Inherited Arrhythmogenic Syndromes

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Inherited arrhythmogenic syndromes are the primary cause of unexpected lethal cardiac episodes in young people. It is possible that the first sign of the condition may be sudden death. Inherited arrhythmogenic syndromes are caused by genetic defects that may be analyzed using different technical approaches. A genetic alteration may be used as a marker of risk for families who carry the genetic alterations. Therefore, the early identification of the responsible genetic defect may help the adoption of preventive therapeutic measures focused on reducing the risk of lethal arrhythmias.

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1. Introduction

Cardiovascular diseases are the leading global cause of death, accounting for 30% of documented mortality (www.who.int/health-topics/cardiovascular-diseases). Sudden cardiac death (SCD) is responsible for most cardiovascular deaths, and coronary artery disease accounts for more than 80% of all SCD cases[1]. SCD accounts for 20% of deaths among young individuals, and results from familial genetic cardiomyopathies. Further, 5% to 10% of SCDs result from inherited arrhythmogenic syndromes (IASs) caused by channelopathies with alterations in ion channels or associated proteins[2]. IASs are usually autosomal-dominant, but autosomal-recessive, X-linked, and even mitochondrial-inheritance cases have been reported, and are usually associated with highly lethal episodes or syndromic phenotypes. Near Mendelian inheritance has been proposed, demonstrating a strong genetic factor modulated by additional genetic variants[3].The four predominant IASs are long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndrome (SQTS)[4]. These inherited disorders are characterized by incomplete penetrance and variable expressivity, usually impeding definite diagnosis. Phenotypic overlap may be observed due to a combination of genetic variants and the additive effect of multiple independent variants[5].

2. Long QT Syndrome

LQTS is an IAS with an estimated prevalence of 1 in 2000. LQTS is characterized by electrocardiographically corrected QT (QTc) interval prolongation in the absence of a secondary cause for prolonged QTc, such as drugs or electrolyte disturbances. This arrhythmogenic disease is associated with ventricular arrhythmias, particularly t*orsade des pointes*, leading to syncope and SCD. Further, LQTS is a common cause of sudden-infant-death syndrome[4]. LQTS can also be diagnosed in an individual with a risk score (modified Schwartz score) of >3.5 or upon identification of an unequivocally pathogenic variant in a LQTS-related gene.

There are currently more than 25 genes associated with congenital LQTS, and comprehensive genetic analysis, including copy-number variants (CNV), identifies the genetic risk in nearly 85% of cases. However, more than 75% of cases are associated with rare nonsynonymous variants in genes encoding potassium or sodium ion channels (*KCNQ1*, *KCNH2*, and *SCN5A*). Current guidelines recommend analysis of only these three genes[6], and a recent international study concluded that only these three genes are linked to LQTS[7]. However, four other genes (*CALM1*, *CALM2*, *CALM3*, and *TRDN*) have strong causality for LQTS, but with atypical features such as sinus bradycardia or atrioventricular block, QT prolongation, seizures, or developmental delay in infancy or early childhood. Therefore, both congenital and acquired (typically drug-induced) LQTS represent distinct but intertwined arrhythmogenic disorders characterized by QT interval prolongation[8].

3. Brugada Syndrome

BrS is a rare IAS with a prevalence of 1 in 2500 characterized by electrocardiographic ST-segment elevation with successive negative T waves in at least one right precordial lead without structural cardiac abnormalities. A characteristic Type 1 Brugada pattern, observed spontaneously or induced during drug challenge, is considered definitively diagnostic.

The most severe clinical symptom of BrS is ventricular fibrillation and SCD, which can be the first manifestation of the disease. Further, BrS is a main cause of SCD in children and young adults, although some patients remain asymptomatic for life[4]. Currently, nearly 30 genes have been linked to BrS, and most follow an autosomal dominant pattern of inheritance, although some studies support autosomal recessive[9] or X-linked inheritance[10].

Comprehensive genetic analysis identifies genetic associations in nearly 35% of BrS cases, and up to 30% of genetic alterations are in *SCN5A*. Current guidelines recommend analysis of *SCN5A* as the most cost-effective approach[6]. *SCN5A* is considered pathogenic[11] despite only a few nonsynonymous variants that are considered deleterious[12]. Beyond *SCN5A*, pathogenic variants associated with BrS are in four minor genes: *SLMAP*, *SEMA3A*, *SCNN1A*, and *SCN2B*[13].

4. Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a very rare (prevalence of 1 in 10,000) highly lethal IAS with a 30% mortality rate in untreated patients. It is characterized by adrenergic stimulated polymorphic ventricular tachycardia in the presence of a structurally normal heart. CPVT is usually diagnosed in patients younger than 40 years old[14]. The diagnostic hallmark is induced ventricular arrhythmias during exercise, particularly bidirectional ventricular tachycardia. A key feature of CPVT is a normal baseline electrocardiogram and echocardiogram. Without exercise stress testing, diagnosis can be missed[15].

Nowadays, nine genes are associated with CPVT, and genetic alteration (noncommon variants and CNV) is a potential cause in almost 65% of cases, although 60% of cases are attributed to rare nonsynonymous variants in the cardiac ryanodine receptor (*RYR2*)[16]. Current guidelines recommend analysis of *RYR2* in CPVT diagnosis[6]. Further, a recent international calmodulinopathy registry identified that nearly 28% of patients diagnosed with CPVT had alterations in calmodulin genes (mainly *CALM2*). All CALM–CPVT patients were symptomatic with early age of onset (around 6 years old)[17]. Identification of a pathogenic variant implies that genetic testing should be extended to first-degree relatives since CPVT is highly lethal.

5. Short QT Syndrome

Short QT syndrome (SQTS) is a very rare entity, with a prevalence of 1 in 10,000. SQTS is associated with paroxysmal atrial and ventricular fibrillation, syncope, and SCD, and is characterized by a short QT interval on the electrocardiogram, lack of normal changes in QT interval with heart rate, peaked T waves (particularly in precordial leads), and short or absent ST segments. The most common initial symptom is cardiac arrest in one-third of cases. Lethal episodes usually occur in infants and young children with no structural heart abnormalities[18]. SQTS is a genetically heterogeneous disease with eight associated genes. Comprehensive genetic analysis identified a genetic cause in 40% of cases, with most diagnosed cases resulting from alterations in *KCNH2*, *KCNQ1*, and *KCNJ2*. Current guidelines recommend analysis of these three genes[6]. Our group recently reported that rare variants in other genes are associated with electrical alterations concomitant with shortened QT intervals, but do not guarantee a diagnosis of SQTS[19]. Thus, other genetic alterations may explain cases without definitive genetic diagnosis. Additional large studies are needed, but low prevalence and high mortality rates impede comprehensive genotype–phenotype studies.

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