Combined assessment of sex- and mutation-specific information for risk stratification in type 1 long QT syndrome

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BACKGROUND Men and women with type 1 long QT syndrome (LQT1) exhibit time-dependent differences in the risk for cardiac events.

OBJECTIVE We hypothesized that sex-specific risk for LQT1 is related to the location and function of the disease-causing mutation in the *KCNQ1* gene.

METHODS The risk for life-threatening cardiac events (comprising aborted cardiac arrest [ACA] or sudden cardiac death [SCD]) from birth through age 40 years was assessed among 1051 individuals with LQT1 (450 men and 601 women) by the location and function of the LQT1-causing mutation (prespecified as mutations in the intracellular domains linking the membrane-spanning segments [ie, S2–S3 and S4–S5 cytoplasmic loops] involved in adrenergic channel regulation vs other mutations).

RESULTS Multivariate analysis showed that during childhood (age group: 0–13 years) men had >2-fold ($P < .003$) increased risk for ACA/SCD than did women, whereas after the onset of adolescence the risk for ACA/SCD was similar between men and women (hazard ratio = 0.89 [$P = .64$]). The presence of cytoplasmic-loop mutations was associated with a 2.7-fold ($P < .001$) increased risk for ACA/SCD among women, but it did not affect the risk among men (hazard ratio 1.37; $P = .26$). Time-dependent syncope was associated with a more pronounced risk-increase among men than among women (hazard ratio 4.73 [$P < .001$] and 2.43 [$P = .02$], respectively), whereas a prolonged corrected QT interval (≥500 ms) was associated with a higher risk among women than among men.

CONCLUSION: Our findings suggest that the combined assessment of clinical and mutation location/functional data can be used to identify sex-specific risk factors for life-threatening events for patients with LQT1.

KEYWORDS: Cytoplasmic-loop mutations; Sex; Long QT syndrome; Sudden cardiac death

ABBREVIATIONS **ACA** = aborted cardiac arrest; **C-loop mutations** = cytoplasmic-loop mutations; **HR** = hazard ratio; **ICD** = implantable cardioverter defibrillator; **LQTS** = long QT syndrome; **LQT1** = long QT syndrome type 1; **MS** = membrane spanning; **QTc** = corrected QT interval; **SCD** = sudden cardiac death

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Introduction

Long QT syndrome type 1 (LQT1) is the most commonly occurring of the congenital long QT syndromes (LQTS).[1] It is caused by mutations in the *KCNQ1* gene that impair the slow-acting potassium channel that gives rise to slow delayed rectifier potassium current (I_{Ks}). The resulting prolongation of ventricular repolarization increases the potential for cardiac arrhythmogenic events that can cause syncope or sudden cardiac death (SCD). Patients with LQT1 experience the majority of their events during exercise, possibly because the phase 3 I_{Ks} repolarizing current activates during increased heart rate and is essential for QT-interval adaptation during tachycardia.[1,2] Prior studies have shown that mutations located at the membrane-spanning (MS) region and missense vs nonmissense mutations are associated with a greater risk for cardiac events in patients with LQT1.[3] The MS region includes the MS domains and the MS linkers. Mutations in the intracellular linkers that connect the MS domains of the KCNQ1 (Kv7.1) channel subunit (defined herein as the S2–S3 and S4–S5 cytoplasmic [C]-loop mutations) were shown to affect adrenergic channel regulation by protein kinase A[4] and may therefore predispose to increased risk for life-threatening events in this population.[5]

The phenotypic expression of LQT1 is affected by sex and age, wherein men with LQT1 experience increased risk for cardiac events, mainly during the childhood period.[6] Prior studies, however, did not relate sex-specific risk in this population to the location and function of the disease-causing mutation in the *KCNQ1* gene. Furthermore, sex differences in the clinical course of LQT1 were related previously to a cardiac event composite end point, which comprised mostly nonfatal syncope. Accordingly, the present study was designed to evaluate whether the combined assessment of clinical and mutation location/functional data can identify sex-specific risk factors for life-threatening cardiac events in men and women with LQT1.

Methods

Study population

The study population comprised 1051 LQT1-positive subjects from 259 proband identified families. Patients were drawn from the Rochester, NY, enrolling center (center 1) of the International LQTS Registry (n = 755), the Netherlands LQTS Registry (n = 85), and the Japanese LQTS Registry (n = 83), as well as from data submitted by other investigators specifically for this collaborative mutation analysis project: Denmark (n = 43), Israel (n = 34), Sweden (n = 4), and Salt Lake City, UT (n = 47). The proband in each family had otherwise unexplained, diagnostic corrected QT-interval (QTc) prolongation or experienced LQTS-related symptoms. Patients with congenital deafness were excluded from the study.

Data collection and management

For each patient, information on personal history, including cardiac events, electrocardiograms, and therapies, as well as family history was obtained at enrollment. Clinical data were then collected yearly on prospectively designed forms with information on demographic characteristics, personal and family medical history, electrocardiogram findings, medical therapies, left cardiac sympathetic denervation, implantation of a pacemaker or an implantable cardioverter defibrillator (ICD), and the occurrence of LQT1-related cardiac events. The QT interval was corrected for heart rate (QTc) by using Bazett's formula.[7] Data common to all LQTS registries involving genetically tested individuals were merged electronically into a common database for the present study.

Genotype characterization

The *KCNQ1* mutations were identified with the use of standard genetic tests conducted in academic molecular genetic laboratories including the Functional Genomics Center, University of Rochester Medical Center, Rochester, NY; Baylor College of Medicine, Houston, TX; Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN; Boston Children's Hospital, Boston, MA; Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan; Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands; and Molecular Cardiology Laboratory, Policlinico S. Matteo and University of Pavia, Pavia, Italy.

Mutations were defined as any nonsynonym rare variants (<1% of the healthy population) identified in a proband with a prolonged QT interval. Based on prior data regarding mutation location/function and arrhythmic risk in LQT1,[3–5,8] mutations were categorized by their location and type in the *KCNQ1*-encoded channel subunit as follows: (1) missense mutations in the MS region: defined as amino acid residues from 120 to 355, excluding mutations within the MS linkers; (2) missense mutations in the C loops: defined as the coding sequence involving amino acid residues from 174 to 190 (S2–S3 linker) and from 242 to 259 (S4–S5 linker); (3) missense mutations in the N-terminus region, defined as amino acid residues before 120, and the C-terminus region, defined as amino acid residues after residue 355, were combined into one category labeled as the other region for this analysis (hence called the N/C terminus); and (4) other LQT1 mutations as the reference group (ie, splice sites, in-frame insertions, in-frame deletions, nonsense, and frameshift).

The specific mutations included in the present study, by location, type, and number of patients, are detailed in the Supplementary Appendix Table 1, and the distribution of the mutations in the *KCNQ1* gene by their frequency among study patients is shown in Figure 1.

End point

The primary end point of the study was the occurrence of a first life-threatening cardiac event, comprising aborted cardiac arrest (ACA) (requiring defibrillation as part of resuscitation), or LQT1-related SCD (abrupt in onset without