Extended Abstract
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The utility of genetic testing in cardiac arrhythmias

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Abstract

Introduction: The common life threatening cardiac arrhythmias, Long QT (LQTS type 1-13) and Brugada (BrS type 1-12) present with syncope/palpitations/ seizures/aborted cardiac arrest. They have incomplete penetrance and variable expressivity. The three common genes (KCNQ1, KCNH2 and SCN5A) account for 75% of all LQTS cases and SCN5A gene in BrS accounts for 25% of all cases.

Aim: To identify the causative variation in the associated genes responsible for causing cardiac channelopathies in Indian patients.

Materials & Methods: Hundred patients who fulfilled the inclusion criteria of the study were enrolled. Mutation analysis was performed in most probable candidate gene by direct sequencing using primers flanking exon-intron boundaries. If a mutation was not identified, NGS was performed to identify mutations in other cardiac genes in patients. Parents and siblings were screened if a mutation was identified in the proband. Novel mutations were evaluated for pathogenicity using ACMG guidelines, bioinformatics and molecular modelling softwares.

Results: Mutations was identified in 23 of 100 (23%) patients by Sanger sequencing, 20 had LQTS and 3 had BrS. Among the LQT syndromes, mutations were identified in 17 in KCNQ1 (LQTS1), one in KCNH2 (LQTS2) and two in SCN5A (LQTS3). Among the LQTS1 patients, ten were identified with biallelic mutations. The three BrS patients had mutations in SCN5A (BrS1). Ten of 23 mutations were novel. NGS identified mutation in 22 (49%) of 45 patients negative for mutations by Sanger and with significant family history and/or strong clinical indication. Of which, 20 had LQTS and two had BrS. Out of these 46 mutations, 18 were novel. Cascade screening identified mutations in two symptomatic and forty asymptomatic family members. Genetic counseling was provided to the proband and family members.

Conclusion: Genotyping is important for confirming type of LQTS/BrS, which has implications for management, cascade screening and risk assessment.

Over the past decade, the discovery that mutations in the genes encoding key cardiac ion channel α-subunit and β-subunit as well as intracellular calcium-handling proteins serve as the primary genetic substrate for a spectrum of heritable cardiac arrhythmia syndromes or 'cardiac channelopathies', including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BrS), has broadened our mechanistic understanding of these sudden cardiac death (SCD)-predisposing genetic disorders. Furthermore, these discoveries have given rise to numerous clinically relevant genotype–phenotype correlations, spurring a number of professional societies to recommend the judicious use of clinical genetic testing for the purpose of identifying genetically predisposed individuals with concealed clinical phenotypes and guiding the genotype-specific risk-stratification and clinical management of individuals with clinically definitive disease. However, as the availability and clinical use of genetic testing increases, so does the probability that rare 'variants of uncertain significance' (VUS), alterations in the normal sequence of a gene whose association with disease risk is unknown, will be identified in putative disease-susceptibility genes. As we enter an era of next-generation sequencing, the interpretation of genetic testing results, particularly when the clinical evidence for disease is insufficient or inconclusive, is bound to present an increasingly daunting challenge. As with any clinical test, the proper interpretation of genetic testing results requires the careful consideration of all potential sources of both false-positive (e.g., background genetic noise or the frequency of genetic variations in a particular gene in a healthy population) and false-negative (e.g., high prevalence of concealed phenotypes due to incomplete penetrance) results. Understanding the 'signal-to-noise' ratio associated with a given genetic test is particularly important in SCD-predisposing conditions in which the balancing act of distinguishing rare pathogenic mutations from equally rare, yet innocuous, genetic variants can have life-altering implications given that highly effective therapeutic interventions are available, but not entirely devoid of complications or comorbidities, particularly for invasive approaches.