Genetic Basis of Ventricular Arrhythmias

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Sudden cardiac death caused by malignant ventricular arrhythmias is the most important cause of death in the industrialized world. Most of these lethal arrhythmias occur in the setting of ischemic heart disease. A significant number of sudden deaths, especially in young individuals, are caused by inherited ventricular arrhythmic disorders, however. Genetically induced ventricular arrhythmias can be divided in two subgroups: the primary electrical disorders or channelopathies, in which no apparent structural heart disease can be identified, and the secondary arrhythmogenic cardiomyopathies. In these "single gene disorders," mutations are restricted to one gene, rendering a predictable mendelian fashion of transmission. The highly variable phenotypic expression of these monogenic mutations (even within the same family) makes risk assessment of a single individual difficult, if not impossible. This article focuses on the genetic background of these electrical disorders and the current knowledge of genotype-phenotype interactions.

Monogenic modes of transmission

Protein-coding sequences comprise less than 1.5% of the human genome [1]. The rest contain RNA genes, regulatory sequences, introns, and so-called "junk DNA." Each individual has two copies of each gene (called alleles), which are localized along 23 chromosome pairs (22 pairs of autosomes, 1 pair of sex chromosomes). Each parent contributes one member of each chromosome pair, thus providing one copy of each gene. An individual is considered "homozygous" for a specific gene locus when both gene loci are occupied by two identical alleles or "heterozygous" when both alleles differ. According to Mendel's first law, each of the two alleles separates independently and is passed on to the next generation. Most of the single gene disorders are caused by point mutations (alteration of a single nucleotide), in which a nucleotide is substituted, resulting in formation of a different amino acid (missense mutation), a truncated protein (caused by mutation to a stop codon), or an elongated protein (caused by elimination of a stop codon). If the phenotype is expressed in the presence of only one mutated allele, the inheritance is called dominant. When phenotype expression requires both alleles to be mutant, the pattern of inheritance is called recessive (Fig. 1).

Autosomal dominant inheritance

The phenotype can be expressed in a heterozygous setting, in which only one of the two alleles is affected. In the presence of identical mutations, different individuals may express different clinical features because of a different degree of expressivity, which is amenable to environmental and genetic factors. In an autosomal dominant trait,

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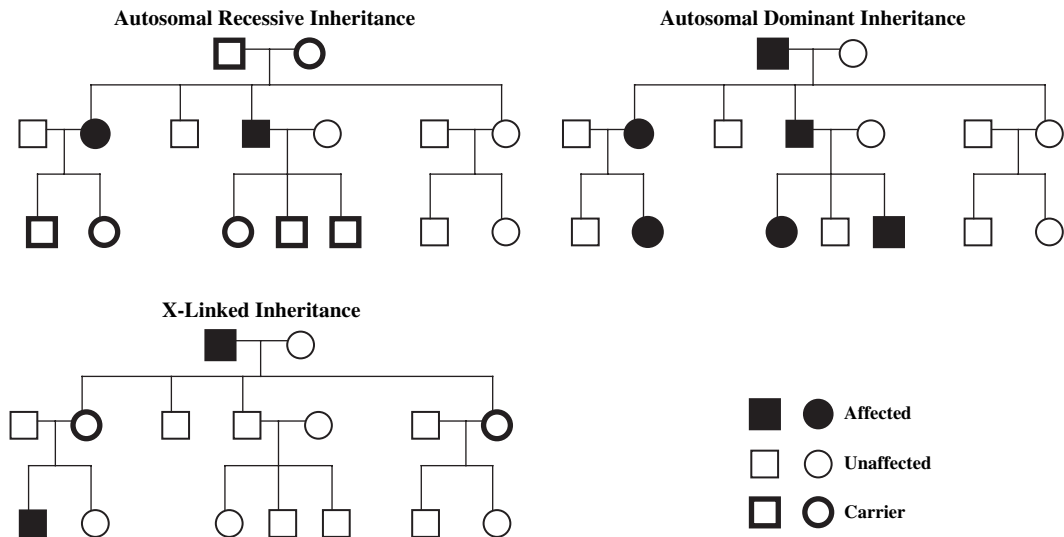*E-mail address:* tboussy@yahoo.com (T. Boussy).

Fig. 1. Monogenic patterns of inheritance.

men and women are equally prone to inherit the mutation, and each child has a 50% chance of being affected by receiving the mutant allele. Each affected person has an affected parent. Normal children of an affected parent are noncarriers and cannot pass on the disease. In most autosomal dominant inherited diseases, the onset of the first phenotypic expression is delayed.

Autosomal recessive inheritance

In autosomal recessive disorders, the phenotype can only manifest when both alleles are mutated at the locus responsible for the disease. Because 1 of the 22 autosomes is involved, there is an equal distribution between male and female subjects. Because of the early onset of expression, recessive disorders are mainly diagnosed during childhood. Each child has a 25% chance of being affected, and heterozygote parents are clinically normal.

X- linked inheritance

Disorders caused by genes located on the sex chromosomes (X-linked) demonstrate a significantly different pattern of transmission with a different clinical outcome between both sexes. In women, one or both X chromosomes can be affected, with dominant or recessive properties. Because men only carry one X chromosome, the probability that the disease will manifest in the presence of a mutant gene is much higher. Mutant X genes can be received

from the affected father or the homozygote (affected) or heterozygote mother. No male-to-male transmission is possible (genetic material from father to son is located on the Y chromosome), and all daughters of affected men are carriers.

Channelopathies

The genetic background and detailed pathogenic mechanisms of these primary electrical disorders have been studied extensively in the last two decades [2]. At first, because of a lack of systematic investigation and low patient numbers, information was obtained from animal models, which were extrapolated to humans. Later, genetic linkage techniques and long-term information of multigenerational families increased our understanding of these relatively new diseases. Currently, several genes have been identified coding for the expression of ion channel proteins, located in the membrane of the cardiomyocyte. The principal function of these cardiac channels is the formation of an electrical potential. Ion currents are regulated by synchronized opening and closing of these channels. Gene mutations alter their pore-forming capacities and gate function, which results in an impaired depolarization or repolarization. This results in an increased vulnerability of the cardiomyocyte for dangerous arrhythmias. The channelopathies show a pronounced genetic heterogeneity, with dispersion of gene mutations within the affected gene.

Voltage-gated sodium channelopathies

The cardiac sodium channel

Voltage-gated sodium channels are responsible for the upstroke of the action potential and play an important role in the propagation of the electrical impulse in all excitable tissues (eg, muscle, nerve, and heart). The opening of sodium channels in the heart underlies the QRS-complex on the electrocardiogram (ECG) and enables a synchronous ventricular ejection. Because the upstroke of the electrical potential primarily determines the speed of conduction between adjacent cells, sodium channels can be found in tissues in which speed is of importance [3–5]. Cardiac Purkinje cells contain up to 1 million sodium channels, which illustrates the importance of rapid conductance in the heart.

Sodium channels consist of a pore-forming α-subunit and one or two β-subunits (Figs. 2 and 3). The α-subunit is a large transmembrane protein encoded by nine genes, in which the SCN5A gene (chromosome 3p21) is the only one coding for the cardiac isoform (Table 1). Mutations in the Na− channel α-subunit gene SCN5A result in multiple cardiac arrhythmia syndromes.

Mutations leading to a voltage-gated sodium channel dysfunction can result in Brugada syndrome, progressive cardiac conduction disturbances (PCCD) or Lenègre disease, and long QT syndrome. Several different types of mutations have been identified, including missense, deletions, insertions, and splicing errors, resulting in a decreased or increased function of the sodium channel. Combinations of all three phenotypes have been documented [6]. Certain mutations may manifest different phenotypes in different individuals of the same family.

Loss of sodium channel function disorders

The Brugada syndrome. Since 1992, Brugada syndrome (BS) has been known as one of the genetically transmittable cardiac channelopathies, characterized by a susceptibility for lethal ventricular arrhythmias in the presence of typical ST-segment changes in the right precordial leads [7]. In patients who have BS, no structural heart disease can be identified despite thorough invasive and noninvasive exploration. The baseline ECG deviations show a dynamic character, with possible transient normalization [8]. They seem to be based on an impaired function of cardiac sodium channels, creating an altered morphology of the cardiac action potential associated with increased arrhythmic vulnerability.

More than 70 gene mutations have been identified in only 20% to 25% of all patients who have BS (most are located in the cardiac SCN5A gene), which suggests that other gene mutations may be responsible [9]. All SCN5A mutations modify the sodium channel function by either creating a truncated protein or increasing the channel inactivation. This results in a shortening of the action potential because of faster phase 1 depolarization. In 2002, Weiss and colleagues [10] located a second locus linked to BS on chromosome 3, and recently the same group identified the causative mutation in the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L) [11]. Patients who have BS, particularly with an SCN5A mutation, show clinical signs of slowed conduction by means of PR, HV, and QRS prolongation, which illustrates the overlap with Lenègres syndrome.

Recently, remarkable genetic data were published regarding the importance of single
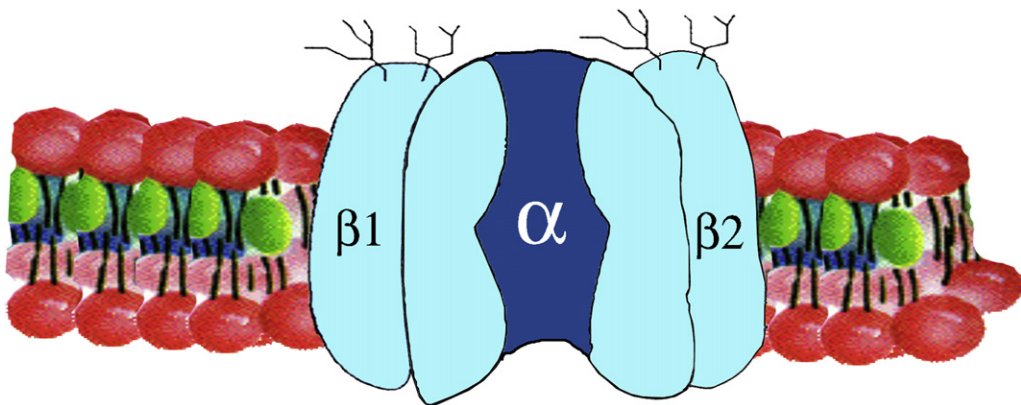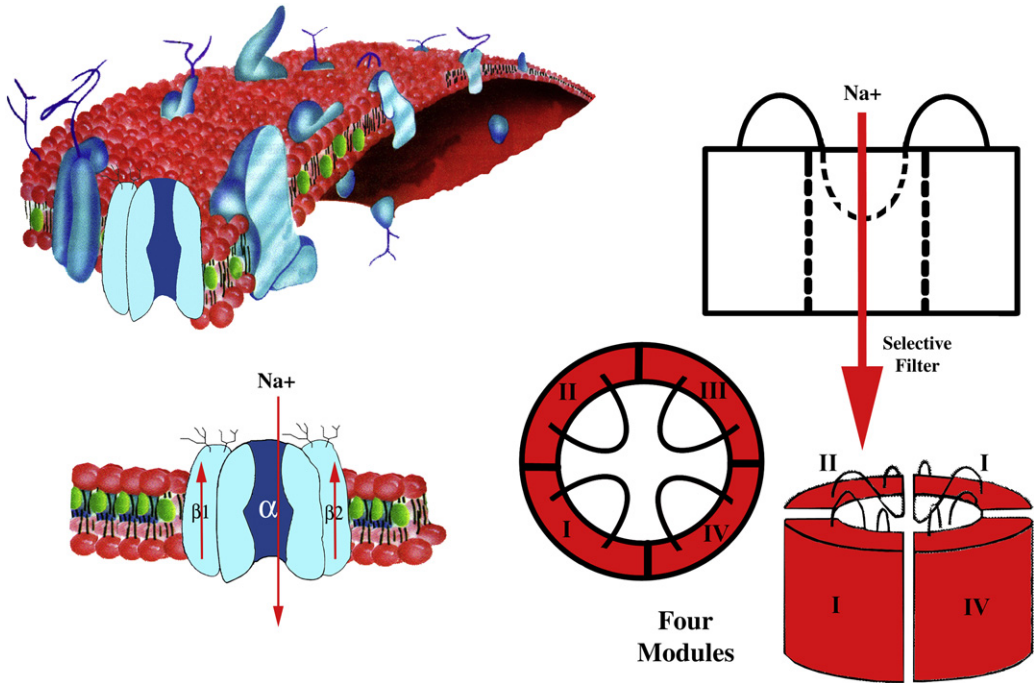

Fig. 2. Sodium channel subunits.

Fig. 3. Sodium channel.

nucleotide polymorphisms, which might possibly explain the different clinical phenotypes and incidence of BS in diverse geographic regions [12]. Ethnic-specific single nucleotide polymorphism distributions in the SCN5A promoter region were reported. A certain combination of six single nucleotide polymorphisms (designated as haplotype B variant) only occurred in Asian subjects (at an allele frequency of 22%) and was absent in the other ethnic groups. This haplotype variant resulted in decreased sodium channel expression and function. In the last years, several case reports proved that certain SCN5A polymorphism in the presence of a BS-causing SCN5A mutation can influence the clinical phenotype and clinical consequences of the mutation. The polymorphism can rescue and restore or—by contrast—further worsen the sodium channel function [13].

Pathophysiology

Antzelevitch [14] performed extensive research on possible pathophysiologic mechanisms explaining the ST-segment changes and the vulnerability for ventricular arrhythmias in BS. According to their findings, the disorder is based on an impaired repolarization of cardiomyocytes. There is a striking difference in action potential morphology in the epicardial, endocardial, and M cells, especially during phases 2 and 3 of the action potential. Whereas the epicardial action potential shows a prominent notch and dome immediately after phase 0 depolarization, the endocardial action potential has a steadier shape during early repolarization. The transmural gradient that originates from this shape difference corresponds to the ST segment on the surface ECG. Alterations of spike and dome morphology (phase 1), in particular in the epicardium, are predominantly mediated by the transient outward current (I_{to}). In BS, the loss of right ventricular outflow tract (RVOT)-epicardial (not endocardial) action potential dome and plateau amplitude, caused by an increase in I_{to} and simultaneous decrease in (inward) I_{Na}, underlies the prominent J-wave and ST-segment elevation (mimicking right bundle branch block morphology). The conduction of the action potential dome from sites at which it is maintained to sites at which it is lost allows local pre-excitation via a phase 2 re-entry mechanism when a closely coupled extra systole occurs in the vulnerable window. These premature beats might eventually trigger the malignant arrhythmia. Because the balance of currents at the onset of phase 2 determines the maintenance of the action potential dome, acquired forms of BS can

Table 1
Overview of sodium channel genes, tissue specificity, and clinical features associated with channelopathies

Gene	Channel	Location	Tissue	Associated disorders
SCN1A	$Na_v1.1$	2q24	Brain, CNS	Brain sodium channelopathies: epilepsy, familial hemiplegic migraine, familial autism
SCN2A	$Na_v1.2$	2q23–q24.3	Brain, CNS	Severe myoclonic epilepsy, familial neonatal- infantile seizures
SCN3A	$Na_v1.3$	2q24	Brain, CNS	Epilepsy, familial hemiplegic migraine, familial autism
SCN4A	$Na_v1.4$	17q23.1–q25.3	Adult skeletal muscle	Muscle sodium channelopathies: hyperkalemic periodic paralysis, paramyotonia congenital, potassium aggravated myotonia
SCN5A	$Na_v1.5$	3p21	Heart muscle, skeletal muscle	Cardiac sodium channelopathies (see text)
SCN6A/SCN7A	Na_x	2q21–q23	PNS, heart muscle, skeletal muscle, uterus	
SCN8A	$Na_v1.6$	12q13	CNS, brain	Cerebellar atrophy, ataxia, mental retardation
SCN9A	$Na_v1.7$	2q24	PNS	Peripheral nerve sodium channelopathies: pain sensitization
SCN10A	$Na_v1.8$	3p24.2–p22	PNS	Peripheral nerve sodium channelopathies
SCN11A	$Na_v1.9$	3p24–p21	PNS	Peripheral nerve sodium channelopathies
SCN1B	$Na_v\beta1$	19q13.1	Brain, heart muscle, skeletal muscle	Brain sodium channelopathies: generalized epilepsy with febrile seizures
SCN4B	$Na_v\beta4$	11q23	Brain, PNS, heart muscle, skeletal muscle	Cardiac sodium channelopathies: long QT syndrome

Abbreviation: PNS, peripheral nerve system.
Data from Koopmann TT, Bezzina CR, Wilde AA. Voltage-gated sodium channels: action players with many faces. Ann Med 2006;38:472–82.

originate from an increase in outward currents (I_{to}, I_{K-ATP}, IKs, and I_{Kr}) or a decrease in inward currents (I_{Ca-L}, I_{Na}). Case reports over the last 13 years described ST changes as in BS caused by drugs, ischemia, electrolyte disturbances, hyper- and hypothermia, elevated insulin levels, and mechanical compression of the RVOT.

Recently, Meregalli and colleagues [15] presented an alternative ''depolarization disorder'' theory, providing another possible explanation for the Brugada ECG abnormalities. This model is based on a conduction delay in the RVOT. Because of action potential differences between the RVOT and the rest of the right ventricle, a closed-loop current originates between these two regions and creates an initial ST elevation followed by a negative T wave at the level of the right precordial leads. It is also possible that both of the mechanisms operate in the pathophysiology of the Brugada ECG pattern and the ventricular arrhythmias.

Lev-Lenègre syndrome

Lev-Lenègre's disease or PCCD is characterized by an age-related alteration of electrical conductance through the His-Purkinje system. This disorder, first described in 1964 [16,17], initially was thought to be degenerative, is caused by selective and progressive fibrosis of the His-Purkinje system. Genetic familial screening of these patients reveals causative gene mutations. Clinically, PCCD manifests as a progressive blockage of the atrioventricular conduction (requiring pacemaker implantation) or—on an infra-hissian level—as a fascicular or bundle branch block. Multiple reports have shown a familial clustering of patients with chronic bundle branch block and various degrees of atrioventricular block (suggesting a genetic origin) [18,19].

In 1995, a South African study group genotyped a large family of 86 members, in which 39 were affected with PCCD [20]. They mapped the first

locus to 19q13.2–13.3 in near proximity of the myo-tonic dystrophy locus, which explained the occurrence of conduction abnormalities in these patients. Another gene locus mapped on 1q32.2–q32.3 was linked to cardiac conduction defects in combination with dilated cardiomyopathy [21]. Probst and colleagues [21] were the first to identify mutations responsible for isolated cardiac conduction defects. They were located on the cardiac sodium channel gene (SCN5A) and segregated in an autosomal dominant fashion. Sequencing the entire SCN5A coding region in a large French family (with 15 affected family members), they identified a $T \geq C$ substitution (IVS22 + 2 $T \geq C$) that resulted in an impaired gene product, lacking the voltage sensitive segment of the sodium channel. In a smaller Dutch family, another SCN5A mutation cosegregated with a nonprogressive conduction deficit. A second, thorough, and more complete investigation of the same French pedigree demonstrated that PCCD related to SCN5A mutations is based on the combination of haploinsufficiency of the cardiac sodium channel gene and an additional unknown mechanism (altering cardiac conduction in relation to aging) [22].

Disorders associated with a gain of function of cardiac sodium channels

Long QT3 syndrome. In contrast to most long QT-syndrome phenotypes, which are based on mutations that modify the cardiac potassium currents, long QT3 mutations are located on the cardiac sodium channel gene SCN5A. These mutations cause a sustained reopening of sodium channels and result in a small inward current that adds up to the peak upstroke of the ventricular action potential. This additional inward current prolongs cardiac repolarization by selective alteration of phase 1 or the early repolarization phase. The surface ECG manifests a long QT interval with late onset of the T wave. Arrhythmic events occur more commonly during rest or sleep. Beta-blockers are contraindicated in this group because inhibition of the sympathetic activity enhances the risk of arrhythmic events.

Potassium channelopathies

The cardiac potassium channel

Potassium channels, which mediate the outward K^+ currents, play a major role in the formation of the cardiac action potential by enabling repolarization currents to counteract the depolarization front (phases 1 through 4) [23–27].

Different expression of voltage-gated potassium channels in the different layers of the cardiac muscle and in different cardiac tissues seems to be responsible for the changes in morphology of the cardiac action potential. The cardiac voltage-gated potassium channel consists of four alpha-subunits ($K_V\alpha$), which together represent a pore-forming unit (see Fig. 2). The assembly of a functional tetramer can only occur in the presence of multiple auxiliary units. The slow and fast component of the transient outward current I_{to} is created through the assembly of four α-subunits from the K_v1-K_v4 subfamilies (KCNA to D gene), while joining of the *HERG* (*human ether-a-go-go*–related) gene and K_vLQT1 α-subunits underlie the delayed rectifier current (I_{Kr} and I_{Ks}). Disorders associated with an impaired function of these potassium channels are the long and the short QT syndrome.

Loss of sodium potassium channel function disorders

The long QT syndrome. In its idiopathic or congenital form, long QT syndrome refers to a group of genetically transmittable disorders that affect cardiac ion channels in a way that results in slowed ventricular repolarization with prolongation of the QT interval. This can lead to early after-depolarizations and life-threatening torsade de pointes. The incidence of long QT syndrome has been estimated to be approximately 1 per 10,000 without apparent ethnic or geographic predilection. Through the last two decades, eight genotypes (LQT1–8) have been described (with up to 500 mutations and 130 polymorphisms). Each subgroup affects the morphology of the ventricular action potential in a different way and shows minor differences in clinical manifestations. Because most of these repolarization disorders involve the cardiac potassium currents (I_{Ks}, I_{Kr}, I_{Ki}), an overview of the potassium-dependent long QT syndrome subgroups is presented in this section (Table 2).

Long QT 1. Long QT 1 syndrome, caused by KCNQ1 mutations, is the most common form of long QT syndrome [27] Mutations in the KCNQ1-gene (α-subunit K_vLQT1) can cause autosomal-dominant Romano-Ward syndrome and autosomal-recessive Jervell and Lange-Nielsen syndrome. KCNQ1 and KCNE1 (minK) form the slowly activating component of the delayed rectifier K^+ current (I_{Ks}), which contributes to cardiac repolarization. Functional expression

Table 2
Long QT-syndrome genotype groups with associated pathophysiologic and clinical features

LQT subgroup	Gene	Locus	Encoded protein	Ion current affected	Effect of mutation	Triggers	ECG findings
LQT1	KvLQT1, KCNQ1	11p15.5	Alpha subunit of potassium channel	I_{Ks}	Loss of function	Exercise, swimming, emotional stress	Broad based T wave, late-onset T wave
LQT2	HERGKCNH2	7q35–36	Alpha subunit of potassium channel	I_{Kr}	Loss of function	Rest, sleep, auditory stimuli, emotional stress, postpartum	Split, notched T wave, low amplitude T wave
LQT3	SCN5A	3p21–24	Alpha subunit of sodium channel	I_{Na}	Gain of function	Rest/sleep	Late onset, peaked, biphasic T wave
LQT4	ANKB, ANK2	4q25–27	Membrane anchoring protein	Na^+, K^+ and Ca^{2+} exchange	Loss of function	Exercise, emotional stress	Inverted or low amplitude T wave, inconsistent QT prolongation, prominent U wave
LQT5	mink,I_sK, KCNE1	21q22.1–2	Beta subunit to KCNQ1	I_{Ks}	Loss of function	Unknown	Unknown
LQT6	MiRP1, KCNE2	21q22.1	Beta subunit to HERG	I_{Kr}	Loss of function	Unknown	Unknown
LQT7	Kir2.1, KCNJ2	17q23	Kir2.1 subunits	I_{K1}	Loss of function	Accompanied by alterations in serum K^+ levels	Prominent U wave, prolonged terminal T downslope
LQT8	CACNA1C	12p13.3	Alpha subunit	$I_{Ca,L}$	Gain of function	Hypoglycemia, sepsis	Severe QT-prolongation, 2:1 atrioventricular block, overt T-wave alternans

Data from Modell SM, Lehmann MH. The long QT syndrome family of cardiac ion channelopathies: a HuGE review. Genet Med 2006;8(3):143–55.

of mutant KCNQ1 α-subunits results in a loss of channel function. More than 100 mutations have been identified and associated with a variety of ion channel dysfunction mechanisms. The net effect of these mutations is a decrease in outward K^+ current during the plateau phase of the cardiac action potential. The channel remains open longer, ventricular repolarization is delayed, and the QT interval is prolonged [28].

Long QT 2. The second most common cause of congenital long QT syndrome is mutation in the *HERG* (*human-ether-a-go-go*–related) gene, which generates the long QT 2 phenotype (35%–45%) [29]. Currently, more than 80 mutations, mostly single amino acid substitutions, have been described. *HERG* encodes the voltage-gated potassium channels that produce the rapidly activating rectifier K^+ current (I_{Kr}). Similar as the I_{Ks} in long QT 1, the I_{Kr} plays an important role in controlling the balance of membrane currents during the plateau phase (phase 2) of the cardiac action potential. Long QT 2 is an autosomal-dominant inherited disease in which normal and mutant *HERG* genes are present. Experiments performed by Sanguinetti and Keating [30,31] contributed to our understanding in possible assembly mechanisms of the α-subunits. They concluded that the presence of a single mutant subunit (in a tetramer) conveys a dysfunctional channel phenotype. They called this the "dominant negative effect," which results in a channel function reduction of much more than the expected 50%. Because the *HERG* channel is considered a target for various cardiovascular and noncardiovascular drugs, it is partly responsible for the striking similarities between congenital and acquired or drug-induced forms of long QT syndrome.

Long QT 5. The congenital long QT5 phenotype has been linked to mutations in the minK gene *KCNE1* [32]. MinK is one of the auxiliary units that coassemble with K_vLQT1 to produce the slow delayed rectifier K^+ current I_{Ks}. As in previous long QT groups, the impaired repolarization prolongs the duration of the action potential by influencing phase 2 and, to a lesser degree, phase 3 of the action potential. The function of the regulatory subunit minK may not be restricted to K_vLQT1 alone in its interactions with the voltage-gated potassium channel. Recently, it has been shown to affect the amplitude and gating properties of the *HERG* subunits, raising the possibility that both I_{Ks} and I_{Kr} currents are altered in the long QT 5 syndrome. Currently, only five mutations have been identified [33].

Long QT 6. Another regulatory protein MiRP1, which is the product of the *KCNE2* gene, is dysfunctional in long QT 6 syndrome [27]. This gene bears many similarities to the *KCNE1* gene, which suggests a common evolutionary origin. Both genes are located next to each other on the same chromosome, and both encode an auxiliary unit of the voltage-gated potassium channel. The *MiRP1* gene product *KCNE2* coassembles as a β-subunit with the *HERG* α-subunits to regulate the I_{Kr} currents. Because it predominantly alters the I_{Kr} currents, it phenotypically mimics the long QT 2 syndrome. The long QT 6 variant is an uncommon variant (<1%) of the disease and is usually associated with minor clinical manifestations (because of its incomplete penetrance).

Long QT 7. The long QT 7 syndrome—or the Andersen-Tawil syndrome—is a skeletal muscle disease associated with periodic paralysis, prolonged QT intervals, and fluctuations in plasma potassium levels [34]. It has been linked to mutations in the *KCNJ2* gene (chromosome 17), encoding for the inward rectifier potassium channel (I_{K1} or Kir2.1). The alterations in action potential morphology occur during phase 3, because the I_{K1} current is predominantly active during late repolarization. Clinically, patients typically present with the triad of periodic paralysis, cardiac arrhythmias, and developmental dysmorphisms. Possible triggers for arrhythmias are hypokalemia and concomitant infections.

Disorders associated with a gain of function of cardiac potassium channels

Short QT syndrome. In 2000, Gussak and colleagues [35] first described a clinical syndrome that linked a short QT interval to an increased risk for malignant ventricular arrhythmias. Two years later, Gaita and colleagues [36] reported two families with short QT syndrome and a high incidence of sudden death, providing evidence for a genetic origin. As in long QT syndrome, mutations are located in genes that encode for subunits of the cardiac potassium channel. In contrast to the long QT syndrome, the gain of function of potassium channels results in faster repolarization with shortening of the action potential duration. Currently, three genes have been associated with the syndrome: $KCNH_2$, $KCNQ_1$, and $KCNJ_2$ [37].

KCNH$_2$ gene mutations. Brugada and colleagues [38] identified two different missense mutations in the *KCNH$_2$* or *HERG* gene in two unrelated families. *HERG* encodes the voltage-gated potassium channels that produce the rapidly activating rectifier K$^+$ current (I$_{Kr}$). *HERG* mutations associated with short QT syndrome block the inactivation of the *HERG* channels, which results in an increase in I$_{Kr}$. Coexpression of the *KCNE$_2$* gene does not alter these changes. The same group showed that *HERG* mutations cause a selective shortening of the ventricular action potentials that is not present in the Purkinje fibers. These differences in duration of action potentials and refractory periods could possibly create a substrate for re-entry arrhythmias. Because atrial fibrillation is frequently correlated with the same mutations, this heterogeneity probably extends to the atrial tissue [39]. This was demonstrated by identification of another family with short QT syndrome, in which atrial fibrillation was the only clinical manifestation.

KCNQ$_1$ gene mutations. To date, only two mutations in the *KCNQ$_1$* gene have been identified [40]. The first one exhibited a voltage-dependent character. A gain of function in the outward potassium current (and subsequent shortening of the action potential) could only be demonstrated at more negative potentials. The second mutation was identified in a newborn, who phenotypically showed atrial fibrillation with slowed ventricular response and a short QT interval. A de novo missense mutation revealed a voltage-independent alteration of the potassium currents, which resulted in shortened ventricular repolarization.

KCNJ$_2$ gene mutations. Recently, Priori and colleagues [41] described a third form of short QT syndrome linked to mutations in the *KCNJ$_2$* gene on chromosome 17, which is encoded for the inward rectifier potassium channel (I$_{K1}$ or Kir2.1). Similarly as in long QT 7, the alterations in action potential morphology occur during phase 3, because the I$_{K1}$ current is predominantly active during late repolarization. This phenotypically manifests as asymmetrical T waves with a rapid terminal phase on the surface ECG. Simulation of the effects of the mutated gene in animal models confirms this selective acceleration of phase 3 of the ventricular action potential.

Calcium channelopathies

The voltage-gated cardiac calcium channel

Cardiac calcium channels play a crucial role in the proper functioning of excitable cardiac cells. The heart expresses different types of voltage-gated Ca^{2+} channels that enable the coupling of electrical signaling to intracellular biochemical changes. In 2000 [42], a new classification model was introduced (Table 3) that presented the

Table 3
Ca^{2+}-dependent arrhythmia syndromes

Gene	Locus	Syndrome	Protein	Functional abnormality
Timothy syndrome				
CACNA1CA	12p13.3	Timothy syndrome1, autism	Ca$_v$1.2 α_{1C}	I$_{Ca-L}$ ↑
CACNA1C	12p13.3	Timothy syndrome1, autism	Ca$_v$1.2 α_{1C}	I$_{Ca-L}$ ↑
Catecholaminergic polymorphic ventricular tachycardia				
RyR2	1q42	CPVT1, SIDS	RyR2α	SR Ca^{2+} leak ↑
RyR2	1q42–q43	CPVT1, QT prolongation	RyR2α	SR Ca^{2+} leak ↑
RyR2	1q42–q43	CPVT1, ARVC2	RyR2α	SR Ca^{2+} leak ↑
CASQ2	1p13.3	CPVT2	Calsequestrin	SR Ca^{2+} leak ↑
KCNJ2	17q23	CPVT3	Kir2.1α	I$_{K1}$ ↑
ANK2	4q25	CPVT?	Ankyrin-B	SR Ca^{2+} leak ↑
Dilated cardiomyopathy				
ABCC9	12p12.1	DCM, VT	SUR2Aβ	Ca^{2+} − overload
PLN	6q22.1	DCM, HF, LVH	PLNβ	Ca^{2+} − overload

Abbreviations: ARVC, arrhythmogenic right ventricular dysplasia; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HF, heart failure; LVH, left ventricular hypertrophy; SIDS, sudden infant death syndrome; SR, sarcoplasmatic reticulum; VT, ventricular tachycardia.
Data from Splaswski I, Timothy KW, Sharpe LM, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 2004;119:19–31.

results of recent genetic, molecular, and biochemical studies. All voltage-gated Ca^2+ channels are large heteromers that contain a minimum of three core units: $\alpha 1$, $\alpha 2/\delta$, and β. The pore-forming $\alpha 1$ subunits contain the gating machinery required for adequate channel function. A wide spectrum of inherited calcium channelopathies results from mutations in these pore-forming α-subunits [44].

The most prominent extracellular cardiac calcium channels (located in the cell membrane or in the sarcolemma) are the high voltage–activated $Ca_v 1.2/Ca_v 1.3$ or slow calcium channels (L-type) (Fig. 4), which trigger the release and refilling of calcium in the sarcoplasmatic reticulum (SR). They predominantly affect phase 0 of the action potential in slow fibers (SA and atrioventricular node) or phase 2 in ventricular and atrial muscle cells (fast fibers). The resulting SR- calcium outflow in these cells can induce early after-depolarizations. L-type calcium channels act as a target for various drugs (calcium antagonists) that are aiming for a decrease in excitability of the cardiomyocytes (Fig. 5).

The low voltage activated $Ca_v 3.1$ and $Ca_v 3.2$ fast T-type channels show a relative prominence in pacemaker cells and conductive tissue and activate at more hyperpolarizing potentials. Based on these findings, T channels are presumed to play a vital role in atrial pacemaking.

Timothy syndrome

Timothy syndrome is a recently described form of long QT syndrome (long QT 8) [43,45]. Extracardiac features of this disease include syndactyly, facial dysmorphy, myopia, immunodeficiency, and generalized cognitive impairment. It results from a de novo, gain-of-function missense mutation in splice exon 8A of CACNA1C that encodes
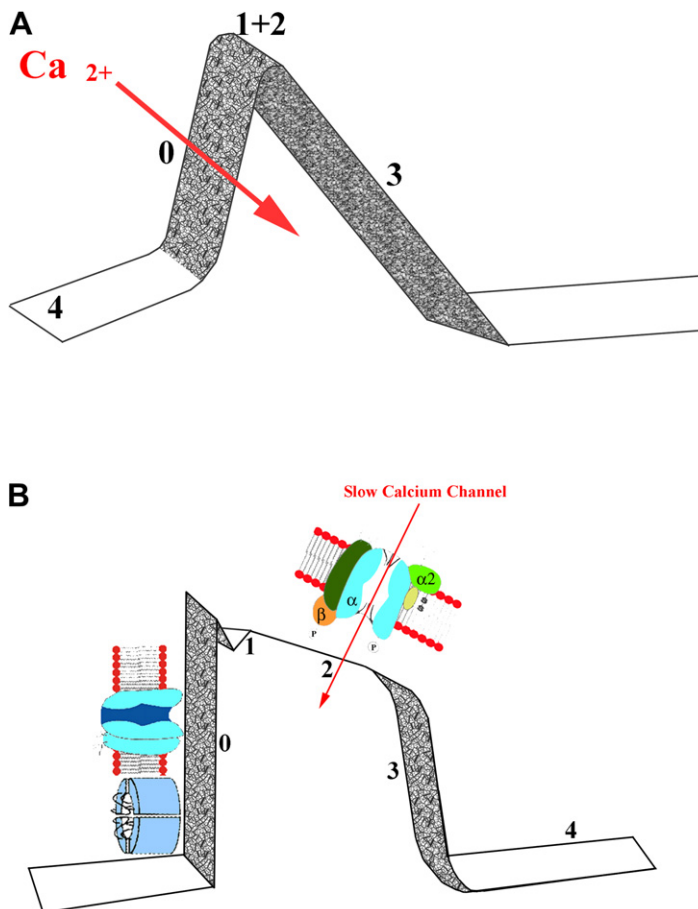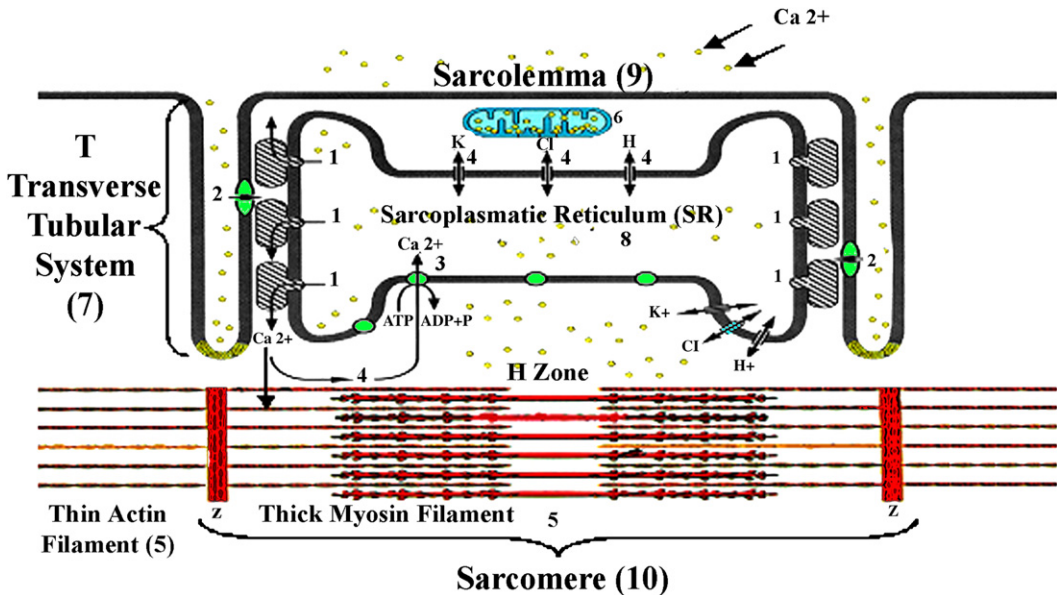

Fig. 4. Calcium channels.

Fig. 5. Outline of cellular activation system.

for the pore-forming subunit ($Ca_v1.2$) of the cardiac L-type Ca^{2+} channel. The causative mutation G406R results in loss of voltage-dependent channel inactivation leading to maintained inward Ca^{2+} currents and prolongation of the action potential. Because the combination of neurologic and cardiac phenotypes has been reported in CACNA1-mutations, special interest for neurologic evaluation is indicated in these cases.

The ryanodine receptor (or intracellular calcium release channel)

Activation of the contractile elements of the cardiac muscle is mainly governed by mobilization of calcium out of the sarcoplasmatic reticulum into the cytosol [46]. An increase in intracellular calcium concentration is obtained through complex interaction between different calcium channels (eg, Ca-ATPase, voltage-gated calcium channels) and auxiliary proteins. The ryanodine receptor (RyR) plays a crucial role in this process and has been identified in the membrane of the sarcoplasmatic reticulum of different excitable cells (RyR1 in skeletal muscle, RyR2 in cardiac muscle, and RyR3 in brain tissue). Depolarization of the cell membrane at the level of the T tubules triggers the voltage-gated L-type calcium channels to release a small amount of calcium. This small rise in intracellular calcium triggers the activation

or opening of the RyR2 with subsequent massive release of calcium out of the SR. A cluster of approximately 100 RyR2 channels and 25 L-type calcium channels form a "junction." The systolic contraction of the heart is the result of the simultaneous activation of hundreds of thousands of these junctions.

Cardiac calsequestrin

Calsequestrin is the most important calcium storage protein in the sarcoplasmatic reticulum. It is able to bind luminal calcium during diastole to prevent Ca^{2+} precipitation and reduce the ionic calcium concentration. In the heart, RyR2 does not act alone but is part of a macromolecular complex that contains several proteins, including calsequestrin, triadin, junctin, and junctophilin, which make up the calcium release unit.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial arrhythmogenic disorder characterized by adrenergically mediated polymorphic or bidirectional ventricular tachycardia [47]. Two genetic variants of CPVT have been identified as an autosomal-dominant trait caused by mutation in the gene encoding for the RyR2 receptor and one recessive form caused by mutations

in the cardiac isoform of the calsequestrin gene (*CASQ2*) [48]. These findings demonstrate that CPVT is caused by mutations of genes that encode for proteins responsible for the regulation of intracellular calcium. Both genes are located on chromosome one (1q42–Q43 and 1p13–p21). More than 70 RyR2 mutations have been identified so far. All are single base pair substitutions, which are mainly located at the carboxy terminus of the protein. Wehrens and colleagues [49] suggested that the common mechanism by which RyR2 mutations cause CPVT is by reducing the binding affinity of RyR2 for the regulatory protein FKBP12.6 (peptidyl-propyl isomerase). The depressed affinity of mutant RyR2 for FKBP12.6 is present in the resting state and worsens when beta-adrenergic stimulation leads to PKA phosphorylation of RyR2. Another theory, proposed by Jiang and colleagues, claims that CPVT is caused by an increased sensitivity to luminal calcium activation. The exaggerated spontaneous calcium release from the SR facilitates the development of delayed after-depolarizations and triggered arrhythmias.

Arrhythmogenic cardiomyopathies

Hypertrophic cardiomyopathy

The prevalence of unexplained left ventricular hypertrophy (LVH) in the general population is estimated to be 1 in 500 [50,51]. Hypertrophic cardiomyopathy (HCM) is a common autosomal-dominant genetic disorder caused by sarcomere mutations; it may account for up to 60% of unexplained cases of LVH, making HCM the most common genetic cardiovascular disorder [52–54]. This clinical entity was first described in 1958 by a pathologist, Donald Teare, as a "benign muscular hamartoma of the heart" [55]. Actually HCM is a well-defined cardiomyopathy characterized macroscopically by LVH, which may be asymmetrical or symmetric. The symmetric form of HCM accounts for more than one third of cases and is characterized by concentric thickening of the left ventricle with a small ventricular cavity dimension. The asymmetrical variant implies thickening of the basal anterior septum, which bulges beneath the aortic valve and causes narrowing of the left ventricular outflow tract; however, HCM may affect any portion of the left ventricle [56]. Another common variant of the asymmetrical form is HCM with apical hypertrophy, which was first described in Japan in 1970 but has been increasingly

diagnosed in western populations. The main pathologic hallmark is the triad of myocyte hypertrophy, disarray, and interstitial fibrosis [57,58].

HCM is caused by dominant mutations in genes that encode constituents of the sarcomere [59]. More than 400 individual mutations have been identified in 11 sarcomere genes, including cardiac α- and β-myosin heavy chains, cardiac troponins T, I, and C, cardiac myosin-binding protein C, α-tropomyosin, actin, titin, and essential and regulatory myosin light chains [60–62]. HCM mutations do not show specific predilections and are unique. Only a few sarcomere mutations have demonstrated a high incidence of premature death or end-stage heart failure, which defines their mutations as potentially "malignant." There are numerous exceptions, however, which indicates the importance of genetic modifiers and the environment on ultimate phenotypic development. Most mutations are single point missense mutations or small deletions or insertions. The most frequent causes of HCM are mutations in cardiac β-myosin heavy chain, cardiac troponin T, cardiac troponin I, and myosin-binding protein C genes [57].

For each gene, several different mutations have been identified, and specific mutations are associated with different severity and prognosis. For example, mutations in troponin T cause only mild or subclinical hypertrophy associated with a poor prognosis and high risk of sudden death (SD). In contrast, mutations in myosin-binding protein C are associated with mild disease and onset in middle age or late adult life. HCM also exhibits intrafamilial phenotypic variation, whereby affected individuals from the same family with an identical genetic mutation display distinct clinical and morphologic manifestations. This finding suggests that lifestyle factors or modifier genes are likely to influence the hypertrophic response [57].

The first pathologic gene identified as responsible for HCM has been the gene encoding for β-myosin heavy chain, mapped on chromosome 14q11 [52]. Cardiac myosin is formed of two heavy chains, two essential and two regulatory light chains. The heavy chains contain two sites for actin interaction and for ATPase activity, respectively. Each heavy chain is compounded by two isoforms: α and β. The first one is predominantly expressed in the atrium, whereas the β isoform preferentially expresses in the ventricle. The genes that encode the β and α isoforms are MYH7 and MYH6, respectively [63,64]. The identified mutations of the first gene number more than

80 and are responsible for HCM in 30% to 40% of patients. These mutations seem to be associated with a severe form of HCM with early onset, complete penetrance, and increased risk of cardiac sudden death. Mutations of MYH6 are rare; most of these mutations are "missense" [65].

Another gene involved in the pathogenesis of HCM is *MYBPC3*, which encodes cardiac myosin-binding protein C; it is located on chromosome 11q1. More than 50 mutations of *MYBPC3* have been identified; they are responsible for an abnormal protein that is unable to interact with myosin and titin. Mutation of cardiac myosin-binding protein C has been found in 30% to 40% of patients [66,67].

HCM also could be caused by a mutation of genes that code for the troponin complex. The gene of troponin T (*TNNT2*) contains 17 exons; "missense" mutations have been found in 15% to 20% of patients with HCM [65]. On the other side, the gene that encodes troponin I (*TNNI3*) is a small gene that is compounded by only 6 exons. It is responsible for a rare asymmetrical HCM characterized by a LV apical hypertrophy; actually only 6 missense mutations have been reported [68].

Mutant essential light chains are responsible for 2% to 3% of HCM; these proteins have a crucial role for calcium linking. *MYL3* is the gene that encodes the isoform light slow ventricular chain (MLC-1 s/v). One single missense mutation (Met 149Val) has been found in this gene causing a form of obstructive HCM [69]. The gene *MYL2* encodes the ventricular isoform regulatory myosin light chain (MLC-2s); 5 different mutations have been reported as causing a phenotype similar to *MYL3* mutation [69].

Cardiac actin has several isoforms also expressed in the skeletal muscle; its gene is *ACTC*. Mutation of this gene causes a mutant product that is not able to interact with β-myosin [54,70,71]. Finally, mutation of gene of α-tropomyosin named *TPM1* is also responsible for 3% of cases of HCM.

Recently genetic studies of familial and sporadic unexplained LVH accompanied by conduction disturbances (progressive atrioventricular block, Wolff-Parkinson-White syndrome, atrial fibrillation) have identified metabolic cardiomyopathies. These genetic forms of hypertrophy reflect mutations in γ2 regulatory subunit (PRKAG2) of AMP-activated protein kinase, an enzyme involved with glucose metabolism, or in the X-linked lysosome-associated membrane protein (LAMP2) gene 22, 23. These clinical entities are distinct from HCM caused by sarcomere protein mutations, despite the shared feature of LVH. A high prevalence of conduction system dysfunction (with the requirement of permanent pacing in 30% of patients) characterizes PRKAG2 mutations. LAMP2 mutations are X linked, which results in male predominance. LAMP2 mutations are associated with early-onset LVH (often in childhood) with rapid progression of heart failure and poor prognosis.

Arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is a disease characterized by the progressive loss of myocytes, and it affects mainly the right ventricular myocardium [72]. It is caused by either massive or partial replacement of myocardium by fatty or fibro-fatty tissue advancing from the epicardium to the endocardium. This infiltration provides a substrate for electrical instability and leads to sustained arrhythmias and sudden death [73].

There are several current concepts surrounding the pathogenesis of ARVD, including the progressive loss of myocytes by programmed cell death (apoptosis) as a consequence of cardiac injury. In some cases of ARVD, myocarditis has been implicated, and entero- and adenoviruses have been identified as potential etiologic agents [72]. There is a strong familial incidence (approximately 50% of cases) with autosomal-dominant inheritance, variable penetrance, and polymorphic phenotypic expression, which suggests that a genetically determined loss of myocytes may account for many cases of the disease. An autosomal-recessive form of ARVD also has been identified. It is associated with palmoplantar keratoderma and woolly hair (Naxos disease). This type of ARVD is caused by a mutation of the plakoglobin gene, the product of which is a component of desmosomes and adherens junctions [73]. The search for the genes responsible for autosomal-dominant ARVD is still underway, and gene linkage analysis of large pedigree has revealed multiple chromosomal loci involved in the pathogenesis of this cardiomyopathy. According to these gene mutations, several different phenotypes of ARVD have been defined.

Arrhythmogenic right ventricular dysplasia 1. This phenotype is caused by mutation in the transforming growth factor beta-3 gene (TGFβ3) on chromosome 14q23–q24. The coding region encodes for a protein of 849 amino acids with a single transmembrane domain and a short

stretch of intracellular domain [25]. Beta-type TGFs are polypeptides that act like hormones and control the proliferation and differentiation of multiple cell types. Rampazzo and colleagues [74] performed linkage studies in two large Italian families, one of which had 19 affected members in four generations. They found that 14q23–q24 locus was frequently involved. They also identified in four affected patients two types of mutations of the TGFβ3 gene: 36 G-A transition in the 5′-UTR and 1723 C-T transition in the 3′ UTR.

Arrhythmogenic right ventricular dysplasia 2. ARVD 2 is an autosomal dominant cardiomyopathy characterized by partial degeneration of right ventricular myocardium, electrical instability, and SD [75]. This disease and catecholaminergic polymorphic ventricular tachycardia (CPVT) can be caused by mutation in the cardiac RyR 2 gene located on chromosome 1q42.1–q43. The channel is a tetramer compounded by 4 RyR2 polypeptides and 4 FK506-binding proteins [76]. In myocardial cells, RyR2 proteins—activated by calcium—induced the release of this ion from the sarcoplasmatic reticulum into the cytosol. Tiso and colleagues [75] have demonstrated that RyR2 mutations provide different effects: ARVD 2-associated mutations increase RyR2-mediated calcium release to the cytoplasm and increase intracellular calcium level. RyR2 is the cardiac counterpart of RyR1, which is located in the skeletal muscle and is involved in malignant hyperthermia susceptibility and in central core disease (CCD).

Studies in a family with a "concealed" form of ARVD demonstrated that affected members did not show any structural heart disease, but they consistently presented effort-induced polymorphic ventricular tachycardias. In this family, however, a linkage to 1q42–q43 was demonstrated. In two other families, linkage to 1q42–q43 and 14q23–q24 (ARVD 1) was excluded, which provided evidence of further genetic heterogeneity [77].

ARVD 3. The existence of a novel ARVD locus on chromosome 14, in addition to ARVD 1 at 14q23–q24, was suggested by Severini and colleagues [78] that studied the linkage in three small different families. They found linkage to markers on the proximal part of 14q, named 14q12–q22. This locus is mapped on the long arm of chromosome 14; the gene responsible for ARVD is still unknown.

ARVD 4. In studies of three families, Rampazzo and colleagues [79] mapped a novel ARVD locus to 2q32.1–q32.3. Affected members of the three families showed clinical characteristics of ARVD according to the diagnostic criteria. Two episodes of SD in young patients were observed. These families were considered unusual in the finding of localized involvement of the left ventricle with left bundle branch block in some affected members. The gene responsible for ARVD 4 is still unknown.

ARVD 5, 6. By linkage analysis in a large North American family, Ahmad and colleagues [80] identified a novel locus for ARVD on 3p23. Asano and colleagues [81] implicated the laminin receptor-1 gene (LAMR1) as responsible for ARVD. An in vitro study of cardiomyocytes expressing the product of mutated Lamr1 showed early cell death accompanied by alterations of chromatine architecture. Asano found that Lamr1 mapped to 3p21, and its mutant product was able to cause degeneration of cardiomyocytes. This mutation is associated with patients affected by ARVD 5.

After exclusion of the five previously known loci, Li and colleagues [82] identified a novel locus on 10p14–p12; they investigated the involvement of the protein tyrosine phosphatase-like gene in a North American family with early-onset ARVD and high penetrance. Protein tyrosine phosphatases mediate the dephosphorylation of phosphotyrosine and are known to be involved in many signal transduction pathways leading to cell growth, differentiation, and oncogenic transformation. Li and colleagues found a missense mutation in gene encoding for protein tyrosine phosphatases; this is the cause of ARVD6.

ARVD 7. Desmin-related myopathy is another term referring to myofibrillar myopathy in which there are intrasarcoplasmic aggregates of desmin. ARVD 7, which maps to chromosome 10q22.3, is another desmin-related myopathy. This is characterized by skeletal muscle weakness associated with cardiac conduction blocks, arrhythmias, heart failure, and intracytoplasmatic accumulation of desmin-reactive deposits in cardiac and skeletal muscle cells [83]. Approximately one third of desmin-related myopathies are thought to be caused by mutations in the desmin gene. The DES gene encodes desmin, a muscle-specific cytoskeletal protein found in the smooth, cardiac, and heart muscles. Melberg and colleagues [84] identified mutations in the ZASP gene, which is located on 10q22.3; patients affected by this mutation showed myopathy, supraventricular arrhythmias, and

bradyarrhythmias. Several patients were found to have dilatation of the right ventricle and showed fibro-fatty replacement of myocardium.

ARVD 8. ARVD 8 is caused by a mutation in the gene encoding desmoplakin, which is the most abundant protein of the desmosomes with two isoforms produced by alternative splicing. The gene mentioned previously is on chromosome 6p24. ARVD 8 seems to be caused by a missense mutation in exon 7 of the desmoplakin gene [85]; another mutation has been identified in exon 23. The first mutation is interesting because a homozygous desmoplakin missense mutation had been reported to cause a dilative cardiomyopathy associated with keratoderma and woolly hair. These data suggest that ARVD 8 results from defects in intercellular connections.

ARVD 9. This form of ARVD is caused by heterozygous mutations in the *PKP2* gene, which encodes plakophilin-2 gene, an essential protein of cardiac desmosome [86]. Desmosomes are a complex of multiprotein structures of the cell membrane and provide structural and functional integrity to adjacent cells. The plakophilins are located in the dense plaque of desmosomes, but they are also found in the nucleus, where they have a role in transcriptional regulation. Gerull and colleagues [87] examined 120 patients with diagnosis of ARVD according the criteria proposed by McKenna. They found a high prevalence of mutation of *PKP2* gene, which was mapped to chromosome 12p11. Gerull and colleagues concluded that lack of plakophilin-2 or incorporation of mutant plakophilin-2 in the cardiac desmosomes impairs cell-cell contacts and provides intrinsic variation in conduction properties that may lead to life-threatening arrhythmias.

ARVD 10. The desmosomal cadherins are cell adhesion molecules, and two classes of desmosomal cadherins are known: the desmogleins and the desmocollins (DSC). The desmogleins gene is mapped to chromosome 18q12.1–q12.2 [88]. ARVD 10 is an autosomal-dominant disorder with reduced penetrance characterized by fibrofatty replacement of cardiac myocytes. The more frequent mutation identified is a transition G-to-A at the nucleotide 134 in exon 3. Another mutation, which causes a premature termination of codon, is a 915G-A transition in exon 8 [89].

ARVD 11. This form is caused by a mutation of the *DSC2* gene on chromosome 18q21. Syrris and

colleagues [90] identified two different heterozygous mutations in the *DSC2* gene. Both mutations resulted in frame shifts and premature truncation of the DSC protein.

Familial dilated cardiomyopathy

Idiopathic dilated cardiomyopathy (DCM) is the most common cause of congestive heart failure and is characterized by an increase in myocardial mass and a reduction in ventricular wall thickness. The heart assumes a globular shape, and there is a pronounced ventricular chamber dilatation and atrial enlargement, often with thrombi in the appendages. It has been estimated that up to 35% of individuals with idiopathic DCM have a familial disease [59]. This estimate has been shown by detailed pedigree analyses of relatives of patients with DCM coupled with the identification of single gene mutations in structural proteins of the myocyte cytoskeleton or sarcolemma [91]. It has been proposed that familial DCM (FDCM) is a form of "cytoskeletalopathy."

The pattern of inheritance of FDCM is variable and includes autosomal-dominant, X-linked, autosomal-recessive, and mitochondrial inheritance [90]. The autosomal form of FDCM is the most frequent and can be further grouped into either a pure CMP phenotype or DCM with cardiac conduction system disease. Major progress has been made in the identification of candidate disease loci and the genes responsible for FDCM, including mutations in the genes that encode cardiac actin, desmin, δ-sarcoglycan, β-sarcoglycan, cardiac troponin T, and α-tropomyosin. Four candidate genetic loci also have been mapped for DCM with cardiac conduction system disease, but to date there has been identification of only one gene, the lamin A/C gene [91,92]. Mutations in the lamin A/C gene also cause autosomal-dominant FDCM with mild skeletal myopathy and autosomal-dominant Emery-Dreifuss muscular dystrophy. Most molecular causes of autosomal DCM are still unknown; linkage analysis allows mapping many mutations in different chromosomes, such as 1p1–1q1, 9q13–q22, and 3p22–p25. The single mutant gene responsible has not been identified, however. Recently, a missense mutation of gene encoding cardiac actin has been localized on 3p22–p25. In these patients a defect of actin-Z band was evidenced [70].

The X-linked forms of DCM include X-linked DCM and Barth syndrome. The first one is a type

of DCM that occurs in boys during adolescence or early adulthood with a rapidly progressive clinical course. Female carriers develop a mild form of DCM with onset in middle age. X-linked DCM is associated with raised concentrations of creatine kinase but without signs of skeletal myopathy and is caused by mutations in the dystrophin gene [91]. Mutations of this gene are also responsible for Duchenne's and Becker's muscular dystrophies. The infantile form of X-linked DCM or Barth syndrome typically affects male infants and is characterized by neutropenia, growth retardation, and mitochondrial dysfunction [93]. One mutant gene, responsible for DCM, is the G4.5, which has been mapped on Xq28. Mutation of this gene causes Barth syndrome, and it seems to be involved in left ventricular noncompaction [91].

Summary

Sudden cardiac death and its devastating consequences still affect millions of individuals throughout the world. Over the last three decades, a tremendous amount of research has focused on possible contributing pathophysiologic mechanisms. The discovery of inherited primary and secondary electrical disorders caused by alterations in our genetic material opened a whole new era of understanding. The knowledge obtained should be incorporated into our new, contemporary approach to malignant ventricular arrhythmias. In the past, the diagnosis of an idiopathic ventricular arrhythmia (without clear cause) was all too readily made. The search for any other plausible explanations ceased whenever structural heart disease could be excluded. Careful familial screening and genetic analysis should be performed in all of these cases. Cardiac channelopathies represent a group of recently discovered arrhythmogenic disorders in structurally normal hearts. In this field, only a fraction of the causative gene mutations have so far been identified. Prognostic assessment of each member of an affected family calls for an individual approach based on clinical features, family analysis, and genetic results.

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