PRIMEVIEW

INHERITED CARDIAC ARRHYTHMIAS

nature reviews disease primers

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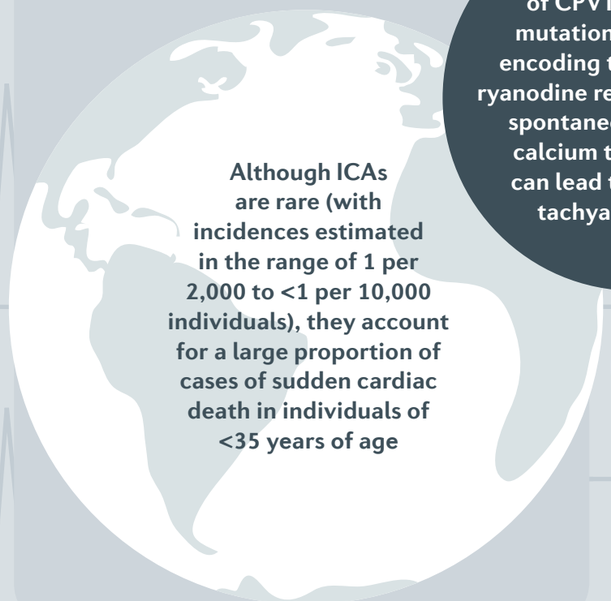
The main inherited cardiac arrhythmias (ICAs) are long QT syndrome (LQTS), short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome (BrS). All these conditions are associated with mutations in genes encoding ion channels or their regulatory proteins.

DIAGNOSIS

Individuals with ICAs are asymptomatic until the sentinel event (fainting, cardiac arrest or other arrhythmic disturbances) occurs, typically during childhood or early adulthood. Diagnosis relies on ECG morphology (at rest and under stress), medical history and genetic analyses, although a causative mutation cannot always be identified. Cascade genetic screening of family members is recommended to identify at-risk individuals.

LQTS is typically an autosomal dominant disorder and is characterized by a prolonged QT interval on the ECG; most cases are caused by mutations in genes encoding potassium or sodium channels

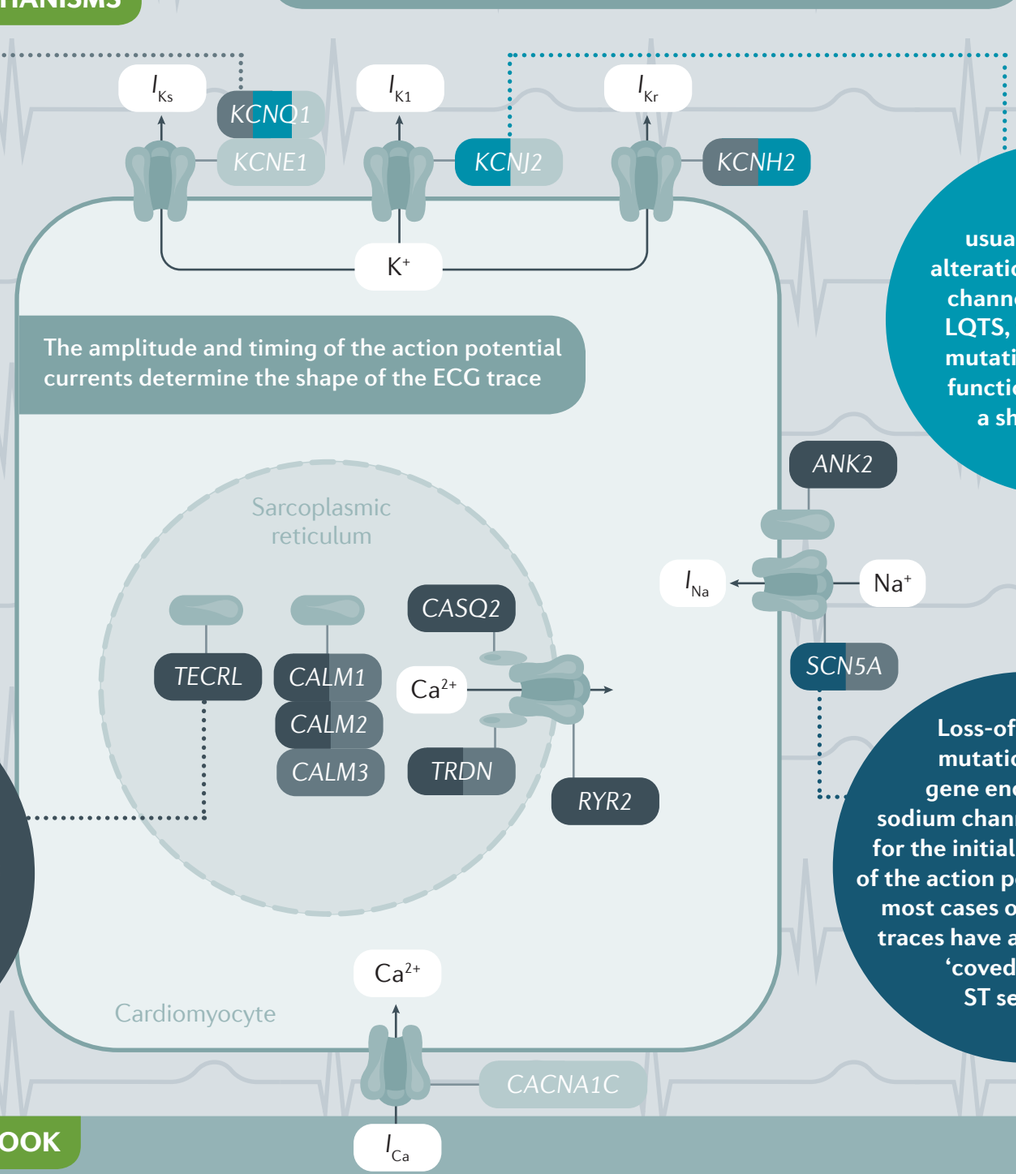
Most cases of CPVT result from mutations in the gene encoding the SR channel ryanodine receptor 2 (RYR2); spontaneous release of calcium through RYR2 can lead to ventricular tachyarrhythmias



Although ICAs are rare (with incidences estimated in the range of 1 per 2,000 to <1 per 10,000 individuals), they account for a large proportion of cases of sudden cardiac death in individuals of <35 years of age

MECHANISMS

The cardiac action potential is the result of several sodium, potassium and calcium currents across ion channels on the plasma membrane and sarcoplasmic reticulum (SR) of cardiomyocytes



The amplitude and timing of the action potential currents determine the shape of the ECG trace

SQTS is usually caused by alterations in potassium channels, but, unlike LQTS, the underlying mutations are gain of function, resulting in a shortened QT interval

Loss-of-function mutations in the gene encoding the sodium channel responsible for the initial depolarization of the action potential underlie most cases of BrS. BrS ECG traces have a characteristic 'coved'-shaped ST segment

MANAGEMENT

Pharmacological therapy with β-adrenergic receptor blockers or sodium channel blockers is indicated for most patients with LQTS or CPVT. An effective surgical intervention for LQTS and CPVT is left cardiac sympathetic denervation to reduce adrenergic stimulation (which can trigger arrhythmic events). For patients at risk despite therapy, an implantable cardioverter–defibrillator (ICD) has to be considered but can be associated with severe comorbidity.

QUALITY OF LIFE

The anxiety associated with the diagnosis of a potentially life-threatening disease can impair an individual's quality of life, along with the limitations that such diagnosis can bring (for example, patients are often advised against practising competitive sport and intense physical activities). ICD shocks are painful and can trigger a vicious cycle of further arrhythmias and shocks. Proper management of these patients requires considerable experience and expertise.

OUTLOOK

As ICAs are rare, registries are essential to collect genotypic and phenotypic data that could help to increase our understanding of the disease mechanisms and course, thereby enabling improved patient risk stratification. Identification of additional causative mutations and of genetic modifiers that can contribute to the clinical manifestations could result in the development of personalized treatments based on the underlying genetic causes.

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