Trigger-specific ion-channel mechanisms, risk factors, and response to therapy in type 1 long QT syndrome

Ilan Goldenberg, MD,* Princy Thottathil, MD,* Coeli M. Lopes, PhD,† Arthur J. Moss, MD,* Scott McNitt, MS,* Jin O-Uchi, MD, PhD,† Jennifer L. Robinson, MS,* Wojciech Zareba, MD, PhD,* Michael J. Ackerman, MD,‡ Elizabeth S. Kaufman, MD,§ Jeffrey A. Towbin, MD,‖ Michael Vincent, MD,¶ Alon Barsheshet, MD*

*From *the Cardiology Division, University of Rochester Medical Center, Rochester, New York; †Cardiovascular Research Institute, University of Rochester Medical Center, Rochester, New York; ‡Departments of Medicine, Pediatrics, and Molecular Pharmacology & Experimental Therapeutics, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic College of Medicine, Rochester, Minnesota; §The Heart and Vascular Research Center, MetroHealth Campus, Case Western Reserve University, Cleveland, Ohio; ‖Department of Pediatrics, University of Cincinnati Children's Hospital, Cincinnati, OH; and ¶Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah.*

BACKGROUND Arrhythmic events in long-QT syndrome type 1 (LQT1) may be associated with exercise, acute arousal, or rest/sleep.

OBJECTIVES We aimed to identify trigger-specific risk factors for cardiac events in patients with LQT1.

METHODS The study population comprised 721 genetically confirmed patients with LQT1 from the US portion of the International LQTS Registry. Multivariate analysis was used to assess the independent contribution of prespecified clinical and mutation-specific factors to the development of a first reported triggered event, associated with exercise, arousal, or sleep/rest.

RESULTS Cardiac events occurred in 221 study patients, of whom 121 (55%) were associated with exercise, 30 (14%) with arousal, 47 (21%) with sleep/rest, and 23 (10%) with other triggers. Multivariate analysis showed that males <13 years had a 2.8-fold ($P < .001$) increase in the risk for exercise-triggered events whereas females ≥13 years showed a 3.5-fold ($P = .002$) increase in the risk for sleep/rest nonarousal events. Cytoplasmic-loop mutations within the transmembrane region, involved in adrenergic channel regulation, were associated with the increased risk for both exercise- and arousal-triggered events (hazard ratio = 6.19 [$P < .001$] and 4.99 [$P < .001$], respectively) but were not associated with events during sleep/rest (hazard ratio = 0.72; $P = .46$). Beta-blocker therapy was associated with a pronounced 78% ($P < .001$) reduction in the risk for exercise-triggered events but did not have a significant effect on events associated with arousal or sleep/rest.

CONCLUSIONS In patients with LQT1, cardiac events triggered by exercise, arousal, or rest/sleep are associated with distinctive risk factors and response to medical therapy. These findings can be used for improved recommendations for lifestyle modifications and therapeutic management in this population.

KEYWORDS Long-QT syndrome; Sudden cardiac death; Triggers

ABBREVIATIONS **ACA** = aborted cardiac arrest; **C-loops** = cytoplasmic loops; **ECG** = electrocardiogram; **LQTS** = long-QT syndrome; **LQT1** = long-QT syndrome type 1; **LQT2** = long-QT syndrome type 2; **QTc** = corrected QT interval; **SCD** = sudden cardiac death; **TM** = transmembrane

(Heart Rhythm 2012;9:49–56)

Introduction

Congenital long-QT syndrome (LQTS) is an inherited channelopathy characterized by QT prolongation and delayed ventricular repolarization that can result in arrhythmias leading to syncope, torsades de pointes, or sudden cardiac death (SCD).[1,2] The most common form of this inherited cardiac disorder, long-QT syndrome type 1 (LQT1), is caused by loss of function mutations in the *KCNQ1* gene that codes for the α subunit of the voltage-gated potassium channel.[3] Mutations in this gene cause decreased outward potassium current, resulting in prolonged channel opening, delayed ventricular repolarization, and increased QT interval.[2] The phenotypic expression of LQT1 was shown to be affected by clinical and mutation-related factors, including age, gender, and the type and location of the mutation in the *KCNQ1* channel.[4–6]

Cardiac events in LQTS were shown to be associated with gene-specific triggers.[7,8] Thus, in LQT1, most events are triggered by exercise activity, whereas in long-QT syn-

This work was supported by research grants HL-33843 and HL-51618 from the National Institutes of Health, Bethesda, Maryland, and by a research grant to the University of Rochester from GeneDx. I.G. and P.T. contributed equally to the original concept and to the authorship of this investigation. M.J.A. has a consulting relationship and license agreement/royalty arrangement with PGxHealth (FAMILION), and E.S.K. receives research support from CardioDx. **Address for reprints and correspondence:** Dr Ilan Goldenberg, MD, Heart Research Follow-up Program, University of Rochester Medical Center, Box 653, Rochester, NY 14642. E-mail address: Ilan.Goldenberg@heart.rochester.edu.

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.08.020

drome type 2 (LQT2) and long-QT syndrome type 3, most events are associated with acute arousal or sleep/rest.[7,8] We have recently shown that the risk factors for cardiac events in LQT2 are trigger specific.[9] The present study was designed to extend these observations to the population with LQT1. Accordingly, we evaluated 721 genetically confirmed patients with LQT1 from the US portion of the International LQTS Registry to (1) identify clinical and mutation-related factors that are associated with trigger-specific risk for cardiac events in patients with LQT1 and (2) evaluate whether response to beta-blocker therapy in LQT1 is trigger specific.

Methods

Study population

The study population of 721 subjects was derived from 138 proband-identified families with genetically confirmed single mutation in the *KCNQ1* gene drawn from the US portion of the International LQTS Registry. The proband in each family had corrected QT interval (QTc) prolongation not due to a known cause. Patients with LQT1 from the US portion of the registry who experienced a cardiac event without a known trigger (n = 11) were excluded from the study. A comparison of the clinical characteristics of registry patients with and without a known trigger for cardiac events is provided in the Supplementary Appendix Table S1. All subjects or their guardians provided informed consent for the genetic and clinical studies.

Phenotype characterization

Routine clinical and electrocardiographic parameters were acquired at the time of enrollment. Measured parameters on the first recorded electrocardiogram (ECG) included QT and R–R intervals in milliseconds, with QT corrected for heart rate by Bazett's formula.[10] Clinical data were recorded on prospectively designed forms and included patient and family history and demographic, ECG, therapeutic, and cardiac event information. Data regarding triggers for cardiac events were collected for each patient (as reported by the patient [if alive], family members, or primary care physician) after the occurrence of an event through a specific questionnaire and further corroborated by the study coordinators through patients' medical files and oral history from individuals about themselves or about family members. Subsequently, the study specialists categorized each reported trigger by using prespecified codes. Follow-up data regarding beta-blocker therapy included the starting date, type of beta-blocker, and discontinuation date in case it occurred. Among subjects who died, the usage of a beta-blocker before death was determined retrospectively.

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; Mayo Clinic College of Medicine, Rochester, MN; and Boston Children's Hospital, Boston, MA.

Prior studies have shown that mutations located at the transmembrane (TM) region and missense versus nonmissense mutations are associated with a greater risk for cardiac events in patients with LQT1.[6] Furthermore, the cytoplasmic loops (C-loops) within the TM region were recently shown to affect adrenergic channel regulation by protein kinase A (PKA).[11,12] Therefore, in the present study, mutations were categorized by their location and type in the *KCNQ1*-encoded channel as follows: (1) missense mutations in the TM region, defined as amino acid residues from 120 to 355, excluding mutations within the C-loop region; (2) missense mutations in the C-loop region, defined as the coding sequence involving amino acid residues from 174 to 190 and from 242 t0 259; (3) missense mutations in the remaining N-terminus region, defined as amino acid residues before 120, and the C-terminus region, defined as after

Table 1 Characteristics of study patients by cardiac event triggers

Characteristics	Exercise (n = 121)	Acute arousal (n = 30)	Sleep/rest nonarousal (n = 47)	Other triggers (n = 23)	No event (n = 500)	*P* value
Gender						
Female (%)	48	70	70	83	56	.003
ECG at enrollment						
QTc (ms)	504 ± 52	491 ± 49	486 ± 58	480 ± 48	471 ± 43	<.001
RR (ms)	887 ± 209	802 ± 196	894 ± 206	782 ± 216	812 ± 211	.002
QRS (ms)	80 ± 15	78 ± 15	82 ± 13	77 ± 11	80 ± 15	.716
LQTS therapies						
Beta-blockers (%)	74	73	64	70	35	<.001
LCSD (%)	2	0	0	0	0	.005
Pacemaker (%)	5	0	4	4	0	<.001
ICD (%)	24	30	13	22	3	<.001
Recurrent cardiac events						
Subsequent events of any trigger (%)	62	63	51	39	NA	NA
Subsequent events of the same trigger among patients who had recurrent cardiac events (%)	89	68	59	67	NA	NA
Follow-up time (y)	30 ± 10	30 ± 12	30 ± 11	30 ± 12	30 ± 14	0.99

ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; LQTS = long-QT syndrome; NA = not applicable; QTc = corrected QT interval.