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Phenotype guided characterization and molecular analysis of Indian patients with long QT syndromes

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ABSTRACT

Background: Long QT syndromes (LQTS) are characterized by prolonged QTc interval on electrocardiogram (ECG) and manifest with syncope, seizures or sudden cardiac death. Long QT 1–3 constitute about 75% of all inherited LQTS. We classified a cohort of Indian patients for the common LQTS based on T wave morphology and triggering factors to prioritize the gene to be tested. We sought to identify the causative mutations and mutation spectrum, perform genotype-phenotype correlation and screen family members.

Methods: Thirty patients who fulfilled the criteria were enrolled. The most probable candidate gene among *KCNQ1*, *KCNH2* and *SCN5A* were sequenced.

Results: Of the 30 patients, 22 were classified at LQT1, two as LQT2 and six as LQT3. Mutations in *KCNQ1* were identified in 17 (77%) of 22 LQT1 patients, *KCNH2* mutation in one of two LQT2 and *SCN5A* mutations in two of six LQT3 patients. We correlated the presence of the specific ECG morphology in all mutation positive cases. Eight mutations in *KCNQ1* and one in *SCN5A* were novel and predicted to be pathogenic by *in-silico* analysis. Of all parents with heterozygous mutations, 24 (92%) of 26 were asymptomatic. Ten available siblings of nine probands were screened and three were homozygous and symptomatic, five heterozygous and asymptomatic.

Conclusions: This study in a cohort of Asian Indian patients highlights the mutation spectrum of common Long QT syndromes. The clinical utility for prevention of unexplained sudden cardiac deaths is an important sequel to identification of the mutation in at-risk family members.

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1. Introduction

Long QT syndromes (LQTS) are inherited autosomal dominant channelopathies associated with prolongation of QT interval on the 12-lead electrocardiogram (ECG) (QTc > 440 ms in men and >450 ms in women). They are caused by mutations in fifteen cardiac ion channels pore forming and auxiliary subunit genes [1–3]. Common symptoms include syncope, seizures, and polymorphic ventricular tachyarrhythmias, that may lead to sudden cardiac death [4]. Among all types of LQTS, Long QT types 1–3 (LQT 1–3) constitute about 75% of the cases [5,6]. LQT1 is also observed as an autosomal recessive trait in patients with sensorineural deafness

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[Jervell-Lange Nielsen syndrome (JLNS)], whereas patients without deafness are referred to as autosomal recessive Romano-Ward syndrome (AR RWS) [7].

Specific triggering factors and T wave morphology on ECG are consistently described in three common types of LQTS [8–10]. Typically, in LQT1 syndrome, physical exertion triggers arrhythmic events with ECG showing broad T waves; in LQT2 syndrome, emotional stress, auditory stimuli, postpartum period trigger cardiac events with ECG demonstrating a biphasic or notched T wave. In LQT3 syndrome, majority of arrhythmic events occur during sleep or rest and they have delayed onset of T wave on ECG [2,11,12].

LQT1 and LQT2 are caused due to mutations in the potassium channel genes, *KCNQ1* (OMIM#607542) and *KCNH2* (OMIM#152427) respectively, while LQT3 is caused by mutations in a sodium channel gene, *SCN5A* (OMIM#600163) [2]. Although hundreds of mutations have been identified in the three genes, studies have shown the presence of common as well as founder mutations in different populations suggesting genetic or allelic heterogeneity [6,13–16].

Molecular testing in LQTS helps to confirm the clinical diagnosis in the proband, perform genotype-phenotype guided management as well identify the at-risk family members who may be asymptomatic and can be missed by ECG studies [12,17]. In this study, we classified a cohort of Asian Indian patients with Long QT syndrome based on T wave morphology and triggering factors. The aim was to identify the causative mutations in patients affected with common types of LQTS, determine the mutation spectrum of this sparsely studied population, perform genotype-phenotype correlation and identify the at-risk family members.

2. Materials and methods

2.1. Patients

Thirty patients of Asian Indian origin from unrelated families were included in the ongoing study on life threatening Long QT syndromes, from January 2011 through July 2015 at Sir Ganga Ram Hospital, New Delhi, India. They were "suspected LQTS" on the basis of prolongation of QTc interval >440 ms in men and >450 ms in women. All probands were <40 years of age, had a structurally normal heart on echocardiography, and were classified in three different groups of LQTS (LQT1, LQT2, LQT3) depending on the ECG morphology (Fig. 1) and triggers. They also had either a) symptoms of syncope/seizures/resuscitated sudden cardiac death (SCD) and/or b) a family history of SCD/LQTS. All those with unclear ECG morphology were excluded. The clinical details such as age at onset of symptoms, age at diagnosis, trigger for arrhythmias, type of cardiac events and the family history, up to three generations was noted for each proband. Patients with structural cardiac abnormality, electrolyte imbalance or on medications known to prolong QT interval were excluded.

An informed consent was obtained from all the probands and their family members included in this study. This study was approved by the Ethics Committee of Sir Ganga Ram Hospital vide no EC/01/12/337.

2.2. Sample collection and DNA extraction

Blood samples (6 ml EDTA) were collected from the patient, their parents and siblings as available. Genomic DNA was extracted using the salt precipitation method. The isolated DNA was quantified by a spectrophotometer at the absorbance ratio of 260/280.

2.3. Mutation screening

2.3.1. PCR amplification

Primers flanking the exon-intron boundaries of all coding exons in three common genes (*KCNQ1* [NM_000218], *KCNH2* [NM_000238] and *SCN5A* [NM_198056]); were designed using web-primer software available in Saccharomyces genome database (http://www.yeastgenome.org/cgi-bin/web-primer). Primer sequences are available on request. On the basis of the T wave morphology on ECG and triggering factors causing the episodes, the candidate gene was selected to be PCR amplified and sequenced in these patients.

2.3.2. Sanger sequencing

PCR products were purified using MicroAmp purification plate and subjected to direct sequencing based on dideoxynucleotide termination methodology using the BigDye terminator cycle sequencing Ready reaction kit (Applied Biosystems, Perkin Elmer Corporation, Foster City, CA). Sequencing was performed bi-directionally on ABI 3500 Genetic Analyzer (Applied Biosystems, UK).

2.3.3. Detection of variants

Analysis of the electropherogram was performed by aligning the patient sequences with the reference sequences of *KCNQ1*, *KCNH2* and *SCN5A* available in the database using Blat tool (https://genome.ucsc.edu/cgi-bin/hgBlat). Forward and reverse primer sequencing results were compared to confirm the presence of the variation. All variations were also verified by sequencing a second amplified amplicon.

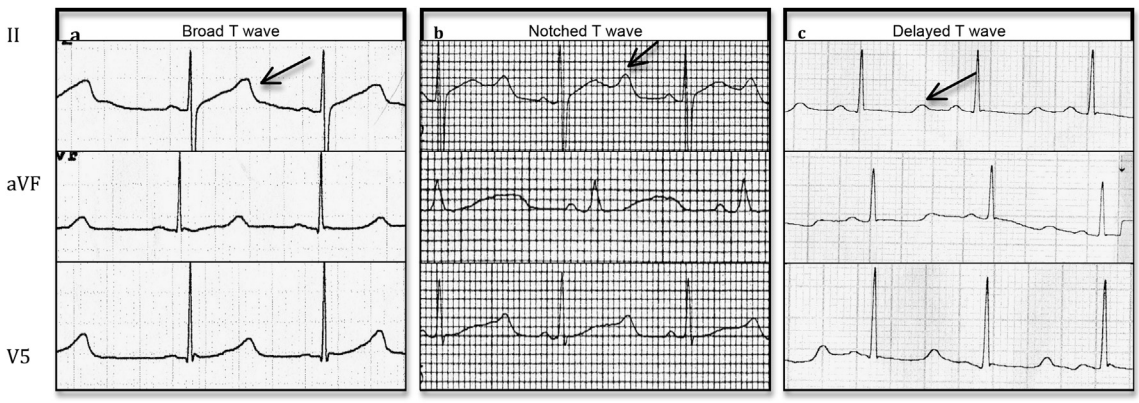

Fig. 1. Classification of LQTS type on the T wave morphology on ECG. LQT1 (a), LQT2 (b) and LQT3 (c).

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