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Original Article

Novel mutations of *KCNQ1* in Long QT syndrome

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ABSTRACT

Background: Autosomal recessive Long QT syndrome is characterized by prolonged QTc along with congenital bilateral deafness depends on mutations in K^+ channel genes. A family of a Long QT syndrome proband from India has been identified with novel *indel* variations.

Methods: The molecular study of the proband revealed 4 novel *indel* variations in *KCNQ1*. In-silico analysis revealed the intronic variations has led to a change in the secondary structure of mRNA and splice site variations. The exonic variations leads to frameshift mutations. DNA analysis of the available family members revealed a carrier status.

Results and Conclusion: It is thus predicted that the variations may lead to a change in the position of the splicing enhancer/inhibitor in *KCNQ1* leading to the formation of a truncated S2–S3 fragment of KCNQ1 transmembrane protein in cardiac cells as well as epithelial cells of inner ear leading to deafness and aberrant repolarization causing prolonged QTc.

1. Introduction

Congenital Long-QT syndrome (cLQTS) is an inherited arrhythmogenic disease characterized on ECG by a prolonged QTc interval. The ECG manifestation reflects an abnormally prolonged ventricular action potential, which can be the substrate for life-threatening arrhythmias that lead to syncope or sudden cardiac death.[1]

Autosomal recessive Jervell and Lange Nielsen syndrome (JLN), characterized by prolonged QTc along with congenital bilateral deafness depends on homozygous or compound heterozygous mutations in either *KCNQ1* and *KCNE1* genes encoding a potassium channel.[2]

The coassembly of these two proteins leads to a slowly activating delayed rectifier potassium channel IKs. *KCNQ1* mapped to chromosome 11p15.5, encodes the larger alpha-

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subunit and *KCNE1* the smaller beta-subunit of the IKs protein. *KCNQ1* consists of 16 exons, spanning 400 kb, has relatively small amino and carboxy termini, and encodes a protein of 676 amino acids. Functional *IK*s channels result from the coassembly of 4 subunits into a tetrameric protein channel that is transported to the myocyte membrane. Each subunit contains 6 membrane-spanning domains (S1 to S6) flanked by amino and carboxyl terminus regions.[3]

To date, numerous mutations have been identified across the coding region of the ion channel genes in JLNS patients but there is a limited data with respect to the Indian population most probably because JLNS, being a recessive disease, is far less prevalent.[4] The precise diagnosis in subclinical patients of LQTS like JLNS warrants molecular analyses in addition to ECG to establish a genotype–phenotype correlation.[5]

In the present context, novel compound heterozygous variations/genetic compounds in a JLN syndrome patient and family members is reported in *KCNQ1* gene with the establishment of genotype–phenotype correlation.

2. Materials and methods

2.1. Clinical evaluation

The proband, a 6-year-old boy of Indian origin, was referred to the Care Hospitals, Hyderabad with a history of multiple syncopal attacks due to stress since 6 months of age and congenital deafness and dumbness. The proband has a 1 year-old normal sibling and a past history of 2 neonatal and a sudden infant death in older siblings with history of parental consanguinity (Fig. 1).

Laboratory investigations of the proband revealed severe anemia in the proband with a normal blood pressure. The Echo revealed a Patent Foramen Ovale. The electrocardiogram (ECG) showed a prolonged QTc of 520 msec (Fig. 2) and diagnosed with Long QT syndrome following the diagnostic criteria of Schwartz et al whereas the ECG of the parents and

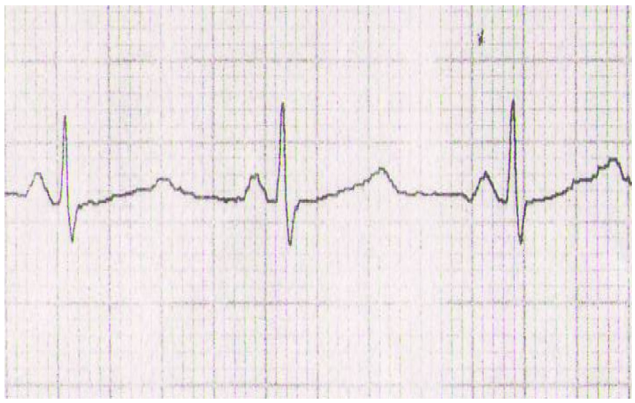


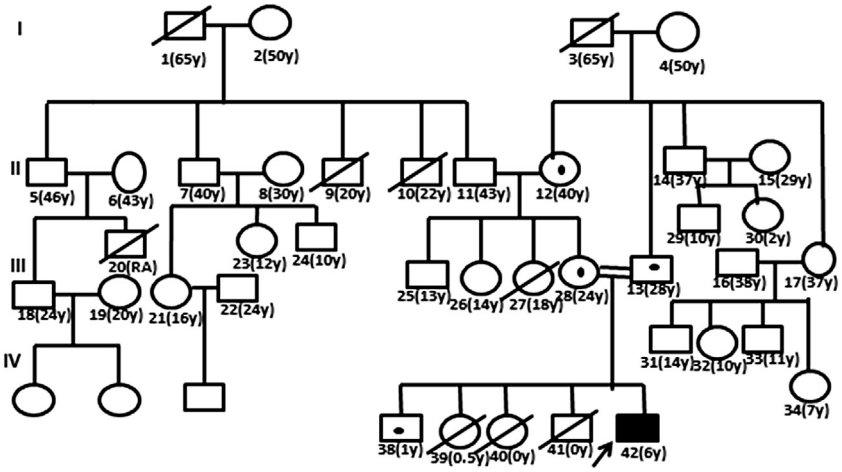
Fig. 2 – Electrocardiogram of LQTS proband showing a prolonged QT_C of 520 msec.

the maternal grandparents was found to be normal.[6] (The proband was put on beta-blockers and pacemaker as recommended by the consultant cardiologist.)

Since, JLN syndrome is an autosomal recessive disorder, peripheral blood samples of the proband and the available family members (I-3, II-11, II-12, II-13, III-28, IV-38, IV-42) were collected for DNA analyses after obtaining Institutional Ethics Committee, Dept. of Genetics, Osmania University, India clearance and informed written consent from the proband and his family members. 100 control blood samples without any history of cardiovascular or systemic conditions were collected from Osmania General Hospital, Hyderabad for comparative analysis.

2.2. Molecular analyses

Genomic DNA was isolated from peripheral blood samples by following standard protocols in 100 controls proband and his family members. The DNA sequences corresponding to *KCNQ1* gene and *KCNE1* gene were amplified using the primer sets as described by Syrris et al.[7] Fragments were amplified on



Pedigree of the patient showing consanguinity and neonatal deaths
'.' – Sequencing analysis revealed heterozygous genotypes; RA-road accident

Fig. 1 – Pedigree of proband.