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Biomarkers and drug responsive genotype in long QT syndrome

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Introduction: Long QT Syndrome (LQTS), an ion channelopathy is a fatal cardiovascular disorder with a propensity to ventricular tachyarrhythmias. Although, gene/s encoding the cardiac sodium, potassium and calcium-sodium channels are implicated in LQTS, apart from the influence of environmental factors and/or modifying genetic effects. Hence, the modifier genes - Beta-1 adrenergic receptor (*ADRB1*), Beta-2 adrenergic receptor (*ADRB2*), Atrial Natriuretic Peptide (*NPPA*) and Tumor Necrosis factor-alpha (*TNF-α*) gene's were considered in the study in view of the variants being susceptible alleles, having pharmacogenomic importance.

Methods: PCR-RFLP analysis was carried out on 46 LQTS, 69 first degree relatives (FDRs) and 150 controls of South Indian origin followed by statistical and *In-silico* analyses.

Results: *ADRB1* polymorphism genotyping revealed that the South Indian cohort was monomorphic for S49 and R389 and *ADRB2* exhibited R16 and E27 homozygous genotypes respectively. It was also hypothesized that the presence of R389 allele of *ADRB1* may pave way for beta-blockers as a good therapeutic agent in LQTS patients and R16/E27 rare haplotype carriers can be evaluated for resistance to agonist-induced down regulation.

TNF-α -308A allele of -308G/A and -1031C allele of -1031C/T were found to be predominant, and -238A allele of -238G/A was found to be significantly associated implying its role in LQTS etiology.

Genotyping of *NPPA* -664C>G and 1766T>C revealed only 'CC' genotype and 'TT' genotypes respectively. In 1364 C>A polymorphism, predominanace of 1364C allele frequency points to its role in LQTS etiology. Three families each with two clinically affected/symptomatic LQTS probands exhibited CC genotype of 1364 C>A substitution.

In-silico analysis of the polymorphisms predicted their effect on mRNA thermodynamic stability; splice site and spliceosome factor binding sites influencing the downstream signalling cascade.

Discussion: It was thus hypothesized that *TNF-α* promoter and *NPPA* polymorphisms may impair the ion channels causing prolonged APD and hence can be considered as potential biomarkers/diagnostic markers in case of LQTS. These polymorphisms play a role in cardiac remodelling/cardiogenesis and may be helpful in risk stratification of FDRs. The ADRB1 and ADRB2 genotypes seem to be of pharmacogenomic implication paving way for beta-blockers in the treatment and management of LQTS.

Biography

Pratibha Nallari is a Professor at Department of Genetics, Osmania University, and Hyderabad carrying out considerable research in Indian population on Dilated Cardiomyopathy (DCM) and Hypertrophic Cardiomyopathy (HCM), Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) and Primary Pulmonary Hypertension (PPH)/Idiopathic Pulmonary Arterial Hypertension (IPAH). She has received an international grant from GlaxoSmithKline, UK apart from international collaboration with Sick kids hospital for research on ARVC. She has 125 papers to her credit in national and international peer reviewed journals apart from being one of the co-authors in a study published in Nature Genetics (2009). Dr. Nallari is also a member of various National/International bodies of human genetics, and has 70 novel variations patented in NCBI database to her credit.

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