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Review Article

# Channelopathies - Emerging Trends in The Management of Inherited Arrhythmias

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**Abstract**

In spite of their relative rarity, inheritable arrhythmias have come to the forefront as a group of potentially fatal but preventable cause of sudden cardiac death in children and (young) adults. Comprehensive management of inherited arrhythmias includes diagnosing and treating the proband and identifying and protecting affected family members. This has been made possible by the vast advances in the field of molecular biology enabling better understanding of the genetic underpinnings of some of these disease groups, namely congenital long QT syndrome, catecholaminergic polymorphic ventricular tachycardia and Brugada syndrome. The ensuing knowledge of the genotype-phenotype correlations enables us to risk-stratify, prognosticate and treat based on the genetic test results. The various diagnostic modalities currently available to us, including clinical tools and genetic technologies, have to be applied judiciously in order to promptly identify those affected and to spare the emotional burden of a potentially lethal disease in the unaffected individuals. The therapeutic armamentarium of inherited arrhythmias includes pharmacological agents, device therapies and surgical interventions. A treatment strategy keeping in mind the risk profile of the patients, the local availability of drugs and the expertise of the treating personnel is proving effective. While opportunities for research are numerous in this expanding field of medicine, there is also tremendous scope for incorporating the emerging trends in managing patients and families with inherited arrhythmias in the Indian subcontinent.

**Keywords:** Channelopathies, Inherited Arrhythmias

## Introduction

Inherited arrhythmias or cardiac channelopathies are primary electrical diseases of the heart characterized by dysfunctional ion channels which in turn lead to a spectrum of clinical manifestations ranging from complete lack of symptoms to life-threatening arrhythmias and sudden cardiac death (SCD) as the first symptom. In spite of their relative rarity they have come to the forefront as a group of potentially fatal but preventable cause of SCD in children

and (young) adults.

Congenital long QT syndrome (LQTS) is the inherited arrhythmia syndrome that has been studied in detail and whose genotype-phenotype correlations have largely been unraveled. Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are currently intensively studied and the rarer entities like short QT syndrome, early repolarization syndrome, familial atrial fibrillation, premature cardiac conduction disease and idiopathic ventricular fibrillation are still largely under the surface. [1] The latter is mainly due to the rarity of these diseases precluding sufficient patient numbers to draw meaningful conclusions.

The mode of inheritance is predominantly autosomal dominant; however, autosomal recessive and sporadic mutations, which subsequently transmit as an autosomal dominant trait, are not uncommon. Comprehensive management of inherited arrhythmias includes diagnosing and treating the proband and identifying and protecting affected family members. [2] It has been shown that this can be achieved effectively with 70-80% of presymptomatically tested family members, after a couple of years of follow-up on treatment. [3] This review aims to throw some light on the emerging trends and their clinical applicability in managing individuals and families with inherited arrhythmia syndromes, highlighting the focus areas for cardiogenetics in the Indian subcontinent.

## Diagnostic evolution

Our understanding of genetic causation, of the correlation between dysfunctional mutant genes and clinical manifestations, and of the various factors that influence disease expression has grown in leaps and bounds in the last couple of decades.

### *Understanding the genetic underpinnings*

The diagnosis of inherited arrhythmias has evolved mirroring the advances in the field of human genetics and genomics itself. [4] The hundreds of genetic aberrations that we now associate with this group of diseases is staggering; especially considering the fact that it was not long ago that the first causative genes for LQTS were discovered. [5] It is also interesting to note how the gap between basic and clinical science, or in other words between geneticists, primary care physicians and electrophysiologists, seems to close rapidly and an interdisciplinary team approach to patient care has emerged in this field of cardiology. [2]

Today, not only are medical professionals more aware and increasingly efficient in picking up the individual and familial manifestations of these diseases, but are also better equipped with the diagnostic and therapeutic armamentarium necessary to confirm clinical suspicion and deploy appropriate treatment. The timely and adequate management of affected patients consists of two arms; firstly, a high level of suspicion and clinical astuteness to recognize the phenotype in an individual who may initially present to the emergency care team or to any other medical specialty, and secondly, a well-coordinated cardiogenetic team to provide genetic counseling and testing, to interpret the genetic data and to carry out family screening, and to make individualized therapeutic and follow-up decisions. [6,7]

In a young patient presenting with the classical textbook features of an inherited arrhythmia syndrome, there is not much diagnostic ambiguity. For instance, aborted sudden cardiac arrest and prolonged heart rate corrected QT (QTc) interval in a previously healthy child with a family history of young sudden unexplained death is a clear indication of an underlying LQTS that can be confirmed by targeted genetic testing. However, knowing that incomplete penetrance is the rule rather than the exception in these diseases and that phenotypic and genetic variability are frequently encountered, next generation sequencing (NGS) techniques