Genetic Variants for Long QT Syndrome among Infants and Children from a Statewide Newborn Hearing Screening Program Cohort

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

Study design In California, we conducted 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 heart rate corrected QT (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 sensorineural hearing loss, 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. *(J Pediatr 2014;164:590-5)*.

The congenital long QT syndromes (LQTSs) 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 1:200 000, but the prevalence in other populations is unknown. Among individuals with SNHL, it has been estimated that up to 4% may have prolonged heart rate corrected 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 1:2500, 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 NHSPs established since the mid-2000s in most of the US.[16,17] The prevalence of SNHL is roughly 1:1000 (for bilateral SNHL of ≥40 dB).[18] Universal newborn hearing screening may provide an opportunity for the early detection of LQTS associated with SNHL. We conducted prospective cardiac screening of infants and children with severe or profound SNHL identified on 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 2008 to all general hospitals with licensed perinatal services. The

bpm	Beats/min
ECG	Electrocardiogram
JLNS	Jervell and Lange-Nielsen syndrome
LQTS	Long QT syndrome
NHSP	Newborn Hearing Screening Program
QTc	Heart rate corrected QT
SNHL	Sensorineural hearing loss

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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 1442 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-December 2011). Eligible children were California residents who were: (1) born between August 2005 and December 2011; and (2) had severe, severe-to-profound, or profound hearing loss (>70 dB) in 1 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 1 of the ears, or hearing loss in 1 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 electrocardiograms (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 LQTS, 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, Ohio). 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 the "Guidelines for the Interpretation of the Neonatal Electrocardiogram" of the European Society of Cardiology[19] 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 V_5 were used. If neither lead II nor V_5 was of sufficient quality or amplitude, the nearest adequate precordial or limb lead was used. QTc intervals were calculated by using the Bazett formula (QT interval divided by the square root of the preceding R-R 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 1 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 or 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*, and *KCNJ5*; Transgenomics, Omaha, NE).

Results

A total of 779 responses were received from 1442 families. Among respondents, 710 were considered eligible, on the basis of hearing diagnoses reported by parents (**Figure 1**). 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/a was the most common ethnicity (59%), followed by white (21%), Asian (8%), multiracial (7%), and black (4%). The percentage of Latino subjects is similar to the percentage of Latino/a 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 1 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 whom also had connexin 30 mutations); trisomy 21, 11 (1.5%); Goldenhar syndrome, 10 (X%); CHARGE syndrome (name originally represented "coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness"), 6 (X%); Waardenburg syndrome, 5 (X%); Mondini syndrome, 4 (X%); branchio-otorenal syndrome, 3 (X%); Stickler syndrome, 3 (X%);