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Genotype–phenotype correlation in long QT syndrome families

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ABSTRACT

Heterogeneity in clinical manifestations is a well-known feature in Long QT Syndrome (LQTS). The extent of this phenomenon became evident in families wherein both symptomatic and asymptomatic family members are reported. The study hence warrants genetic testing and/or screening of family members of LQTS probands for risk stratification and prediction.

Of the 46 families screened, 18 probands revealed novel variations/compound heterozygosity in the gene/s screened. Families 1–4 revealed probands carrying novel variations in *KCNQ1* gene along with compound heterozygosity of risk genotypes of the *SCN5A*, *KCNE1* and *NPPA* gene/s polymorphisms screened. It was also observed that families- 5, 6 and 7 were typical cases of "anticipation" in which both mother and child were diagnosed with congenital LQTS (cLQTS). Families- 16 and 17 represented aLQTS probands with variations in IKs and INa encoding genes. First degree relatives (FDRs) carrying the same haplotype as the proband were also identified which may help in predictive testing and management of LQTS. Most of the probands exhibiting a family history were found to be genetic compounds which clearly points to the role of cardiac genes and their modifiers in a recessive fashion in LQTS manifestation.

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Introduction

Long QT Syndrome (LQTS) is associated with prolongation in ventricular repolarisation and is diagnosed by a prolonged QTc value exceeding 450 ms and documented syncopal episodes. However, QTc measurement on electrocardiogram (ECG) is not always a reliable surrogate marker for prolonged repolarisation as not all patients who present the LQTS phenotype exhibit prolonged QTc interval and some asymptomatic individuals may have prolonged QTc. The detection of a genetic defect within a family allows for the identification of all subjects at risk of developing cardiac events. This information has a direct impact on the clinical management of prophylactic therapy for defective gene carriers against fatal arrhythmias. Hence, a pressing need arises to screen the LQTS-associated genes for pathological mutations in high-risk individuals [1]. Molecular screening of family members of probands would unmask many affected relatives, thus allowing effective preventive measures [2].

Genetic disorders have been associated with carrying common haplotypes mostly carrying risk alleles. Identification of such a common haplotype can be of importance in the prognostic evaluation of first degree relatives (FDRs). The Finnish population represents a genetic isolate due to effective geographical and linguistic separation within the historical period. The geographical distribution of the birthplaces for the oldest *KCNQ1*-Fin carriers closely matches the internal migration wave commenced from the southeast in the sixteenth century. The founder gene phenomenon is further supported by the common haplotype associated with the disease in virtually all affected individuals examined [3].

Previously, a founder *KCNQ1* mutation has been reported to occur in five South African families based on identical haplotype around the disease locus [1]. Thus, one can envision not only genotype-specific treatment algorithms but even mutation-specific considerations. The clinical message is that in the future attention should be paid to families with a high percentage of symptomatic individuals and that, once the disease-causing mutations have been identified, collaborative studies should be undertaken to test the possibility of identifying other clinically malignant mutations. This will contribute to the development of a more accurate risk stratification grid for patients affected by LQTS [4].

Considering the previous reports and suggestions, screening of available family members is warranted in the present study. Along with controls and patients, the available family members were also screened for any variations in IKs (slowly activating delayed rectifier potassium current) and INa (sodium current) channel encoding genes (already implicated in LQTS), and single nucleotide polymorphisms of gene/s which may have a modifying effect on LQTS i.e. beta-adrenergic receptor-1 & 2 (*ADRB 1 & 2*), atrial natriuretic peptide (*NPPA*) and tumor necrosis factor-alpha (*TNF-α*) gene/s. The present study on LQTS families is in continuation to our previous report which revealed mutations in a JLN Syndrome proband and his family members [5]. In this study, mutations were identified in three probands and their family members. It was also observed that the probands were carrying more than one risk allele leading to compound heterozygosity/genetic compounds. Predictive genetic testing was also carried out for family members to establish specific haplotype segregating as in the proband, to identify if the risk of such haplotypes to LQTS can co-exist in the siblings and first degree relatives (FDRs) and to predict prognosis of the condition.

Methodology

Study subjects

Blood samples were collected for molecular and genetic analyses from confirmed 46 LQTS probands and 69 first degree relatives referred to Care Hospitals, Hyderabad, Sri Jayadeva Institute of Cardiovascular Science and Research, Bangalore, Institute of Maternal and Child Health, Calicut Medical College, Calicut and Krishna Institute of Medical Sciences, Hyderabad. Samples were collected from 2009 to 2013 due to the rarity of the disorder. The QTc of the LQTS patients and their FDRs was confirmed by electrocardiogram. LQTS patients with prolonged QTc with/without syncope and family history of sudden cardiac death were included in the study. Available first degree relatives of the LQTS probands (with/without any history of cardiovascular disease) were also included. This study has been approved by the Institutional Ethics Committee, Dept. of Genetics, Osmania University, Hyderabad and informed written consent was obtained from the probands and their available family members. Blood samples from 150 controls (75 M: 75 F), without any history of cardiovascular or systemic conditions, was collected from Osmania General Hospital, Hyderabad for comparative analysis.

Inclusion and exclusion criteria

Patients who satisfied the diagnostic criteria Schwartz et al. [24] for LQTS referred by the cardiologists were included in the study. And cases exhibiting hearing loss other than JLN syndrome were excluded.

Molecular analyses

Genomic DNA was isolated from peripheral blood samples by standard protocols in 150 controls, 46 probands and their family members. PCR was carried out for all the gene/s mentioned in a thermal cycler (Eppendorf, Germany) using specific primers obtained from published reports and mutation database. The primers for *KCNQ1*, *KCNE1* and *SCN5A* were as described by Syrris et al., [6] *ADRB1* were by Maqbool et al. [7] and for *ADRB2* by Martinez et al. [8]. *NPPA* primers used were as given by Kato et al. [9] For amplification of *TNF-alpha* gene −308 G/A SNP, primers sequences from Wu et al. [10] further modified by Verjans et al. [11] were taken. For −1031 T/C and −238 G/A SNPs, primers described by Soga et al. [12] and Malivanova et al. [13] respectively were used.

For *KCNQ1*, *KCNE1* and *SCN5A* PCR-SSCP analyses was carried out on native PAGE gels followed by silver staining. And for *ADRB*, *NPPA* and *TNF-α* polymorphisms, PCR-RFLP and ARMS-PCR products were checked on 10% native PAGE gel

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