Chapter 7

GENETIC BASIS OF LIFE-THREATENING ARRHYTHMIAS

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INTRODUCTION

Sudden cardiac death (SCD) in an otherwise healthy young person is unusual, and considerable effort has been devoted to delineation of the clinical features and often familial nature of such cases. The availability of chromosomal markers that span the human genome and improved high-throughput technology for genotyping and sequencing have led to major advances against genetic diseases. In the past 50 years, considerable success has been achieved in prolonging survival and improving the quality of life of patients with cardiac arrhythmias. However, despite innovations in technology and pharmacology, cures are not available, partly because of poor understanding of the basic mechanisms responsible for these diseases. New developments in molecular genetics and biology provide tools to elucidate the fundamental mechanisms of cardiac arrhythmias, opening new possibilities not only for improved therapeutic and diagnostic measures but also for prevention.

1. ARRHYTHMIAS ASOOCIATED WITH STRUCTURAL HEART DISEASES

Various genetic cardiac diseases predispose to arrhythmias, both with and without structural abnormalities (Table). These cardiac diseases result from abnormal genes that encode primarily for three main families of proteins: the sarcomeric proteins, which generate the mechanical contraction of the myocyte, manifested as hypertrophic cardiomyopathy; the cytoskeletal proteins, which coordinate and transmit this force to the neighboring cells, manifested as dilated cardiomyopathy[1]; and the ion channels, which generate and coordinate electrical activity in the heart, responsible for familial arrhythmias[2]. Risk stratification based on genotype/phenotype correlations has also indicated that predicting prognosis is more complex than once thought. Nevertheless, this simplistic classification by protein families has provided the impetus to explore the various mechanisms responsible for these diseases. Identification of underlying genetic factors has added to our understanding of arrhythmogenic triggers and determinants of sudden death. Some of the genetic factors used to determine risk for sudden death or arrhythmias are the result of research in only a few families, so longer and more extensive studies are required.

2. ION CHANNELOPATHIES

Coordinated cardiac activity requires ion currents, ion channels, structural proteins, and gap junctions responsible for the transmission of electrical and mechanical impulses across the cardiac myocytes. Research into the structure,

Table

Arrhythmias with structural heart diseases				
Syndrome	Arrhythmias	Inheritance	Gene	Locus
Hypertrophic cardiomyoathy (HCM)	VT/Af	AD	β myosin heavy chain	14q12
			Troponin T	1q32
			α tropomyosin	15q22
			Myosin binding protein C	11p11
			Myosin light chain	12q23-24
			Myosin light chain	3p21
			Titin	2q31
			Troponin I	19q13
WPW syndrome+HCM	VT/Af	AD	PRKAG2	7q36
Dilated cardiomyopathy (DCM)	VT	AD	Actin	15q14
			Desmin	2q35
			δsarcoglycan	5p33
			Titin	2q31
			β myosin heavy chain	14q12
			Troponin T	1q32
			Lamin A/C	1q21
		XR	Dystrophin	Xp.21
			G.4.5	Xq28
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	VT	AD	RyR2	1q42-43
			Desmoplakin	6p24
			?	2q32.1-32.3/3p23/14q12-22/14q23-24

Arrhythmias without structural heart diseases					
Syndrome		Arrhythmias	Inheritance	Gene	Locus
Congenital LQTS	LQT1	TdP	AD	KCNQ1	11p15.5
	LQT2			KCNH2	7q35-36
	LQT3			SCN5A	3p21
	LQT4			ANK2	4q25-27
	LQT5			KCNE1	21q22.1
	LQT6			KCNE2	21q22.1
Andersen syndrome	(LQT7)			KCNJ2	17p23.1-24.2
Congenital LQTS	JLN1		AR	KCNQ1	11p15.5
	JLN2			KCNE1	21q22.1-22
Acquired LQTS		TdP	?	KCNH2	7q35-36
				KCNE2	21q22.1
				SCN5A	3p21
Brugada syndrome		VF	AD	SCN5A	3p21
				?	3p22-25
Cardiac conduction defect		AV block, Bundle branch block	AD	SCN5A	3p21
				?	19q13.2-13.3
Catecholaminergic polymorphic VT		VT	AD	RyR2	1q42-43
			AR	CASQ2	1p13.3-11
Familial atrila fibrilation		Af	AD	KCNQ1	11p15.5
				?	10q22-24

* AD: autosomal dominant, AR: autosomal recessive, XR: X-linked recessive

function, and pathophysiology of ion channels has helped to clarify the roles of various ionic currents in both electrical activity and electromechanical coupling. The discovery of mutations that cause familial arrhythmias has enabled the translation of basic science into the clinical arena. Familial single-gene disorders such as long QT and Brugada syndromes, though rare, provide the opportunity to study a

disease in which a single abnormal protein is responsible for arrhythmogenecity. Genetic discoveries have also allowed new insights into how genes interact with the damaged heart muscle, drugs, or environment to trigger acquired arrhythmias.

a. Congenital Long QT Syndrome

Long QT syndrome (LQTS) is a disease of repolarization identified by prolongation of the QT interval on the ECG[2]. It is characterized by malignant ventricular arrhythmias and syncopal episodes. The most typical ventricular arrhythmia is torsades de pointes (TdP). The syndrome has two main forms, acquired and congenital. To date, a total of seven genes have been identified. All the genes except for LQT4 encode cardiac ion channels responsible for automaticity of electrical activity. The disruption alters the cardiac action potential and creates a voltage gradient, especially at the ventricular level, which is responsible for reentrant arrhythmias[2]. Genes responsible for the disease include those that encode cardiac ion channels: potassium channels *KCNQ1* and *KCNE1*, which interact to form the cardiac IKs (inward slow potassium) current[3]; *KCNH2* and *KCNE2*, which integrate to form the IKr (inward rapid potassium) current[4]; and the sodium channel *SCN5A*[5], which has also been linked to Brugada syndrome[6] and familial conduction disease[7].

Since the identification of these channelopathies, investigators have attempted to customize treatment based on understanding of molecular pathogenesis. Sodium blockers have been used to decrease repolarization abnormalities in a few patients with LQTS. The use of mexiletine in patients with *SCN5A* mutations[8] and the use of intravenous potassium in patients with mutations in the potassium channel *KCNH2*[9] have shown electrocardiographic improvement of the QT interval. The studies are too small to justify any conclusions as to whether improving the QT with these antiarrhythmics would decrease sudden death in this disease. Although preliminary, these first studies represent an important step toward genetically based therapy.

b. Brugada Syndrome

Since its original description in 1992[10], the syndrome of right bundle branch block, ST segment elevation in V_1 to V_3, and sudden death (Brugada syndrome) is increasingly recognized worldwide. This clinical and electrocardiographic diagnosis is based on syncope or sudden death occurring in patients with a structurally normal heart but with the characteristic ECG pattern. The episodes of syncope and sudden death are caused by fast polymorphic ventricular tachycardia. It has been known for many years that some countries in Southeast Asia record an abnormally high incidence of sudden death. The fatal event usually occurs at night and only affects males. It is known as sudden unexpected death syndrome (SUDS). The incidence of this form of sudden death has been estimated between 26 and 38 per 100,000 people per year. In Thailand, it is the second most common cause of

death, following car accidents, in individuals below the age of 50. It was recently discovered that SUDS and Brugada syndrome share defects in the same gene, indicating that they are allelic diseases if not the same[11].

The genetic defects have been located in the cardiac sodium channel *SCN5A*[6], affecting the same gene that causes LQT3. Many mutations have been published to date. As is the case with other familial cardiac diseases, some of the families studied are not linked to the gene, indicating that Brugada syndrome is genetically heterogeneous. Basic functional analysis in *Xenopus* oocytes has produced interesting results that may be compared to the mutations causing LQT3[12]. The functional defect in the sodium channel that causes LQT3 is the lack of complete inactivation[13], allowing a continuous leak of sodium ions to the interior of the cell, whereas in Brugada syndrome there is a faster inactivation of the sodium channel, leaving the potassium current Ito unopposed in phase 1 of the action potential[14]. Nevertheless, the end result in both LQT3 and Brugada syndrome is the same: the creation of a voltage gradient that provides a substrate for reentrant arrhythmias.

The identification of individuals at risk is complicated by the variability of the ECG, which can normalize over time. For this same reason, it is difficult to estimate the prevalence of the disease[15]. The use of modulators has improved the diagnosis of these individuals. The use of intravenous pilsicainide or flecainide is very sensitive and specific for the identification of carriers with a normal ECG, at least for individuals who have a mutation in the *SCN5A*[16]. Since the initial description of individuals with sudden death, the ECG is now recognized in symptomatic or asymptomatic patients, their family members, and patients with a persistent or variable ECG pattern. It is still a matter of controversy whether individuals who are not inducible during clinical electrophysiology testing, or who require intravenous antiarrhythmic to elicit the ECG pattern, have a better prognosis[17, 18], and longer follow-up is needed to obtain the conclusive evidence No pharmacological therapy has been proven useful in the prevention of sudden death in these individuals; only implantable defibrillators have shown a benefit[14].

c. Catecholaminergic Polymorphic Ventricular Tachycardia

Two distinct genes have been identified in catecholaminergic polymorphic ventricular tachycardia (CPVT); cardiac ryanodine receptor (RyR2)[19], the major calcium release channel on the sarcoplasmic reticulum (SR), and calsequestrin 2 (CASQ2)[20]. Eleven RyR2 missense mutations have been linked to these diseases. Sympathetic nervous system stimulation leads to phosphorylation of RyR2 by protein kinase A (PKA). PKA phosphorylation of RyR2 activates the channel. In conditions associated with high rates of SCD such as heart failure RyR2 is PKA hyperphosphorylated resulting in "leaky" channels. SR calcium leak during diastole can generate "delayed after depolarizations" that can trigger fatal ventricular tachycardia.

d. Acquried Long QT Syndrome

Acquired LQTS is often iatrogenic, mainly associated with medications such as antiarrhythmics, antidepressants, and phenothiazines. Especially in association with these medicines, LQTS can also be due to electrolyte imbalances such as hypokalemia, hypomagnesemia, and hypocalcemia. Patients with acquired drug induced TdP share a number of clinical features with the congenital form of LQTS: female preponderance, apparent increased risk with hypokalemia, QT prolongation and TdP, and evidence for adrenergic activation prior to TdP. These findings, as well as the relatively unpredictable nature of drug-associated QT prolongation suggest that there may be a population at risk because of genetic factors but whose phenotype remains subclinical until drug challenge. In fact, genetic screening in 92 patients with drug-induced TdP has demonstrated 6 mutations in 3 major pore-forming ion channel subunits (*KCNQ1, KCNH2*, and *SCN5A*)[21]. These include mutations with mild, but discernable, biophysical phenotypes, which are possibly conferring risk of TdP on drug challenge. Moreover, several DNA polymorphisms including single nucleotide polymorphisms (SNP), such as D85N in *KCNE1*, confer normal action potential phenotype at baseline but increase the likelihood of arrhythmias on challenge with an I_{Kr} blocker. DNA variants associated with increased risk of drug-associated TdP are one manifestation of a generalized framework for considering genetic and environmental factors in mediating the development of arrhythmias[22].

Clinical and genetic studies have identified a variety of apparent risk factors for TdP in both congenital and drug-associated LQTS. However, even in a subject with a malignant form of the LQTS, most sinus beats do not generate TdP[23]. It has been proposed that repolarization in the heart is accomplished by multiple redundant mechanisms and that each one of the risk factors impairs such mechanisms to a variable extent. However, because of redundancy in the system, there is considerable "repolarization reserve", and it is only when this reserve is exhausted by the presence of multiple risk factors that arrhythmias develop[24].

CONCLUSIONS

The first gene responsible for a cardiac arrhythmia was discovered only ten years ago. Since then, we have learned a great deal about the pathophysiological mechanisms of monogenic arrhythmic diseases. The sequencing of the human genome promises to accelerate identification of new genes and targets for more common forms of cardiac arrhythmia.

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