

Chapter

10

Inherited Arrhythmia Syndromes

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Familial cardiac arrhythmias with a potential risk of sudden cardiac death can be divided into two main categories: diseases in which alterations in the cardiac electrical properties cause arrhythmias (primary electrical diseases), and diseases in which structural alterations create an arrhythmogenic substrate (cardiomyopathies). Primary electrical diseases include the long and short QT syndromes (LQTS and SQTS), Brugada and Andersen syndromes and catecholaminergic polymorphic ventricular tachycardia (CPVT). Cardiomyopathies include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). In both categories the predominant mode of inheritance is autosomal dominant. Reduced penetrance and varying expressivity are common.

The identification of several causally involved genes has boosted insight into the pathophysiology of the primary arrhythmia syndromes^{1,2}. Indeed, aberrations in genes encoding ion channels or their subunits underlie the congenital LQTS and SQTS, Brugada syndrome and idiopathic atrial fibrillation. 'Loss-of-function' mutations of KCNQ1 and KCNH2, encoding the slow and the rapid component of the delayed rectifier (potassium) current, respectively, are responsible for the vast majority of LQTS (types 1 and 2), whereas 'gain-of-function' mutations in either gene may shorten the QT-interval and cause SQTS. 'Gain of function' mutations in SCN5A, encoding the cardiac sodium channel, also lead to QT-prolongation (LQTS3). In contrast, 'loss of function' SCN5A mutations are involved in Brugada syndrome, isolated cardiac conduction disease, sinus node dysfunction and atrial standstill. Very recently, other potentially causally related genes have been identified

in patients with Brugada syndrome, including GPD1-L (encoding a 'chaperone' protein influencing Na-channel expression), the L-type Ca²⁺ channel gene CACNA1C and one of its subunits. Two genes underlying exercise-induced polymorphic VT/VF are involved in calcium homeostasis. In general, genes encoding proteins involved in the cardiac sarcomeres, the cellular cytoskeleton and in cell-cell interaction are involved in HCM, DCM, and in ARVC, respectively.

An active search in patients recruited worldwide has revealed relevant genotype-phenotype relationships in different primary arrhythmia syndromes with impact on the clinical picture, treatment and prognosis. In both LQTS and in Brugada syndrome this includes electrocardiographic characteristics (T-wave morphology and conduction parameters, respectively) and in LQTS symptom-related triggers, electrocardiographic aspect of the arrhythmia (and presumably its mechanism), age of onset of symptoms and treatment also relate to the genetic basis.

Finally, it becomes increasingly clear that the above familial arrhythmia disorders underlie a significant subset of sudden cardiac deaths, particularly in the young^{3,4}. An active search for these disorders is hitherto warranted in relatives of sudden cardiac death victims. Identification of the molecular substrate in these families greatly facilitates the identification of relatives at risk, subsequently resulting in timely treatment^{3,4}.

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