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Gene-specific therapy for inherited arrhythmogenic diseases

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Abstract

In the last few years, major advancement has been made in the understanding of the genetic basis of inherited arrhythmogenic diseases. Interestingly, the information obtained with the application of molecular genetics to these diseases is now influencing their clinical management, allowing gene-specific risk stratification and gene-specific management.

The first attempt for a gene-specific therapy was made in 1995 with the use of mexiletine in long-QT syndrome (LQTS) patients with mutations in the *SCN5A* gene. Since then, several investigators have proposed novel therapeutic approaches based on the identification of the functional consequences of genetic mutations. In some instances, these novel therapies have already been introduced in clinical practice, and data are being collected to establish their long-term efficacy. In this review, we will summarize the current understanding of the molecular bases of inherited arrhythmias, with a specific focus toward discussing the most recent advancements toward the development of gene-specific therapies.

Keywords: Cardiac arrhythmias; Sudden death; Genetic; Genotype–phenotype correlation; Gene specific therapy

Abbreviations: AS, Andersen syndrome; AV, atrioventricular; BrS, Brugada syndrome; CCD, cardiac conduction defect; CICR, calcium-induced calcium release; CPVT, catecholaminergic polymorphic ventricular tachycardia; DADs, delayed afterdepolarizations; ECG, electrocardiogram; FAF, familial atrial fibrillation; GI, gastrointestinal; ICD, implantable cardioverter defibrillator; LQTS, long-QT syndrome; PES, programmed electrical stimulation; QTc, heart rate corrected QT interval; SCD, sudden cardiac death; SQTS, short-QT syndrome; SR, sarcoplasmic reticulum; SSS, sick sinus syndrome; TS, Timothy syndrome; VF, ventricular fibrillation.

Contents

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1. Introduction

Cardiac channellopathies are genetic disorders that are caused by DNA mutations of proteins involved in the control of cardiac excitability. The clinical manifestations of these disorders range from distinguishing electrocardiographic patterns to life-threatening ventricular arrhythmias. Multiple genes and allelic variants of channellopathies have been discovered in the last decade (http://pc4.fsm.it:81/cardmoc), and genetics is now emerging as an important tool contributing not only to a better diagnosis but also to risk stratification and management of patients.

The growing understanding of the pathophysiology of cardiac ion channel diseases has highlighted a high degree of genetic heterogeneity and results of genotype–phenotype correlation studies have unveiled the distinguishing features of each genetic variant. As a practical consequence for each disease, there are multiple genetic forms that present specific clinical characteristics.

For example, the long-QT syndrome (LQTS) is no longer considered as *one* disease, but rather, it is seen as a family of diseases that share the common feature of a prolonged QT interval at surface electrocardiogram (ECG) but that may have different severity and different prognosis depending on the underlying genetic abnormality (Priori et al., 2004a).

Accordingly, in this disease, gene-specific risk stratification algorithms and gene-specific treatments are being developed, providing a novel twist in the management of patients affected by this family of disorders (Priori et al., 2003a).

In this review, we will summarize the perturbations induced by mutations that cause cardiac channellopathies, and we will present the most recent advancements in the development of therapeutic strategies to counteract these derangements.

2. Diseases of potassium currents

Mutations in the genes encoding cardiac ion channels that conduct different potassium currents (I_{Ks}, I_{Kr}, and I_{K1}) have been associated with different cardiac channellopathies. The genes implicated are *KCNQ1* and *KCNE1* encoding for the Iks channel, *KCNH2* and *KCNE2* encoding for the I_{Kr} channel, and *KCNJ2* encoding for the I_{K1} channel (Fig. 1).

Mutations in these genes generates at least 5 different clinical phenotypes: Romano-Ward long-QT syndrome (LQTS), Jervell and Lange-Nielsen LQTS (Priori et al., 2004a), short-QT syndrome (SQTS; Gussak et al., 2000), Andersen Syndrome (AS; Andersen et al., 1971), and familial atrial fibrillation (FAF; Chen et al., 2003).

At first sight, it may seem surprising that so many phenotypes are linked to mutations in few genes; however, the clinical manifestations reflect the electrophysiological abnormalities caused by the specific genetic defect. Two types of mutations can be identified: those in which the function of the channel is increased ("gain of function" mutations) and those in which the activity of the ion channels is substantially diminished or even lost ("loss of function" mutations). There are therefore diseases caused by loss of function mutations of