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The Genetic Basis of Malignant Arrhythmias and Cardiomyopathies

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The remarkable advances that have taken place in biomedicine over the past 50 years have resulted in dramatic improvements in the prevention, diagnosis, and treatment of many diseases. Although cardiology has adopted these advances at a relatively slow pace, today it is fully immersed in this revolution and has become one of the most innovative medical specialties. Research is continuing to give rise to new developments in genetics and molecular biology that lead, almost daily, to innovative ways of preventing, diagnosing, and treating the most severe forms of heart disease. Consequently, it is essential that clinical cardiologists have some basic knowledge of genetics and molecular biology as these disciplines are having an increasing influence on clinical practice.

Bases genéticas de las arritmias malignas y las miocardiopatías

La biomedicina ha experimentado en los últimos 50 años unos avances sorprendentes que han permitido obtener espectaculares mejoras en la prevención, el diagnóstico y el tratamiento de muchas enfermedades. La cardiología, a pesar de que ha ido incorporando estos avances a un ritmo más lento, hoy está completamente sumergida en esta revolución e incluso es una de las especialidades médicas más innovadoras. Se sigue investigando para lograr nuevos avances en genética y biología molecular que nos abren, día a día, nuevos métodos de prevención, diagnóstico y tratamiento clínico de las afecciones cardíacas más severas. Así pues, para el cardiólogo clínico es imprescindible adquirir conocimientos básicos en genética y biología molecular, ya que este campo está influyendo cada vez más en la práctica clínica.

Key words: Genetics. Arrhythmias. Cardiomyopathies.

Palabras clave: Genética. Arritmias. Miocardiopatías.

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INTRODUCTION

In the last 20 years, genetics has played an increasingly important role in the progress of medical science. The impact of new techniques has been particularly felt in the cardiovascular field and even given birth to the term cardiogenetics. Cardiology has progressively incorporated the latest advances in molecular biology and genetics, allowing many of the genes responsible for cardiac disease to be identified in the space of a few years. There are many types of heart disease in which genetic factors, with or without accompanying structural heart disease, may predispose an individual to arrhythmias or sudden death.^{1,2} These diseases result from mutations in the genes that encode 3 large protein families:

1. Sarcomeric proteins, which are responsible for generating force in cardiac myocytes and which are associated with etiology of hypertrophic cardiomyopathy.³
2. Cytoskeletal proteins, which are responsible for transmitting this force to the surrounding cells and which are associated with the etiology of dilated cardiomyopathy.⁴
3. Proteins that encode ion channels, which are responsible for maintaining intracellular and extracellular electrolyte balance and which cause inherited arrhythmias.⁵

Despite the advances made, nothing is as straightforward as it seems, as there is an important overlap between diseases and genes.⁶ For example, troponin T can cause both dilated cardiomyopathy and hypertrophic cardiomyopathy⁷ while the *SCN5A* sodium channel gene is one of the genes responsible for the Brugada syndrome, type 3 long QT syndrome and also familial conduction disorders.^{8,9} Integration

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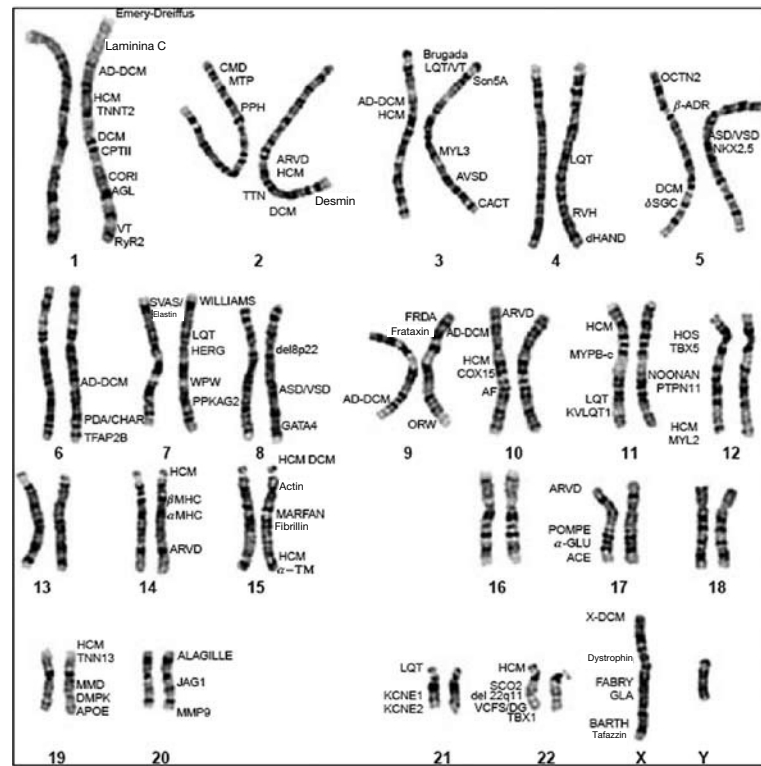


Figure 1. Normal human karyotype in which some of the genes that may be implicated in different cardiomyopathies are indicated along with their location on each of the chromosomes.¹⁰

of knowledge on these genetic mutations will lead to key information for stratifying risk of sudden death associated with some of these diseases.

GENETICS

All living organisms have their own genetic information contained within the DNA molecule. Within this molecule, we find the units of inheritance, the genes. We humans have 70 000 genes distributed on 23 chromosome pairs located in the cell nuclei (22 autosomal and 1 sexual pair) and a single mitochondrial chromosome. Each chromosome pair (homologue) has the same genes and we each have 2 copies of these genes denominated alleles (Figure 1). Each gene contains the information necessary for synthesizing a protein, the functional units of the organism. All necessary proteins should be perfectly synthesized for the organism to function properly.

The DNA molecule is made up of 4 types of nucleotide, repeated millions of times. Each group of 3 nucleotides encodes a given amino acid. This is a production line; the first 3 nucleotides encode the first amino acid and the next 3 the second, and so on. This synthesis is determined by the order of the DNA nucleotide sequence. Progressive accumulation of all amino acids of the gene gives rise

to the creation of the protein. It has been reported that at least 1.5% of the human genome contains sequences that encode proteins.¹¹ The remaining parts of the genome may help the organism to function correctly, but their exact function has yet to be clearly established.

At times, an insertion, deletion, or change may occur in the nucleotide sequence. These genetic defects are known as mutations (Figure 1) and may result in the synthesis of a different or defective protein, leading to disease. Whether or not an individual develops a disease due to a mutation depends on the importance of the protein in the general functioning of the human body. If the mutation affects the DNA of a germ cell or a reproductive cell, it will be transmitted to the following generations and give rise to a hereditary disease. Hereditary diseases are classified as:

1. Chromosomal disorders, with the deletion or addition of part of a chromosome or an entire chromosome.
2. Polygenic diseases (the most common), which are due to the interaction of different genes.
3. Monogenic diseases, which are caused by a single gene and follow a Mendelian pattern of inheritance:

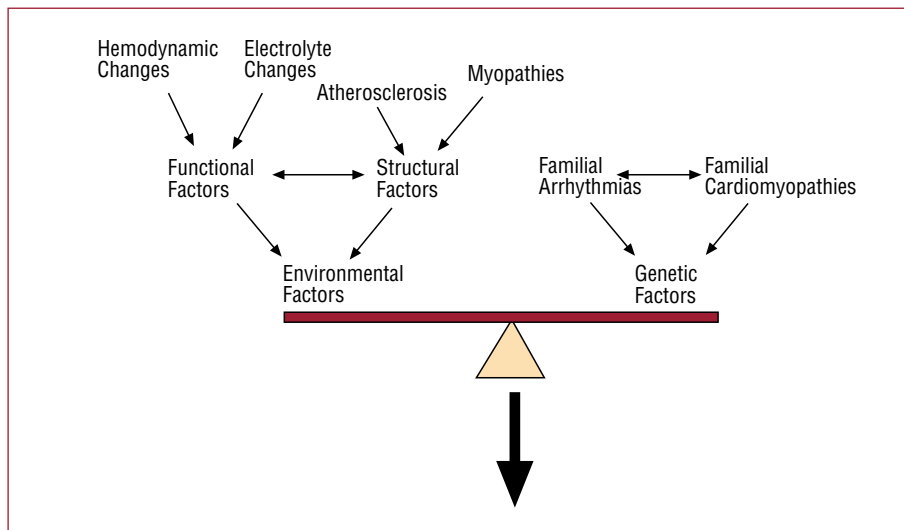


Figure 2. Arrhythmogenesis depends on the interaction of various factors, both environmental and genetic. Equilibrium between these factors prevents the formation of arrhythmias. A predisposing environmental factor or a prior genetic factor may be sufficient to generate the substrate necessary for arrhythmogenesis.¹²

– Autosomal dominant diseases. One of the inherited alleles is defective and the other normal. The dominant character of the disease means that only 1 allele need be affected by a mutation to cause disease. The offspring have a 50% risk of being carriers of the disease if 1 of the parents is affected. Affected individuals are present in every generation and both men and women can inherit and transmit the disease

– Autosomal recessive diseases. Two defective alleles are required for the disease to arise. Therefore, it is less common than the autosomal dominant form. If both parents are carriers, their offspring has a 25% risk of suffering from the disease and a 50% risk of being carriers

– Sex-related disease. Female individuals are carriers on 1 of the X chromosomes. Male individuals, given that they only possess a single X chromosome, suffer from the disease if they inherit the mutated chromosome

– Mitochondrial diseases. These are always transmitted along the female line because the mitochondrial chromosome always comes from the mother. Therefore, transmission from male to male does not occur

In general, all humans have small variations at some DNA sites. These variations are known as polymorphisms. Unlike mutations, polymorphisms are not sufficiently important in themselves to cause disease, but they can alter the response of the individual to disease and lead to variations in predisposition, clinical course, and response to treatment.^{12,13}

ARRHYTHMIAS

Cardiac arrhythmias are one of the leading causes of death and disease in the general population,

particularly in patients with prior heart disease.¹⁴ Every year, they are responsible for almost 1 million cases of syncope and sudden death in Europe and America.¹⁵ Arrhythmias, like all diseases, are the result of interaction between environmental and genetic factors (Figure 2).¹² In recent decades, many studies have investigated environmental arrhythmogenic factors—both structural and functional—in addition to ethnic factors.¹⁶ It has been found that some complications of arrhythmias only present when there is a perfect interaction between different factors. The basic mechanisms that predispose individuals to arrhythmias, with or without prior heart disease, have yet to be fully elucidated, although mutations in genes that encode cardiac ion channels have been identified as risk factors in the pathogenesis of fatal and nonfatal arrhythmias.^{17,18}

Inherited arrhythmias can be classified into 2 large groups according to their association with other heart diseases¹⁹: *a*) primary arrhythmias, in which the arrhythmia results from the electrical properties of the heart itself²⁰; and *b*) secondary arrhythmias, in which the arrhythmia is due to an underlying familial cardiomyopathy, characterized by hypertrophy,³ dilatation,⁴ or fibroadipose infiltration.²¹ Although the mechanism of the 2 groups is different, sudden death is the common feature of all these devastating diseases.²²

ION CHANNEL DISEASES

Ion channels are transmembrane proteins that allow ions to travel into and out of the cardiac myocyte; this process follows the synchronized opening and closing of the channels in response to the electric gradient that gives rise to the cardiac action potential.²³ If ion channel proteins are defective, the functionality of the cardiac channels may be enhanced or reduced.²⁴⁻²⁸

TABLE 1. Ion Channel Diseases of Genetic Origin

Channel	Syndrome	Transmission	Locus	Gene	
Sodium	Long QT 3	Autosomal dominant	3p21-23	<i>SCN5A</i>	
	Long QT 10	Autosomal dominant	11q23	<i>SCN4B</i>	
	BrS	Autosomal dominant	3p21	<i>SCN5A</i>	
	Lev-Lenègre syndrome		Autosomal dominant	3p24	<i>GPD1-L</i>
			Autosomal dominant	19q13.2	?
			Autosomal dominant	3p21	<i>SCN5A</i>
AF		Autosomal dominant	<i>3p21</i>	<i>SCN5A</i>	
Sodium related	Long QT 9	Autosomal dominant	3p25	<i>Cav3</i>	
Potassium	Long QT 1	Autosomal dominant	11p15.5	<i>KCNQ1</i>	
	Long QT 2		7q35	<i>KCNH2</i>	
	Long QT 5		21p22.1-22-2	<i>Mink(KCNE1)</i>	
	Long QT 6		21p22.1-22-2	<i>MIRP1(KCNE2)</i>	
	Long QT 7		17p23.1-24.2	<i>KCNJ2</i>	
	Long QT 1	Autosomal recessive	11p15	<i>KCNQ1</i>	
	Long QT 5		21q22	<i>Mink</i>	
	Short QT 1	Autosomal dominant	7q35	<i>HERG(KCNH2)</i>	
	Short QT 2		11p17	<i>KCNQ1</i>	
	Short QT 3		17q23	<i>KCNJ2</i>	
	AF	Autosomal dominant	10q22	?	
			11p15.5	<i>KCNQ1</i>	
			11q23	<i>KCNA5</i>	
			12p13	<i>KCNE3</i>	
			21q22	<i>KCNE2</i>	
		17q23	<i>KCNJ2</i>		
Calcium	BrS and Short QT 4	Autosomal dominant	12p13.3	<i>CACNA1C</i>	
	BrS and Short QT 5		10p12.33	<i>CACNB2b</i>	
	Timothy syndrome (QTL8)	Autosomal dominant	12p13.3	<i>CACNA1C</i>	
	PVT	Autosomal dominant	1q42	<i>RYR2</i>	
		Autosomal recessive	1p13	<i>CASQ2</i>	
Calcium related	Long QT 4	Autosomal dominant	4q25-27	<i>ANKB (ANK2)</i>	

AF indicates atrial fibrillation; BrS, Brugada syndrome; PVT, polymorphic ventricular tachycardia.

The cardiac cell is depolarized by a massive and rapid influx of positively charged ions, mainly through the sodium channel (Na^+). This produces phase 0 of the action potential. The repolarization phase is initiated immediately. In this process, the cells eliminate positively charged ions in order to return to the resting potential. This is a slower process and is achieved mainly through an equilibrium between the potassium channels (K^+) and calcium channels (Ca^{2+}), giving rise to phases 1, 2, and 3 of the action potential.²⁹

Several elements are necessary to achieve a coordinated cardiac activity. These include ion currents, ion channels, and structural proteins responsible for transmitting the electrical and mechanical impulses to the cardiac myocytes.²³ The complexity of this process remains the main obstacle to a better understanding of arrhythmogenesis.³⁰

With the incorporation of molecular biology into cardiology, we can now resolve some of the mysteries surrounding the structure, function, and pathophysiology of the ion channels. This helps us understand the role that these channels play in the generation and transmission of electric current.

Functional analysis of the ion channels has led to a better understanding of the basic arrhythmogenic mechanisms, but not until the development of genetic techniques and the discovery of mutations responsible for inherited diseases has it been possible to extrapolate part of the basic science to clinical practice (Table 1).

Ion channel diseases, characteristically, are not accompanied by structural cardiac defects and their first manifestation is usually sudden death. In addition, some of these diseases are not accompanied by underlying electrocardiographic (ECG) disorders, thereby making their diagnosis even more difficult. Bearing in mind that these diseases are determined by a genetic mutation, their diagnosis, prevention, and treatment may be expected to improve greatly with the availability of genetic tests. However, these tests have not been successfully incorporated into routine clinical practice as a means to screen for these diseases.

Research into cardiac arrhythmias that predispose a patient to sudden death has benefitted from the advances in genetics and molecular biology.³¹

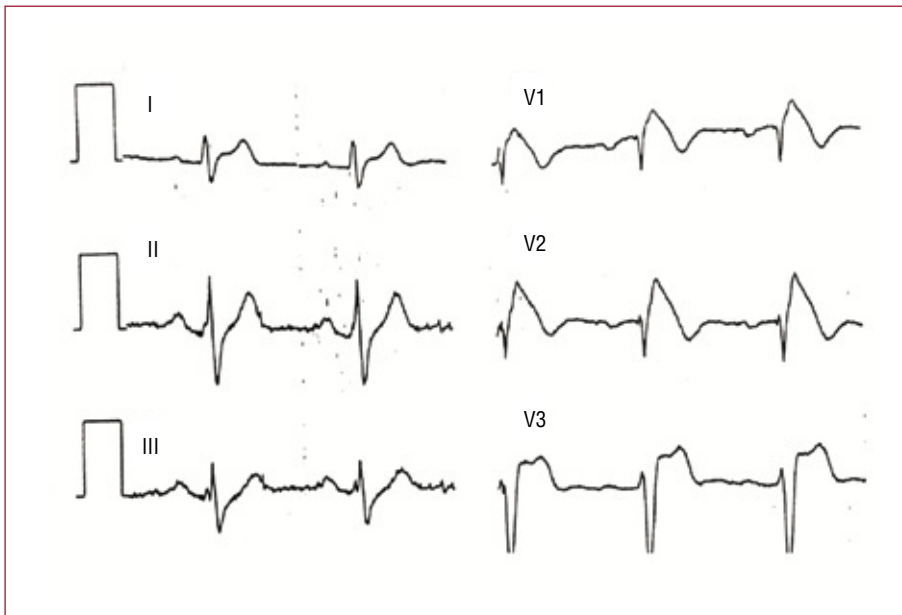


Figure 3. Electrocardiograms of Brugada syndrome.

These conditions have allowed the pure form of the disease to be studied, in which a single gene causes the arrhythmia (that is, monogenic disorders),³² such as Brugada syndrome, long QT syndrome and short QT syndrome (Figures 3-5), and polymorphic ventricular tachycardia (PVT).^{24,25,31} However, with genetics, knowledge is not limited to the inherited form, as it opens up new hypotheses as to how the gene interacts with the environment, drugs, and damaged muscle, and how arrhythmias arise in acquired or noninherited forms.

In general, depending on which ion channel is affected, different syndromes will be present. Nevertheless, the same syndrome may show a certain degree of overlap if different types of channel can be affected.

Ion Channel Diseases Associated With the Sodium Channel

Sodium channels play a key role in the propagation of the cardiac action potential. The opening of these channels allows synchronization of ventricular contraction and the conduction velocity.³³⁻³⁶ Several types of mutation which can give rise to arrhythmias have been described, with enhanced or reduced channel function.³⁷ Certain mutations can give rise to different phenotypes, and even combinations of phenotype.³⁸

Three diseases, among others, have been associated with sodium channel dysfunction due to genetic mutations affecting ion channel structure: long QT syndrome, Brugada syndrome, and Lev-Lenègre syndrome.

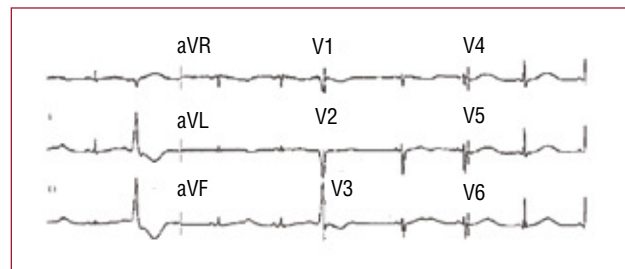


Figure 4. Electrocardiograms of long QT syndrome.

Long QT Syndrome

Long QT syndrome is one of the leading causes of sudden death among young people. It can be congenital or acquired, generally in association with drugs and hydroelectric imbalance (hypokalemia, hypocalcemia, and hypomagnesemia).³⁹ The clinical presentation can be variable, ranging from asymptomatic patients (diagnosed through family screening) to syncope, convulsions, malignant ventricular arrhythmias, ventricular fibrillation, and, typically, torsade de pointes.⁴⁰⁻⁴⁵

The congenital form is associated with mutations in the genes encoding ion channels and related proteins. Prolongation of the QT interval may arise due to a decrease in the potassium repolarization currents or to an in appropriate delay in the entry of sodium into the myocyte.⁴⁶

To date, more than 500 mutations and 130 polymorphisms have been described in long QT syndrome, giving rise to 10 different types.⁴³ Although most mutations that induce long QT intervals are related to potassium channel disorders,

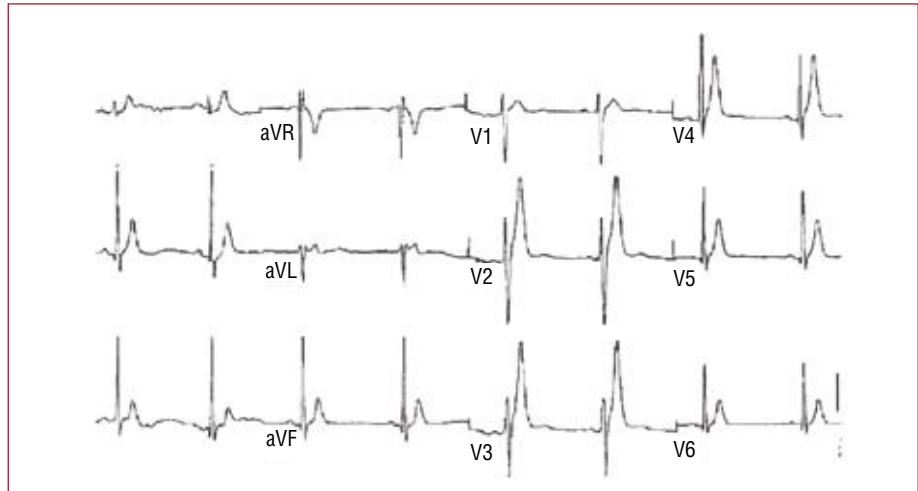


Figure 5. Electrocardiograms of short QT syndrome.

some types are associated with sodium channel disorders.⁴⁷

Type 3 long QT syndrome is associated with mutations in the *SCN5A* gene.^{48,49} The mutation causes a functional defect based on incomplete inactivation of the channel, thereby allowing continued entry of sodium ions into the cell during repolarization and leading to enhanced function.⁵⁰ Patients with type 3 long QT syndrome present arrhythmias associated with bradycardia and symptoms at rest (especially during the night).⁵¹

The type 10 long QT syndrome is caused by a mutation in the *SCN4B* gene that encodes the beta subunit (NaV β 4) of the sodium channel. The beta subunit plays an important role in regulating channel kinetics, signal transduction, and expression of the subunit of the sodium channel. The NaV β 4 subunit causes a negative change in the sodium dependent voltage in the activation channel. This mutation in the *SCN4B* gene induces a positive change in the inactivation of sodium channels, which increases in the sodium current and delays the repolarization in a similar fashion to type 3 long QT syndrome.⁵²

Type 9 long QT syndrome is caused by *caveolin-3* mutation; it is believed that this type increases the QT interval by affecting the functionality of the sodium channels. Mutations in this gene lead to enhanced function of the sodium channels,⁵³ as occurs in type 3 long QT syndrome.

Brugada Syndrome

Brugada syndrome, described in 1994,⁵⁴ is characterized by electrocardiographic findings (ST elevation at leads V₁₋₃) without structural heart disease. It is an important cause of sudden death, generally due to PVT, with an incidence of around 26-38/100 000 person/years. Although the mean age

of onset of events is around 40 years, sudden death can affect individuals of any age, particularly men (75%). Of the patients affected, 20% to 50% have a family history of sudden death.

Brugada syndrome is a disease of autosomal dominant transmission and variable penetrance.^{55,56} More than 70 mutations have been reported distributed among various genes, pointing to its genetic heterogeneity.⁵⁷ Although most mutations occur in genes related to sodium channels, other channels may also be implicated in Brugada syndrome. The pathophysiology of this condition may therefore be multifactorial through interaction with several mechanisms.

Between 20% and 25% of patients affected by Brugada syndrome have mutations in the *SCN5A* gene.⁵⁸ The mutations lead to a premature closing or failure to activate the channel, giving rise to a loss of sodium channel function.^{55,58} This induces a shortening of phase 1 of the action potential, leaving the Ito potassium current without any opposition in this phase.⁵⁹ A voltage gradient is created as a result, thereby producing conditions conducive to reentry arrhythmias.⁴⁹ In addition to mutations, several polymorphisms have been described that affect the sodium channel function⁶⁰ and that might explain the different clinical phenotypes and increased incidence of Brugada syndrome in certain geographic regions,⁶¹ such as southeast Asia, where a very high incidence of sudden death due to Brugada syndrome has been reported.⁶²

Another sodium channel gene that has been reported to induce Brugada syndrome is *GPD1-L*. It has been shown that mutation of the *GPD1-L* gene reduces the surface membrane expression and reduces the inward sodium current.⁶³ In addition, *GPD1-L* has been shown to be the cause of some of the sudden deaths in nursing infants.⁶⁴

Lev-Lenègre Syndrome

Lev-Lenègre syndrome is a rare condition characterized by disruption of the conduction system, in which a block gradually develops, resulting in ventricular arrhythmias or asystolia.^{48,65,66} The amount of sodium and the speed with which it enters the cell determine the velocity of conduction of the electric impulse through the sodium-dependent cells (muscle cells of the ventricle and atrium and cells of the His-Purkinje system). If a mutation leads to a reduction in the quantity of sodium that enters the cell, the velocity of conduction of the impulse is reduced resulting in a loss of function in phase 0 of the action potential (channel opening).⁶⁷ This is the case in the Lev-Lenègre syndrome.

In 1995, for the first time, chromosomal abnormalities (19q13.2-13.3) associated with bundle branch block were reported,⁶⁸ and in 1999, the first mutations, located on the *SCN5A* gene.⁵⁸

Ion Channel Diseases Associated With the Potassium Channel

Potassium channels are key participants in the cardiac action potential as they allow repolarization currents to counteract the preceding depolarization.⁶⁹⁻⁷³ Mutations in the genes that encode the proteins of the potassium channel may lead to dysfunction of this channel and give rise to 3 types of disease: long QT syndrome, short QT syndrome, and atrial fibrillation (AF).

Long QT Syndrome

Long QT syndrome is usually caused by repolarization abnormalities with implication of the potassium channels (Iks, Ikr, Iki).⁴⁵ All mutations in these channels lead to a loss of function; this gives rise to a decrease in the release of potassium from the cells, thereby inducing the channels to remain open for longer and the QT interval is prolonged due to a longer ventricular repolarization time.^{41,42}

Many mutations have been reported; of these, around 300 are located on 6 different potassium channel genes and account for 50% to 60% of the clinical cases of long QT syndrome.⁷⁴⁻⁷⁷

One of these genes is *KCNQ1* (*KvLQT1*), whose product binds to the protein encoded by the *KCNE1* gene (*minK*) to form the Iks functional complex. Mutations in *KCNQ1* are responsible for 40% to 50% of the cases of prolonged QT interval, giving rise to type 1 long QT syndrome,⁷⁸ the most common of the long QT syndromes,⁷⁹ characterized by delayed repolarization and subsequent prolonged QT interval.⁸⁰ When inheritance follows an autosomal dominant transmission pattern, the resulting

condition is known as Romano-Ward syndrome and when it is autosomal recessive, the syndrome is known as Jervell and Lange-Nielsen syndrome, often associated with deafness.⁸¹

Recently, 6 new mutations have been reported, 2 in exons and 4 in introns.⁸² Five mutations have so far been reported in the *KCNE1* gene,⁸³ which induce 2% to 5% of the cases of so-called long QT syndrome.⁵ It is believed that both Iks and Ikr can be affected.⁸⁴

Another affected gene is *KCNH2* (human-ether-a-go-go-related [HERG]),⁸⁵ which encodes the α subunit of the Ikr complex; the α subunit is determined by the *KCNE2* (*MiRP1*) gene.⁸⁶ This Ikr complex is the most important inducer of fast repolarization in phase 3.⁸⁷ Mutations in the *KCNH2* gene (more than 80 have been reported) lead to loss of function in the Ikr channel, and account for 35% to 45% of cases of the so-called type 2 long QT syndrome of autosomal dominant transmission.⁸⁸ In the case of the *KCNE2* gene, the mutation also leads to loss of channel function, thereby causing type 6 long QT syndrome, a very rare syndrome (<1%).⁷⁹

Another gene implicated in long QT syndrome is *KCNJ2*, located on chromosome 17. This gene encodes Ik1 (Kir2.1), and contributes to phase 3 of repolarization, sustaining the membrane potential. Mutations in this gene are associated with functionality losses that give rise to type 7 long QT syndrome, or Tawil-Anderson syndrome.⁸⁹ The incidence of this syndrome in the population is very low and rarely associated with syncope or sudden death,⁹⁰ although episodes of polymorphic or bidirectional tachycardia may occur.⁹¹

Short QT Syndrome

Short QT syndrome—first described in 2000⁹²—is a highly malignant condition characterized by a short QT interval (<330 ms), with a high sharp T wave and a short interval between the peak and the end of the T wave, leading to ventricular arrhythmias and sudden death.^{43,93}

Most patients with short QT syndrome have a family history of sudden death and/or AF. Clinical manifestations may appear as early as childhood, and so it is considered a possible cause of sudden death in nursing infants. The clinical manifestations of short QT syndrome vary in seriousness from lack of symptoms to AF, recurrent syncope, and sudden death.

The genetic origin of this condition has been reported recently, with an autosomal dominant pattern of transmission and a high penetrance.^{94,95} The mutations that induce this syndrome are located on 5 genes,⁴³ of which 3 (*KCNQ1*, *KCNJ2*,

and *KCNH2*) encode potassium channels, with enhanced function and, therefore, shortened repolarization.^{96,97}

Type 1 short QT syndrome has been associated with mutations in the *KCNH2* gene (*HERG*) that induce a fast activation of potassium currents, with enhanced I_{Kr} function and a shortened ventricular action potentials.⁹⁸⁻¹⁰⁰ In general, cardiac events are associated with adrenergic situations such as noise or exercise, although they have also been reported at rest.¹⁰¹ Short QT syndrome has been associated with AF in some families.

Type 2 short QT syndrome has been linked to 2 mutations in the *KCNQ1* gene.^{94,99,100} These mutations enhance the function of the potassium channel, leading to a shortening of the action potential with AF. There is a particular entity caused by mutation in this same gene which is manifest in utero as bradycardia and which is diagnosed as AF and short QT in the neonatal period.^{99,100}

Type 3 short QT syndrome is related to mutations in the *KCNJ2* gene on chromosome 17, leading to an acceleration of the phase 3 action potential.¹⁰²

Atrial Fibrillation

Atrial fibrillation is the most common arrhythmia in clinical practice. The prevalence of 1% among the general population increases to 10% among individuals aged over 80 years. The most feared complication is cerebral embolism and it is thought that this is the cause of a third of all embolisms.¹⁰³

In 1997, for the first time, it was described as a genetic disease with an autosomal dominant pattern of inheritance.^{104,105} Nevertheless, there are numerous genes that are related to AF, particularly those that encode potassium channel proteins (*KCNQ1*, *KCNE2*, *KCNJ2*, and *KCNH2*).¹⁰⁶ Likewise, environmental factors have been reported to be particularly important in the onset and course of the condition.¹⁰⁷⁻¹⁰⁹ In addition, it has been reported that mutations or polymorphisms in the *SCN5A* gene may predispose individuals to AF,¹¹⁰ even though variations in the *SCN5A* gene do not seem to be an important cause of familial AF.^{17,18}

Ion Channel Diseases Associated With Calcium Channels

Calcium channels have been implicated in an increasing number of inherited cardiac arrhythmias.¹¹¹

Calcium ions participate in phase 2 of the cardiac action potential and increase the release of calcium to the sarcoplasmic reticulum, thereby allowing activation of the contraction of the heart. With functions so closely related to electromechanical activity, it was to be expected that defects in the

proteins that participate in the calcium balance might give rise to cardiac arrhythmias.¹¹²

The following have been reported to be linked to calcium channels: combination syndrome of Brugada and short QT syndromes, Timothy syndrome, and PVT.

Combination Syndrome of Brugada and Short QT Syndromes

Mutation in the *CACNA1C* gene is responsible for a defective α unit of the type-L calcium channels. This induces a loss of channel function, linked to the combination of Brugada syndrome with type 4 short QT syndrome. Transmission follows an autosomal dominant pattern.

With the same phenotype, mutation of the *CACNB2b* gene leads to a defect in the L-type calcium channel, giving rise to a combination of Brugada syndrome and type 5 short QT syndrome.^{111,113,114}

Timothy Syndrome

Type 8 long QT syndrome, or Timothy syndrome, is a type of long QT syndrome that has been described recently.¹¹⁵ In this syndrome, the defects are due to a mutation in the *CACNA1C* gene that encodes the pore (Cav1.2) of the L-type cardiac calcium channel.¹¹⁶ This type of long QT syndrome is uncommon, but it has the highest associated mortality. The mutation induces an enhanced function with I_{Ca} abnormality, and loss of the channel dependent voltage, leading to a prolongation of the action potential. This gives rise to an ECG with an extremely long QT interval.

Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic tachycardia is a familial arrhythmogenic disorder characterized by a 2-way polymorphic ventricular tachycardia.¹¹⁷ It is triggered exclusively by adrenergic stimulus (vigorous exercise, fear), and has a high mortality (30% by the age of 30 years).

Two genetic variants have been identified, an autosomal dominant one caused by mutation in the gene encoding the ryanodine receptor *RyR2* (*1q42-Q43*) and a recessive one, caused by mutation in the calcichestrine isoform gene (*CASQ2*).¹¹⁸⁻¹²¹ Both genes are implicated in regulating intracellular calcium and both types of defect lead to increased function of these proteins, and so outflow of calcium from the sarcoplasmic reticulum is increased. This excess calcium is associated with abnormalities in the sarcolemmal membrane potential, leading to late depolarizations that cause a predisposition to arrhythmias.¹²⁰

The ryanodine receptor is an intracellular calcium channel that is located in the sarcoplasmic reticulum and activated by the influx of small amounts of calcium, thereby allowing the outflow of stored calcium.¹²² More than 70 mutations have been identified in *RyR2*. In the heart, the ryanodine receptor is associated with 2 different diseases: type 2 right ventricular arrhythmogenic dysplasia (ARVD2)¹²³ and familial PVT.¹¹⁹ It is interesting that the same gene is responsible for 2 such different diseases, one with a structural abnormality—ARVD2—and the other with a structurally normal heart. Currently, investigators are trying to determine whether this difference is due to the type of mutation, genetic modifiers, or the environment.

Other Genes That Induce Ion Channel Diseases

There are other genes, such as *ANK2* (chromosome 4, 4q25-27), which are involved in the type 4 long QT syndrome. Although no specific channel is affected, this syndrome is included in this group of ion channel diseases. This gene encodes the ankyrin B protein, whose function is to adapt different structures in the cell membrane, such as the Na/K ATPase pump, the Na/Ca exchanger, and the inositol triphosphate receptor.^{124,125} A decrease in ankyrin B function affects calcium homeostasis, prolongs repolarization, and generates fatal ventricular arrhythmias.¹²⁶

Another gene is *Caveoline-3* (*Cav3*), implicated in membrane traffic and correctly positioning the proteins of the ion channels in the sarcoplasmic membrane. Mutations are responsible for enhancement of the sodium channel function, leading to type 9 long QT syndrome.⁵³

Cardiomyopathies

Several mutations that cause arrhythmogenic cardiomyopathies have been detected in humans¹²⁷; these mutations have been found in a large number of genes that encode contractile and structural proteins as well as proteins for cardiac energy production (Figure 3, Table 2).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a disease of the myocardium characterized by an unexplained asymmetric hypertrophy of the left ventricle with findings indicative of myocyte disarray and fibrosis.^{128,129} This is the most common genetic cardiovascular abnormality, with a prevalence in the general population of 1/500,¹³⁰⁻¹³⁴ affecting

TABLE 2. Cardiomyopathies of Genetic Origin

Disease	Locus	Gene	
Hypertrophic cardiomyopathy	14q12	<i>MYH6</i>	
	14q12	<i>MYH7</i>	
	11p11.2	<i>MYBPC3</i>	
	12q24.3	<i>MYL2</i>	
	3p21	<i>MYL3</i>	
	1q32	<i>TNNT2</i>	
	19q13.4	<i>TNNI3</i>	
	15q22.1	<i>TPM1</i>	
	15q14	<i>ACTC</i>	
	2q24.3	<i>TTN</i>	
	3p	<i>TNNC1</i>	
	11p15.1	<i>CRP3</i>	
	17q12	<i>TCAP</i>	
	Dilated cardiomyopathy	14q12	<i>MYH7</i>
		15q14	<i>ACTC</i>
		1q32	<i>TNNT2</i>
		15q22.1	<i>TPM1</i>
2q24.3		<i>TTN</i>	
11p15.1		<i>CRP3</i>	
17q12		<i>TCAP</i>	
Xp21		<i>Dystrophin</i>	
2q35		<i>Desmin</i>	
10q22.1-10q23		<i>Metavinculin</i>	
4q12		β -sarcoglycan	
5q33		δ -sarcoglycan	
Xq28		<i>Tafazzin</i>	
1q21		<i>Lamin A/C</i>	
6q22.1		<i>Phospholamban</i>	
ARVD 1		14q23-24	<i>TGFβ3</i>
ARVD 2		1q42-q43	<i>RyR2</i>
ARVD 3	14q12-q22	?	
ARVD 4	2q32.1-q32.3	?	
ARVD 5	3q21.3-3p23	<i>LAMR-1</i>	
ARVD 6	10p12-p14	?	
ARVD 7	2q35	<i>Desmin</i>	
ARVD 7	10q22.3	<i>ZASP</i>	
ARVD 8	6p24	<i>Desmoplakin (DSP)</i>	
ARVD 9	12p11	<i>Plakophilin-2 (PKP2)</i>	
ARVD 10	18q12.1-q12.2	<i>Desmoglein-2 (DSG2)</i>	
ARVD 11	18q12.2	<i>Desmocollin-2 (DSC2)</i>	
Naxos	17q21	<i>Plakoglobin (JUP)</i>	

ARVD indicates arrhythmogenic right ventricular dysplasia.

children and young people. Clinical manifestations appear initially as diastolic dysfunction and systolic-diastolic dysfunction in more advanced stages. Thus, a patient may be asymptomatic or present with heart failure or sudden death. Mortality is higher in young patients (often athletes) than in adults, and the first manifestation of the disease may be sudden death itself. The disease is considered inherited in 90% of the cases, generally with an autosomal dominant pattern of transmission, except for cases with mutations in mitochondrial DNA (mtDNA), which are inherited from the mother.

This clinical entity was first described in 1958,¹³⁵ but it was not until 1989 when the first gene implicated in this disease was discovered. Since then, more than 400 mutations have been identified,¹³⁶ although 60% of patients with hypertrophic cardiomyopathy have mutations in only 9 genes, which form the basis of genetic screening.

These genes encode the proteins of the sarcomeric structure of cardiac muscle, such as heavy chain β -myosin (*MYH7*)^{137,138} and myosin binding protein C (*MYBPC3*)¹³³; others encode heavy chain α -myosin (*MYH6*), troponin I (*TNNI3*),¹³⁹ troponin T (*TNNT2*),^{140,141} α -tropomyosin (*TPMI*),^{140,141} essential myosin light chains (*MYL3*),¹⁴² regulatory light chain (*MYL2*), titin, and α -actin (*ACTC*).¹⁴³⁻¹⁴⁶ Mutations have also been detected in genes implicated in the metabolism of the heme and Fe²⁺ group, and in genes involved in mitochondrial bioenergetics.

Genetic studies of families with left ventricular hypertrophy have shown metabolic cardiomyopathies with mutations in the *PRKAG2* and *LAMP2* genes. Up until present, mutations have not been thought to predict phenotype because individuals with different degrees of hypertrophy or with a greater predisposition to sudden death may be present in the same family and have the same mutation. This is due to the intervention of modifying genes and polymorphisms, which require more exhaustive studies to achieve a full understanding.¹²⁸

In view of these results, it is assumed that interruption of mitochondrial energy metabolism in the heart is the cause of hypertrophic cardiomyopathy in patients with problems of sarcomeric contraction; this sheds some light on several clinical observations such as heterogeneity, variability in clinical presentation, and asymmetry in hypertrophy. The identification of the genotype may contribute to risk stratification, but further genotype-phenotype studies need to be done to confirm whether this is useful.

Dilated Cardiomyopathy

Dilated cardiomyopathy is characterized by ventricular dilation that leads to abnormal systolic function, mainly in the left ventricle. Patients present signs of heart failure, palpitations, or sudden death. The prevalence is 1/2500 individuals. There are many factors that can trigger dilated cardiomyopathy, making it a highly heterogeneous entity. Even so, systematic studies of family members of patients with dilated cardiomyopathy indicate that at least 35% of the cases are hereditary.¹⁴⁷ The arrhythmias that present in patients with familial dilated cardiomyopathy are usually the same as in the acquired forms, with atrioventricular and

intraventricular conduction defects, ventricular arrhythmias, and AF. Normally, a progressive decline in ventricular function occurs in these patients and they die of heart failure or arrhythmias. Five-year mortality is between 40% and 80%.

In 1994, the first locus of dilated cardiomyopathy with atrioventricular block was identified on chromosome 1.¹⁴⁸ This is an extremely complex disease, and so the clinical usefulness of genetic analysis is limited. More than 20 mutations have been identified in genes that encode proteins of the cytoskeleton, cell nucleus, and sarcomere. One of the most important mutations (30%) is that found in the *lamin A/C* gene (*LMNA*),^{148,149} which encodes a protein that is expressed in almost all cell types and whose function is to contribute to the integrity of the nucleus by providing mechanical support.^{150,151} Other genes, such as *MYH7* and *TNNT2*, identified previously as the cause of hypertrophic cardiomyopathy can also cause dilated cardiomyopathy. Indeed, a mutation in the *SCN5A* gene was identified in a large family with dilated cardiomyopathy.¹⁵²

There are several patterns of transmission in the inherited forms: *a*) autosomal dominant disease, a locus for which has been reported in several chromosomes (actin, desmin, lamin A/C, δ -sarcoglycan); *b*) X-linked disease, in which the dystrophin gene was described as the cause of the disease. Direct mutations in the dystrophin gene give rise to Duchenne or Becker-type muscular dystrophy, which affect both cardiac muscle and skeletal muscle. However, mutations in this gene are not a common cause of dilated cardiomyopathy; *c*) mitochondrial diseases, which typically affect other organs besides the myocardium; so far, 2 loci of dilated cardiomyopathy have been reported in association with primary arrhythmias, without one being the cause of the other. These families had autosomal dominant disease.

Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is a disease characterized by progressive replacement of myocardial tissue by adipose tissue and fibrosis, with progressive involvement of the epicardium towards the endocardium, typically in the right ventricle.^{21,153,154} It affects approximately 1/5000 individuals, although the prevalence is higher in men (80%). Most cases are diagnosed before the age of 40 years. Normally, the individuals affected have symptomatic ventricular arrhythmias that originate in the right ventricle, with syncope and a high risk of sudden death.^{155,156} This entity is responsible for 5% of all sudden deaths, particularly in young athletes.

The disease has 2 different patterns of transmission. The most common one is the autosomal dominant pattern. So far, mutations in 6 genes have been identified, including 4 that encode desmosome proteins (intercellular binding proteins).¹⁵⁷ Forty-five percent of the patients with this disease have a mutation that affects plakophilin protein 2 (PKP2).¹⁵⁸ The remaining genetic mutations are detected in a low proportion of patients and are responsible for defects in proteins such as desmoplakin, plakoglobin, desmoglein-2, or desmocollin-2.¹⁵⁹

Given that there are so many loci involved in the disease, several ARVD phenotypes have been reported: type 1 ARVD due to mutation on chromosome 14q23–24,¹⁶⁰ type 2 ARVD due to mutation on chromosome 1q42–q43,¹²³ type 3 ARVD due to mutation on chromosome 14q12–q22,¹⁶¹ type 4 ARVD due to mutation on chromosome 2q32,¹⁶² type 5 ARVD due to mutation on chromosome 3q23,¹⁶³ type 6 ARVD due to mutation on chromosome 10p12–p14,¹⁶⁴ type 7 ARVD due to mutation on chromosome 10q22.3,¹⁶⁵ type 8 ARVD due to mutation on chromosome 6p24,¹⁶⁶ type 9 ARVD due to mutation on chromosome 2p11,¹⁶⁷ type 10 ARVD due to mutation on chromosome 8q12.1–q12.2,¹⁶⁸ and, finally, type 11 ARVD due to mutation on chromosome 18q21.¹⁶⁹

An autosomal recessive pattern of transmission has been reported on the Greek island of Naxos, giving rise to the name Naxos syndrome. This syndrome comprises ARVD, palmoplantar keratoderma, and typically curly hair.

As the familial incidence is 50%, genetic analysis can be useful for family screening as it allows diagnosis to be established in cases of uncertainty and identification of carriers of the asymptomatic mutation. In such individuals, genetic counseling against having children is important. Studies of genotype-phenotype correlation are needed to assess the role of genetic studies in this disease.

CONCLUSIONS

Advances in the understanding of the human genome have opened up new avenues in genetic research for all types of disease. Cardiology is one of the fields to have benefitted most from the tremendous potential of genetics and from the application of genetic-molecular technology.

More than a decade has passed since the discovery of the first gene that caused inherited cardiac disease and the new multidisciplinary focus of the management of these diseases comprises the integration of both basic and clinical research, opening up new possibilities for prevention, risk stratification, diagnosis, and treatment.¹⁷⁰ An understanding of cardiovascular diseases at the

genomic level would allow a better stratification of subclasses of patients to optimize and tailor specific therapies for each patient.^{20,171}

It is to be expected that future research will lead to a change in the way in which we fight against these diseases. The fields related to pharmacogenetics embrace the promise to improve the development of personalized drugs that take into account how age and genetic make-up modify the transport and metabolism of the drugs. The goal is not to eliminate the disease-causing genes, but rather to allow the transition from palliative and reactive care towards preventative treatments that reduce or avoid the expression of mutations or polymorphisms associated with greater predisposition to fatal arrhythmias.¹⁷²

There are 3 key elements in the advance of biomedicine towards personalized therapies: patients, clinicians, and researchers in basic science. The interaction between these elements will help improve treatment of the different diseases.

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