the initial screening was completed. ECGs could not be performed on 3 subjects due to technical reasons. Therefore, 707 children completed initial cardiac screening and formed the cohort. Among the 707

subjects, the mean age was 27 ± 20 months (range 1–76 months). Latino was the most common ethnicity (59%), followed by white (21%), Asian (8%), multi-racial (7%) and black (4%). The percentage of Latino subjects is similar to the percentage of Latino births in California (51%, according to 2009 vital statistics.) Five-hundred twenty-three (74%) were later confirmed by audiogram reviews to have sensorineural or mixed hearing loss at a severe, severe-to-profound, or profound level in one or both ears. Hearing loss characteristics are summarized in Table I.

Various syndromes or genetic conditions were reported by parents: presence of connexin 26 mutations, 30 (4%) subjects (5 of which also had connexin 30 mutations); trisomy 21, 11 (1.5%); Goldenhar syndrome, 10; CHARGE association, 6; Waardenburg syndrome, 5; Mondini syndrome, 4; branchiootorenal syndrome, 3; Stickler syndrome, 3; and other chromosome abnormalities, 4. Medical records could not be obtained to confirm diagnoses in all cases.

ECG data

The mean heart rate was 132 ± 18 beats per minute (range, 66–184; inter-quartile range, 107–133). The mean QTc interval was 424 ± 18 ms (range, 363–493; inter-quartile range, 414–435; the QTc duration 2 standard deviations above the mean was 460 ms). Fifty-seven subjects (8.1%) had a screening QTc interval of ≥ 450 ms (3 were later lost to follow-up; Figure 2A and Table II; available at www.jpeds.com). Four subjects with right bundle branch block due to cardiac surgery were not evaluated further for LQTS. No subjects were considered to have acquired QT prolongation, such as due to medications. No subject had T wave alternans, and no significant arrhythmias were noted.

Follow-up testing

Based on initial screening results, 631 subjects had QTc intervals <450 ms and no symptom or suggestion of a cardiac problem (89%). Fifty-seven subjects (8.1%) had QTc intervals ≥ 450 ms, but no symptom or suggestion of a heart problem. Another 19 subjects had a possible indicator of a heart condition (10 had seizures; 6 had fainting; 3 had sudden death of a sib), but their QTc intervals were <450 ms (2.7%). Among the 76 subjects with QTc intervals ≥ 450 ms or a possible indicator of a heart condition, 3 were lost to follow-up. Repeat ECGs were performed on 73 subjects, 21 (3%) individuals had QTc intervals ≥ 450 ms and were offered genetic testing (2 declined). Ages at the time of ECGs, sex, ethnicity, and QTc intervals of the 73 subjects who underwent repeat ECG testing are summarized in Table 2.

Genetic testing Frameshift, splicing, and nonsense variants

Three subjects had a heterozygous variant predicted to cause protein truncation or aberrant splicing -- 2 in *KCNQ1* and one in *SCN5A*. Clinical characteristics of these subjects are in Table IV, and their ECGs are in Figure 2, B-D. The 2 *KCNQ1* mutations disrupt the C-terminus and are predicted to impair formation of KCNQ1 tetramers, causing loss of function (Figure 3, A; available at www.jpeds.com). The p.Glu449Argfs*14 mutation causes a frameshift in which the normal glutamate at position 449 becomes arginine, and codon 462 in the new reading frame is a stop codon.²⁴ The p.Gln530sp *KCNQ1* mutation changes the first nucleotide of the 5' splice site after exon 12 and is predicted to disrupt the amino acid sequence after the glutamine at position 530.

The p.Arg1958* variant in the *SCN5A* C-terminus changes arginine codon 1958 from CGA to a TGA stop codon (Figure 3, B). The mutant *SCN5A* is shortened by 59 amino acids from its normal length of 2,016. Possible clinical importance of the p.Arg1958* truncation mutation is suggested by mutations reported within the 1958–2016 region -- one causing

LQTS (p.Arg1958Gln or c.5873G>A),²⁴ and 2 causing Brugada syndrome (p.Phe2004Val or c.6010T>G; p.Phe2004dup or 6010_6012dupTTC).²⁵ The *SCN5A* C-terminus regulates channel function through various protein interactions.²⁶

Variants of uncertain significance

Two other subjects had variants of uncertain significance: *KCNJ2* p.Arg325His and *KCNH2* p.Arg1033Trp. The *KCNH2* p.Arg1033Trp variant was reported by Kapplinger et al as a disease-causing mutation.²⁷ However, further information regarding the reported family was unavailable.

Benign polymorphisms

Four common benign polymorphisms were found: *KCNE1* c.112G>A (p.Gly38Ser), *SCN5A* c.1673A>G (p.His558Arg), *KCNH2* c.2690A>G (p.Lys897Thr), and *KCNQ1* c.1927G>A (p.Gly643Ser). No subject with a negative genetic test was diagnosed with LQTS based on clinical criteria.

Further follow-up

We re-contacted all subjects by phone and mail at the end of the 2-year study, to identify potentially missed JLNS cases. We asked about current status (alive or deceased), any therapy (eg, beta-blocking drugs, implantable cardioverter-defibrillators), events during anesthesia or surgery for cochlear implantation or other procedures, and any symptoms (fainting, seizures, arrhythmia, or cardiac diagnoses). We received responses from 555 families (79%). Four subjects had new symptoms of seizures or fainting, and underwent a repeat ECG. The QTc intervals of these 4 subjects remained <450 ms, and no other follow-up was offered.

DISCUSSION

In contrast to prior retrospective reports of an incidence of JLNS as high as 4% among children with SNHL, we did not find a single child with homozygous or compound heterozygous mutations compatible with JLNS (among 523 subjects with severe or profound SNHL). Possibly, the earlier figures for JLNS prevalence among children with profound SNHL were overestimates, partly due to lack of gene testing. Connexin mutations were the most frequent genetic cause of hearing loss among our subjects (4%). Several malformation syndromes known to produce hearing loss were also reported (each with a frequency <2%).

However, we did identify 3 heterozygous potential LQTS variants, as described above. The *KCNQ1* frameshift mutation (p.Glu449Argfs*14)²⁴ resembles the *KCNQ1* frameshift seen in Romano-Ward syndrome (p.Pro448Argfs*18).²⁸ The novel *KCNQ1* splicing mutation (p.Gln530sp) is similar to a *KCNQ1* truncation variant reported in JLNS (p.Gln530*),^{2, 29, 30} The novel *SCN5A* truncation variant (p.Arg1958*) needs further study to define clinical effects, if any.

Our protocol used 450 ms as the threshold value for requesting repeat ECGs and then gene testing. We would have missed the *KCNQ1* splicing mutation (p.Gln530sp) and the *SCN5A* truncation variant (p.Arg1958*), if 460 ms were used, as in earlier studies.¹³ Therefore, we tentatively favor 450 ms as a cut-off value for research involving population screening (not diagnosis). However, the repeat QTc intervals were <450 ms in 52 out of 73 subjects (Table II). Approximately 40% of the individuals with repeat QTc values <450 ms were younger than 1 year of age. Possibly, these infants had transient QTc prolongation.³¹ However, the individual with the largest decrease (55 ms) and the highest initial QTc value (487 ms) was a 5-year-old boy (Table II).

The 3 heterozygous truncation or splicing mutations in our study were interpreted to be unrelated to SNHL. Specifically, the girl with the *KCNQ1* frameshift mutation (p.Glu449Argfs*14) had connexin 26 mutations as a cause for hearing loss. The girl with the *KCNQ1* splicing mutation (p.Gln530sp) had unilateral sensorineural hearing loss, rather than the bilateral hearing loss found in JLNS. Her mother and half-sister had the mutation but no hearing loss. The *SCN5A* ion channel is not found in the cochlea, so the *SCN5A* nonsense variant (p.Arg1958*) should not affect hearing.

Therefore, the 3 mutations are most likely variants in the general population that occurred by coincidence in the SNHL group. Both of the *KCNQ1* variants were associated with QTc intervals >470 ms -- one in a study subject and the other in a half-sister of a subject (472 and 479 ms, respectively; Table IV). The data are consistent with a LQTS prevalence in the range of the published value of 1/2,500.¹³ For example, a calculated prevalence would be 2/707, with a 95% confidence interval of 1/2,920 – 1/98 (Clopper-Pearson), if the *KCNQ1* frameshift and splicing variants are viewed as LQTS mutations.³² (The denominator is 707, rather than 523, because these variants are unrelated to hearing in heterozygous individuals.)

The strengths of our study include population-based recruiting through state mandated newborn hearing screening -- at an early age before infants and young children developed cardiac symptoms. Moreover, our participation rate was 91% (following an initial response rate of 54%). A limitation of newborn hearing screening is that the initial diagnoses of type and degree of hearing loss may change at later stages of testing. However, such information became available during the study. Finally, we did not include children without SNHL as a comparison group in this population survey.

One question is whether infants with JLNS (and abnormal hearing screens) could have died suddenly -- before being invited to take part in the study. For example, California death registry and NHSP data from 2009 showed 6 sudden infant deaths after abnormal initial hearing screens. The infants died before hearing tests could be repeated. Questions about JLNS in such infants cannot be settled without more information, such as ECG or genetic data.

Our findings are consistent with the published LQTS prevalence. Follow-up studies will be useful to define the consequences of heterozygous variants found in LQTS genes in asymptomatic children. Larger sample sizes are needed, particularly when focusing on infants with profound SNHL for estimating the JLNS prevalence. ECG screening of infants from the general population will also be needed to assess the prevalence of more common forms of LQTS in ethnically diverse populations, such as California. Until larger studies are done, it may be difficult to determine whether ECG screening of newborns -- with or without SNHL -- is practical for early diagnosis of LQTS.

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Figure 1. Summary of subject recruitment, cardiac screening, and risk assessment. Numbers of subjects are in parentheses.

Figure 2.

ECG results in the newborn hearing screening study. **A.** Distribution of QTc intervals among 707 participants. Shaded bars indicate QTc intervals > 450 ms. **B.** ECG of the 25-month-old girl with the *KCNQ1* p.Glu449Argfs*14 variant. **C.** ECG of the 4-month-old girl with the *KCNQ1* p.Gln530sp variant. **D.** ECG of the 47-month-old boy with the *SCN5A* p.Arg1958* variant.

Figure 3.

Sites of the *KCNQ1* and *SCN5A* variants found in the newborn hearing screening and ECG study. **A.** Sites of the *KCNQ1* p.Glu449Argfs*14 (shown by *449) and p.Gln530sp (shown by *530) mutations in the C-terminus (amino acids 352-676). *KCNQ1* forms a tetrameric channel. Each *KCNQ1* monomer is shown as 2 spheres of the same color (striped spheres represent pore forming domains; plain spheres represent voltage sensor domains). The cytoplasmic C-terminus with its 4 helices (A-D) is shown for 2 *KCNQ1* monomers. The p.Glu449Argfs*14 mutation disrupts the C-terminus after position 448, removing helices B, C, and D. The p.Gln530sp mutation disrupts the C-terminus after position 530 (in helix B). **B.** Site of the *SCN5A* p.Arg1958* variant (shown by *1958) in the C-terminus (amino acids 1785-2016). *SCN5A* (a) forms a complex with sodium channel β subunits (b), neuronal nitric oxide synthase 1 (c), plasma membrane Ca^{++} transporting ATPase 4 (d), $\alpha 1$ -syntrophin (e), the dystroglycan complex (f), and cytoskeletal scaffolding. The scaffold contains dystrophin (g), dystrobrevin (h), laminins (i), F-actin (j), syncoilin (k), and desmin (l). Loss of the C-terminal residues in the p.Arg1958* variant is predicted to untether *SCN5A* from the macromolecular complex.

Table 1

Percentage of subjects with various characteristics of hearing loss.

Characteristic	Ear involved		Among all 707 subjects ^a	Among 523 subjects with verified severe or profound SNHL ^b
<i>Presence of SNHL versus mixed hearing loss at severe, severe-to-profound, or profound levels</i>	Uncertain		7	0
	Left only	SNHL	18	20
		Mixed	1	1
	Right only	SNHL	14	16
		Mixed	1	1
	Bilateral ^c	SNHL	59	62
		Mixed	1	1
<i>Degree of hearing loss present^d</i>	Left	Moderate or milder	23	33
		Severe	14	13
		Severe-to-profound	16	14
		Profound	47	40
	Right	Moderate or milder	26	36
		Severe	16	12
		Severe-to-profound	16	13
		Profound	42	39
<i>Hearing loss managed with cochlear implantation</i>	Left		3	4
	Right		7	8
	Bilateral		12	15

^aTypes and degree of hearing loss were reported by families or referring centers at the time of referral to the study.

^bTypes and degree of hearing loss were verified by audiogram reviews. These 523 subjects all had unilateral or bilateral severe, severe-to-profound, or profound sensorineural or mixed hearing loss.

^cWith bilateral hearing loss, at least one ear at severe, severe-to-profound, or profound levels.

^dNumbers of subjects with bilateral profound and bilateral severe-to-profound or profound SNHL were 208 and 286, respectively (based on 523 subjects with verified eligible hearing diagnoses)

Table 2

Characteristics of the 73 subjects who had repeat ECGs.

No.	Subject		QTc intervals (ms) ¹				LQTS variants ²	
	F/M	Ethnicity	Initial	Age ¹	Repeat	Age ¹	Protein change	Class
1	F	Latino	408	14	392	14	--	
2	F	Latino	410	42	400	43	--	
3	F	White	416	30	405	33	--	
4	F	Black	433	51	441	53	--	
5	F	Latino	434	37	426	37	--	
6	F	Latino	439	26	408	27	--	
7	F	Latino	444	30	388	31	--	
8	F	Latino	450	10	415	11	--	
9	F	Latino	451	2	423	2	--	
10	F	Latino	451	12	428	17	--	
11	F	White	451	56	457	56	KCNH2 p.Lys897Thr	III
12	F	White	452	9	465	10	Declined testing	
13	F	Latino	453	53	405	56	--	
14	F	Asian	454	42	435	43	--	
15	F	Latino	455	3	428	4	--	
16*	F	Latino	455	5	457	6	KCNQ1 p.Gln530sp KCNE1 p.Gly38Ser	I II
17	F	Latino	455	4	459	5	None	
18	F	Latino	458	35	441	35	--	
19	F	Latino	460	37	439	37	--	
20	F	Latino	464	2	454	3	KCNE1 p.Gly38Ser	III
21	F	Latino	465	7	374	10	--	
22	F	Latino	465	5	440	5	--	
23	F	Latino	466	10	435	11	--	
24	F	Pacific Islander	466	4	463	4	Declined testing	

Subject			QTc intervals (ms) ¹				LQTS variants ²	
No.	F/M	Ethnicity	Initial	Age ¹	Repeat	Age ¹	Protein change	Class
25*	F	Latino	467	25	472	26	KCNQ1 p.Glu449fs*14 KCA/W2p.Lys897Thr	I III
26	F	White	469	3	459	4	KCNE1 p.Gly38Ser SCN5A p.His558Arg	III III
27	F	White	470	56	454	57	KCNH2 p.Lys897Thr SCN5A p.His558Arg	III III
28	F	Multi-racial	477	35	394	36	--	
29	F	Asian	483	19	485	20	-- (RBBB on ECG) ³	
30	F	White	488	45	480	46	KCNE1 p.Gly38Ser	III
31	M	Latino	411	15	410	18	--	
32	M	Latino	411	9	425	13	--	
33	M	Latino	411	8	430	9	--	
34	M	Latino	411	43	434	43	--	
35	M	Asian	412	60	426	61	--	
36	M	Latino	413	13	412	30	--	
37	M	Latino	414	14	433	12	--	
38	M	Latino	415	58	411	58	--	
39	M	Latino	421	72	438	72	--	
40	M	Latino	424	21	417	21	--	
41	M	Latino	431	4	439	5	--	
42	M	Latino	437	46	422	48	--	
43	M	Latino	450	28	413	29	--	
44	M	Latino	450	7	428	8	--	
45	M	Asian	450	11	445	13	--	
46	M	Black	451	8	430	8	--	
47	M	Latino	451	41	445	43	--	
48	M	Latino	451	8	451	9	KCNE1 p.Gly38Ser	III
49*	M	Latino	451	48	456	48	SCN5A p.Arg1958* KCNE1 p.Gly38Ser SCN5A p.His558Arg	I III III

Subject			QTc intervals (ms) ¹				LQTS variants ²		Class
No.	F/M	Ethnicity	Initial	Age ¹	Repeat	Age ¹	Protein change		
50	M	Latino	451	66	468	68	KCNH2 p.Arg1033Trp KCNH2 p.Gly38Ser KCNH2 p.Lys897Thr		II III III
51	M	Latino	452	23	451	24	KCNH2 p.Gly38Ser SCN5A p.His558Arg		III III
52	M	Asian	453	76	402	77	--		
53	M	White	453	50	409	51	--		
54	M	Multi-racial	453	3	414	3	--		
55	M	Latino	453	4	436	5	--		
56	M	Latino	453	69	442	69	--		
57	M	White	453	7	457	8	KCNH2 p.Arg325His SCN5A p.His558Arg		II III
58	M	Latino	454	28	437	29	--		
59	M	Latino	454	12	440	12	--		
60	M	Asian	457	3	439	5	--		
61	M	Latino	459	50	443	51	KCNH2 p.Gly38Ser KCNH2 p.Lys897Thr SCN5A p.His558Arg		III III III
62	M	Latino	462	56	432	57	--		
63	M	Latino	462	4	443	4	--		
64	M	Asian	462	3	466	3	KCNH2 p.Gly38Ser		III
65	M	Latino	463	3	417	6	--		
66	M	Latino	465	29	448	29	--		
67	M	Latino	471	22	434	23	--		
68	M	Asian	473	7	459	8	KCNH2 p.Gly643Ser SCN5A p.His558Arg		III III
69	M	Latino	477	11	434	12	--		
70	M	Latino	480	53	468	53	None		
71	M	Latino	483	35	473	42	-- (RBBB on ECG) ³		
72	M	Multi-racial	487	59	432	61	--		
73	M	Latino	490	59	462	60	None		

¹ Age in months

* Subjects had a frameshift, splicing, or nonsense mutation (ie, a class I variant). Class II variants were genetic variants of unknown significance. Class III indicates benign polymorphisms. “-” indicates no testing.

³ The subject had a prolonged QTc due to right bundle branch block (RBBB), which resulted from surgery for a congenital heart disorder. Genetic testing was not done.

Table 3

Genetic variants identified among 19 subjects with QTc intervals 450 ms.

Gene	Protein (LQT subtype)	Nucleotide alteration	Protein alteration	Protein region	No. of cases	Sex & ethnicity ^a
Frameshift, splicing, or nonsense variants						
<i>KCNQ1</i>	K _v 7.1 (LQT1)	c.1343dupC	p.Glu449fs*14	C-terminus	1	F Latino
<i>KCNQ1</i>	K _v 7.1 (LQT1)	c.1590+1 G>A	p.Gln530sp	C-terminus	1	F Latino
<i>SCN5A</i>	Na _v 1.5 (LQT3)	C.5872C>T	p.Arg1958*	C-terminus	1	M White
Rare genetic variants of uncertain clinical significance						
<i>KCNH2</i>	HERG/K _v 11.1 (LQT2)	C.3097C>T	p.Arg1033Trp	C-terminus	1	M Latino
<i>KCNJ2</i>	Kir2.1 (LQT7)	c.974G>A	p.Arg325His	C-terminus	1	M White
Common benign variants						
<i>KCNQ1</i>	K _v 7.1 (LQT1)	c.1927G>A	p.Gly643Ser	C-terminus	1	M Asian
<i>KCNH2</i>	HERG/K _v 11.1 (LQT2)	c.2690A>C	p.Lys897Thr	C-terminus	5	2 FL, 1 FW, 2 ML
<i>SCN5A</i>	Na _v 1.5 (LQT3)	c.1673A>G	p.His558Arg	DI/DII	7	3 ML, 2 FW, 1 MW, 1 MA
<i>KCNK1</i>	MinK (LQT5)	c.112G>A	p.Gly38Ser	N-terminus	10	5 ML, 2 FL, 2 FW, 1 MA

^a Abbreviations: A, Asian; Eth, ethnicity; F, female; HL, hearing loss; L, Latino; M, male; NT, not tested; P, profound; SNHL, sensorineural hearing loss; S-P, severe-to-profound; W, white.

Table 4

Clinical characteristics of the 3 subjects with a frameshift, splicing, or nonsense variant.

Variant	Age (mo)	Sex (Eth)	Hearing Loss		QTc (ms)	Other condition	Family studies		
			R	L			Relative	QTc	HL Variant
<i>KCNQ1</i> ^a c.1343dupC p.Glu449Argfs*14	25	F(L)	SNHL	SNHL	472	Connexin 26 mutations	Mother	418	–
			S-P	S-P			Father	NT	–
							Brother	412	+
<i>KCNQ1</i> ^a c.1590+1G>A p.Gln530sp	4	F(L)	SNHL	None	457		Mother	436	–
			P				Father	398	–
							Half-sister	479	–
<i>SCN5A</i> ^a c.5872C>T p.Arg1958*	47	M(L)	SNHL	SNHL	456		Mother	440	–
			P	P			Father	421	–
							No sib		–

^aSee NCBI sequences NM_000218.2 for *KCNQ1* and NM_198056 for *SCN5A*, for reference sequences.