EXPERT REVIEWS

The usual suspects in sudden cardiac death of the young: a focus on inherited arrhythmogenic diseases

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Up to 14,500 young individuals die suddenly every year in Europe of cardiac pathologies. The majority of these tragic events are related to a group of genetic defects that predispose the development of malignant arrhythmias (inherited arrhythmogenic diseases [IADs]). IADs include both cardiomyopathies (hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy) and channelopathies (long QT syndrome, short QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia). Every time an IAD is identified in a patient, other individuals in his/her family may be at risk of cardiac events. However; if a timely diagnosis is made, simple preventative measures may be applied. Genetic studies play a pivotal role in the diagnosis of IADs and may help in the management of patients and their relatives.

KEYWORDS: cardiomyopathy • channelopathy • genetic testing • inherited arrhythmogenic diseases • sudden cardiac death

In this review, we will analyze the epidemiology of sudden cardiac death (SCD) in the young and discuss the pivotal role that a group of rare disorders of genetic origin, the so called 'inherited arrhythmogenic diseases' (IADs), plays in predisposing young hearts to the development of life-threatening arrhythmias. We will also outline the key clinical features and management strategies of the most prevalent IADs, while highlighting the contribution that genetic analysis brings to the management of patients with IAD and their families.

SCD: the magnitude of the problem

Sudden death (SD) due to cardiac disorders is known as SCD, and it is the leading cause of nontraumatic mortality in Western countries, accounting for more than 400,000 cases every year both in the USA and Europe [1,2]. The rate of SCD in the general population ranges broadly in different studies, due to the varying incidences at differing ages. Overall, it is estimated to be between 36 and 128 cases/100,000 person-years and exponentially increases with age due to the greater impact that coronary artery disease has on individuals over the age of 40 years [3–6]. SCD in individuals under the age of 40 years has an incidence of 0.5–6 events per 100,000 person-years [7], corresponding to 14,500 deaths in Europe and 10,000 deaths in the USA each year [8,9]. Although 'SCD in the young' is often regarded as an 'infrequent' event, numbers show that it is not as rare as previously thought. In fact, to make a comparison, SCD in the young is much more common than the risk of death due to influenza (0.1/100,000 person-years) [9].

Over the last 50 years, it has become clear that the majority of SCD in young individuals are linked to underlying genetic disorders that predispose them to the development of life-threatening arrhythmias (ventricular fibrillation and ventricular tachycardia [VT]), which lead to cardiac arrest (CA). Several entities have been identified in this context, including gene defects that result in structural abnormalities of cardiac muscle (cardiomyopathies) and those that alter the electrical properties of a structurally 'normal' heart (channelopathies).

A large part of our current understanding of the causes of SCD in the young derives from

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Table 1. Autopsy series of sudden cardiac death in young individuals, according to the underlying pathology, divided by athletes versus general population.

Study (year)	Country	Period	Age (years)	SCD (n)	HCM (%)	DCM (%)	ARVC (%)	Total CM (%)	SUD (%)	Ref.
Athlete population										
Van Camp (1995)	USA	1983–1993	13–24	105	45	5	1	51	7	[12]
Corrado (2003)	Italy	1979–1999	12–35	52	2	2	23	27	2	[11]
Maron (2009)	USA	1980–2006	8–39	690	36.3	2	4.3	42.6		[10]
Holst *et al.* (2010)	Denmark	2000–2006		15			26.6	26.6	26.6	[13]
General population										
Topaz (1985)	USA	1960–1983	7–35	50	12			12	14	[14]
Drory (1991)	Israel	1976–1985	9–39	137	11	3		14	14	[15]
Shen (1995)	USA	1960–1989	20–40	41	5			5	17	[16]
Wisten (2002)	Sweden	1992–1999	15–35	181	10.5	12.2	6.6	29.3	21	[17]
Cho (2003)	Korea	1999–2000	<35	38	5		42	47	18	[18]
Corrado (2003)	Italy	1979–1999	12–35	277	8.5	4	13.5	26	7	[11]
Eckart (2004)	USA	1977–2001	18–35	108	7	1	1	9	40	[19]
Puranik (2005)	Australia	1995–2004	5–35	241	5.8	5.4	1.6	12.8	26.5	[20]
di Gioia *et al.*(2006)	Italy	2001–2005	2–40	100	4	4	12	20	19	[21]
Papadakis (2009)	UK	2002–2005	1–34	1677	5	12		17	14	[22]
Lim (2010)	Canada	2005–2007	0–35	100	8	1	4	13	35	[23]
Fragkouli (2010)	Greece	1998–2008	1–35	28	7	3.7		10.7	39	[24]
Winkel *et al.* (2011)	Denmark	2000–2006	1–35	314	0.6	1.3	5	7	43	[25]
Eckart *et al.* (2011)	USA	1998–2008	18–35	298	12.8	4.7	1.3	18.8	41	[6]
Margey *et al.* (2011)	Ireland	2005–2007	15–35	116	14.7	2.6	1.7	19	27	[26]
Pilmer *et al.* (2013)	Canada	2008	2–40	174	7	14	1.7	22.7	48	[27]

ARVC: Arrhythmogenic right ventricular cardiomyopathy; CM: Cardiomyopathies; DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy; SCD: Sudden cardiac death; SUDS: Sudden unexplained death syndrome.

epidemiological investigations of SD in athletes, mainly carried out in the USA and in Italy.

The National Registry of SD in athletes was established at the Minneapolis Heart Institute in the 1980s and has reported on 1866 SD in individuals under the age of 40 years, during a 27-year observational period [10]. Data showed that 56% of all SD in this registry were classified as cardiovascular, of which 36% were caused by hypertrophic cardiomyopathy (HCM), a common genetically determined disease of cardiac muscle [10].

In Italy, investigators in the Veneto region conducted a prospective cohort study enrolling individuals under 36 years of age involved in competitive sports between 1979 to 1999, where more than 20% of SCD among these athletes were caused by arrhythmogenic right ventricular cardiomyopathy (ARVC), another inherited cardiomyopathy [11].

The US registry also showed that 34% of SCD in athletes occurred in the absence of any structural cardiac disease [10]. Similar observations were made by other studies conducted on SD in the general population under the age of 40 years (Table 1) [10–27], where between 7 and 43% of SCDs were considered unexplained (sudden unexplained death syndrome). The introduction of DNA screening in postmortem studies, the so-called 'molecular autopsy', has demonstrated that cardiac channelopathies may be responsible for 15–25% of sudden unexplained death syndrome [28,29].

IADs as a cause of SCD in the young

Cardiomyopathies and channelopathies are a major cause of SCD in the young: these two entities are often grouped together under the name of IADs.

IADs are generally considered rare disorders, having an estimated average prevalence of less than 1 in 2000 in most cases (Table 2) [30–38]. This figure, however, is not based on systematic population studies and should be considered with caution:

Table 2. Inherited arrhythmogenic diseases.

Inherited arrhythmogenic disease	Estimated prevalence	Yield of genetic screening (%)	Genes associated with >5% of disease		Current contribution of genetic testing?		
					Diagnosis	*Prognosis*	*Therapy*
HCM	1:500	60–70	MYBPC3	20–45%	+++	++	+
			MYH7	15–20%			
			TNNT2	1–7%			
			TNNI3	1–7%			
ARVC	1:5000	60	PKP-2	25–40%	+	+/-	-
			DSG-2	5–10%			
			DSP	2–12%			
			DSC2	2–7%			
DCM	1:2700	30%	No gene >5% individually (>25 known)		+/-	-	-
LQTS	1:2000	75–80	KCNQ1	30–35%	+++	+++	++
			KCNH2	25–40%			
			SCN5A	5–10%			
BrS	1:1000	20–30	SCN5A	20–30%	+	+	-
CPVT	1:10,000	60–70	RYR2	60%	+++	+	-
SQTS	<1:10,000	<20	KCNH2	<5%	+/-	-	-
			KCNQ1	<5%			
			KCNJ2	<5%			

Information about prevalence, current yield of genetic screening and the principal genes involved in every IAD are reported. Additionally, the impact of the genetic testing on diagnosis, prognosis and therapy is shown (from +++: strong to -: negligible).
ARVC: Arrhythmogenic right ventricular cardiomyopathy; BrS: Brugada syndrome; CPVT: Catecholaminergic polymorphic ventricular tachycardia; DCM: Dilated cardiomyopathy; DSC: Desmocollin; DSG: Desmoglein; DSP: Desmoplakin; HCM: Hypertrophic cardiomyopathy; LQTS: Long QT syndrome; SQTS: Short QT syndrome. Modified with permission from [42].

indirect evidence suggests that the real prevalence of some IADs is higher (e.g., HCM may affect up to 1 in 500 individuals) [30,35,39].

From a pathophysiological standpoint, the seminal discovery of mutations in HCM [40] and in the long QT syndrome (LQTS) [41] in the early 1990s has been critical for the comprehension of the mechanisms underlying IADs. Cardiomyopathies and channelopathies represent a model of 'monogenic disorders', whereby a single gene mutation affects the function of key cardiac proteins such as: elements of the contractile apparatus of cardiomyocytes (sarcomere); constituents of the specialized intercellular structures called desmosomes that connect cardiac cells; components of the cytoskeletal or nuclear scaffold; and ion channels that regulate the electrical function and the excitability of cells.

From a clinical standpoint, the consequence of a genetic defect in any of the aforementioned cardiac components is an increased susceptibility to the development of ventricular arrhythmias, with clinical manifestations spanning from palpitations to syncope caused by self-limiting VT and to SCD.

IADs are most often transmitted in families as autosomal-dominant traits, though less frequent forms of inheritance have been described, including autosomal recessive, X-linked and mitochondrial patterns [42]. As for most genetic disorders, however, the expressivity of IADs varies greatly among individual patients, even within the same family, due to the influence of environmental and genetic modifiers.

Although a CA may be the first presentation of IADs in a subgroup of cases, the identification of at-risk individuals in the presymptomatic phase is now possible and allows for the implementation of effective and often-simple prophylactic measures. This is especially important considering that only a small proportion of out-of-hospital CA (<15%) are successfully resuscitated without any devastating disability caused by cerebral hypoxia [43].

The diagnosis of IADs is based, in most instances, on the assessment of the ECG, which may reveal specific diagnostic features. Diagnostic characteristics may be overtly apparent or, as in some cases, concealed and therefore DNA screening may be required to complement clinical data [44]. Several tactics are available to attempt identification of individuals with IADs, with 'population screening' being the most intuitive. Another more

targeted approach is with 'cascade screening' of family members of affected individuals, which has been proven to be particularly rewarding: convincing data by Earle *et al.* suggests that over 50% of affected individuals' within the population can be identified through a thorough cascade screening approach [45]. The optimal clinical management of patients with IADs is mainly based on experts' recommendations that are incorporated into guidelines or Expert Consensus Documents developed by international scientific societies [44]. Like for most rare disorders, due to the lack of randomized studies, data on which recommendations are based derive from registries that follow patients over time and record outcome information. Our group has been one of the medical teams that actively participates in this undertaking through the creation and maintenance of registries of IADs over the last 20 years [39,46–49].

In recent times, genetic data have been incorporated into the management of patients with IADs, contributing to the diagnosis, risk stratification and therapeutic considerations in certain instances [42,44]. In 2011, the Heart Rhythm Society and European Heart Rhythm Association published a Consensus document in order to help physicians who deal with the complexities of molecular information, to rationally address the use of genetic testing, allowing for maximal mutation detection while retaining cost–effectiveness (Table 2) [42,50].

In the following sections, we will provide a schematic outline of the clinical and genetic characteristics of the principal IADs, focusing on the aspects associated with SCD.

Readers may refer to the latest guidelines for a thorough description of diagnosis, risk stratification and management of IADs [44,51–58].

Cardiomyopathies

Cardiomyopathies are myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of acquired heart diseases [51].

The diagnosis of a cardiomyopathy is largely based on the detection of morphological and functional alterations by cardiac imaging. The presence of ECG abnormalities, although not the key diagnostic features of cardiomyopathies, may help contribute to the diagnosis [59–61].

Not all individuals with a cardiomyopathy show clinical signs that allow for a conclusive diagnosis. The term 'incomplete penetrance' is used to define the proportion of mutation-positive subjects who have clinically detectable disease. The lower the penetrance of a disease, the higher is the contribution of genetic screening to the clinical diagnosis. Penetrance usually increases with age [62–65].

The cardiomyopathies most frequently associated with SCD include (Table 2): HCM, ARVC and dilated cardiomyopathy (DCM) [11,52].

Hypertrophic cardiomyopathy

HCM is defined by an increased left ventricular (LV) wall thickness or mass in the absence of diseases that may cause secondary hypertrophy such as systemic hypertension or aortic stenosis [51]. HCM is the most common IAD, with an estimated prevalence of about 1 in 500 [30,66]. A genetic substrate can be identified in up to 60% of cases by screening the genes known to be associated with the disease [42]. In adolescents and adults, HCM is primarily caused by mutations in one of the several genes encoding cardiac sarcomeric proteins, with the majority of mutations (80–90%) being found in the *MyBPC3* gene encoding myosin-binding protein C, *MYH7* gene encoding the β-myosin heavy chain and *TNNT2* gene encoding troponin T [42,67]. HCM in the pediatric population also includes congenital multisystem syndromes (e.g., Noonan's syndrome), inborn errors of metabolism (e.g., glycogen and lysosomal storage diseases) and neuromuscular disorders (e.g., Friedreich's ataxia) that are beyond the scope of this review [68].

The diagnosis of HCM is frequently suspected on the electrocardiographic evidence of LV hypertrophy, and it is confirmed by measurements of ventricular wall thickness using echocardiography and MRI [69] (Figure 1). The hypertrophy is more often asymmetrical and classically involves the interventricular septum [70]; in approximately 25% of patients, a dynamic gradient in the LV outflow tract (LV outflow tract obstruction) can be observed at rest [70] and in up to 70% of symptomatic individuals, it is identified during effort [71]. A cardiac biopsy may help to identify additional diagnostic criteria such as myocyte hypertrophy and disarray with interspersed fibrosis and small vessel disease [72].

While the clinical course is benign for the majority of HCM patients, up to 10% of individuals develop heart failure symptoms caused by deteriorations in LV systolic and diastolic function. Prognosis can be further compounded by atrial arrhythmias and strokes [69,73,74].

SCD occurs with a rate of 1% per year in HCM patients [71]. Given its high prevalence, HCM is often considered the most frequent cause of SD in people under the age of 30 years [52]. The presence of nonsustained VT, unexplained syncope, blunted increases in systolic blood pressure in response to exercise, family history of SCD and extreme LV hypertrophy are considered major risk factors for SCD. Minor risk factors include: the presence of LV outflow tract obstruction; a history of atrial fibrillation; the evidence of late gadolinium enhancement (LGE) in cardiac MRI as an expression of extracellular myocardial collagen deposition; LV systolic dysfunction; myocardial ischemia; and certain high-risk mutations (e.g., Arg403Gln, Arg453Cys and Arg719Trp in *MYH7* [75,76]). The overall utility of genetic information, however, is still controversial, considering the lack of genotype–phenotype correlations for the remaining majority of mutations.

The presence of two or more major risk factors is associated with a 4–5% annual incidence of SCD, and therefore, prompts consideration for the placement of an implantable cardioverter defibrillator (ICD) [77]. The presence of a single major risk factor, if accompanied by a few minor risk factors, may also lead to the consideration of a prophylactic ICD [53,75]. Amiodarone (a class III antiarrhythmic drug) can be recommended in HCM patients with an indication for an ICD, when the device is either unavailable or not accepted by the patient [75,78].

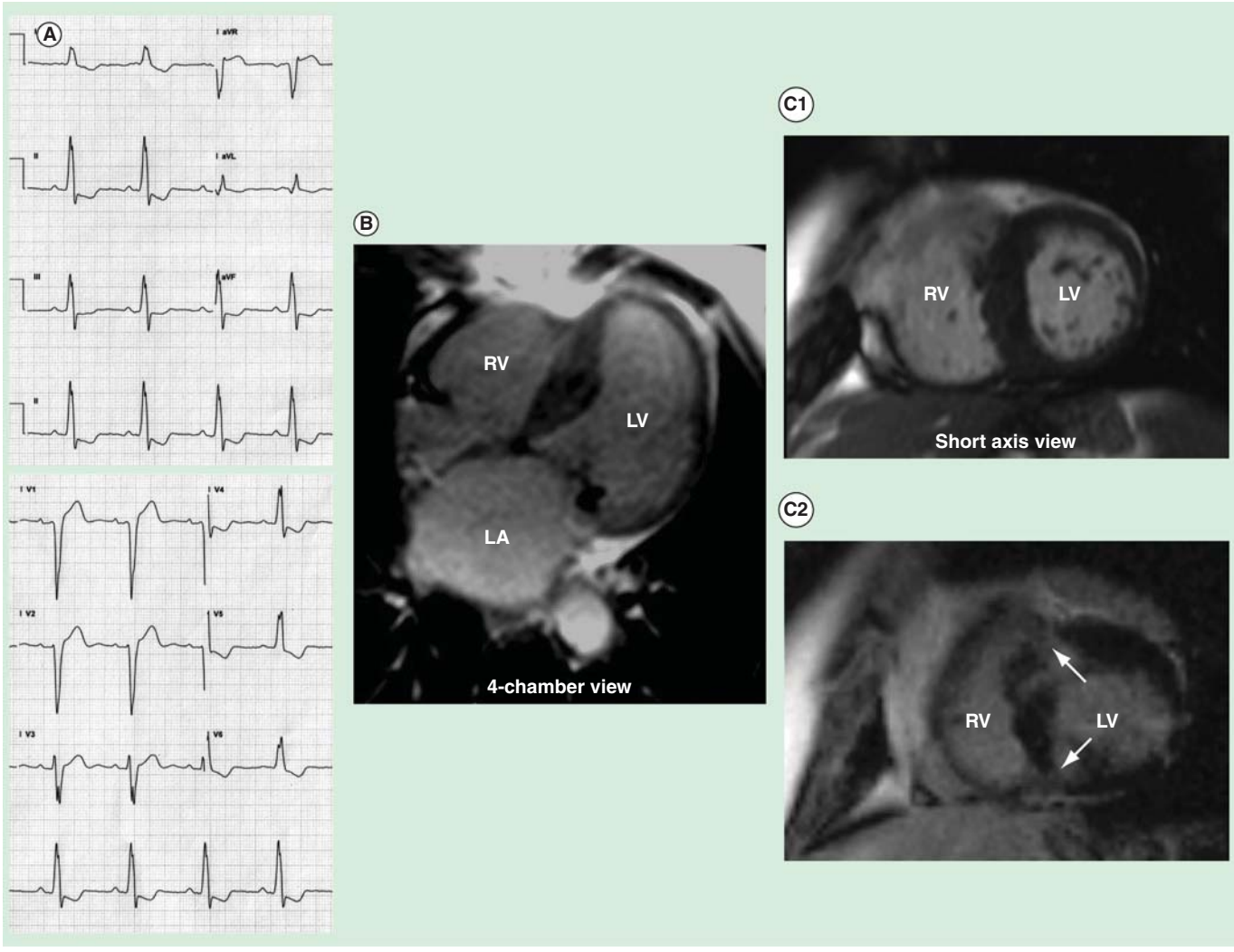

Figure 1. Hypertrophic cardiomyopathy. 12-lead ECG and cardiac MRI from a 73-year-old lady with a diagnosis of obstructive HCM and symptoms of exertional dyspnea, angina and presyncope. Her family history was remarkable for multiple sudden deaths. **(A)** ECG showing sinus rhythm and a long-standing left bundle branch block. Coronary angiography demonstrated normal coronary arteries. **(B)** Cardiac MRI four-chamber view showing asymmetric hypertrophy of the basal interventricular septum (max 20 mm) and an enlarged left atrium. **(C1)** Cardiac MRI short axis view showing localized hypertrophy of the interventricular septum. **(C2)** Cardiac MRI short axis view 20-min post gadolinium showing two areas of delayed enhancement in the anterior and posterior septum (white arrows).
LA: Left atrium; LV: Left ventricle; RV: Right ventricle.

Arrhythmogenic right ventricular cardiomyopathy

ARVC, formerly known as arrhythmogenic right ventricular dysplasia [79], is defined histologically by the progressive replacement of ventricular myocardium with adipose and fibrous tissue [51], conferring a scarred appearance to the ventricular walls [79,80] and results in structural alterations that range from subtle regional wall motion abnormalities to ventricular aneurysms and global ventricular dilation and dysfunction [80]. Although the RV is more typically affected, the LV may also be involved [81,82]. As the name implies, the clinical hallmark of ARVC is the predisposition to the development of ventricular arrhythmia and SCD, which may also occur in the context of grossly preserved ventricles [83,84]. The prevalence of ARVC varies among different geographical regions [85], with a frequency of about 1 in 5000 in most series.

The genetic basis of ARVC is predominantly attributable to mutations in genes encoding proteins of the desmosomal complex: PKP-2, DSG-2, DSC-2, DSP and JUP [42]. It has been estimated that up to 60% of ARVC cases are related to alterations of the aforementioned proteins and are typically transmitted as autosomal-dominant traits, although autosomal-recessive forms have also been described and confer a severe cardiac phenotype with added extra cardiac manifestations such as wooly hair and skin abnormalities (e.g., Naxos [86,87] and Carvajal [88] syndromes).

With regards to genotype–phenotype correlations, initial data suggest that desmoplakin mutations may result in more

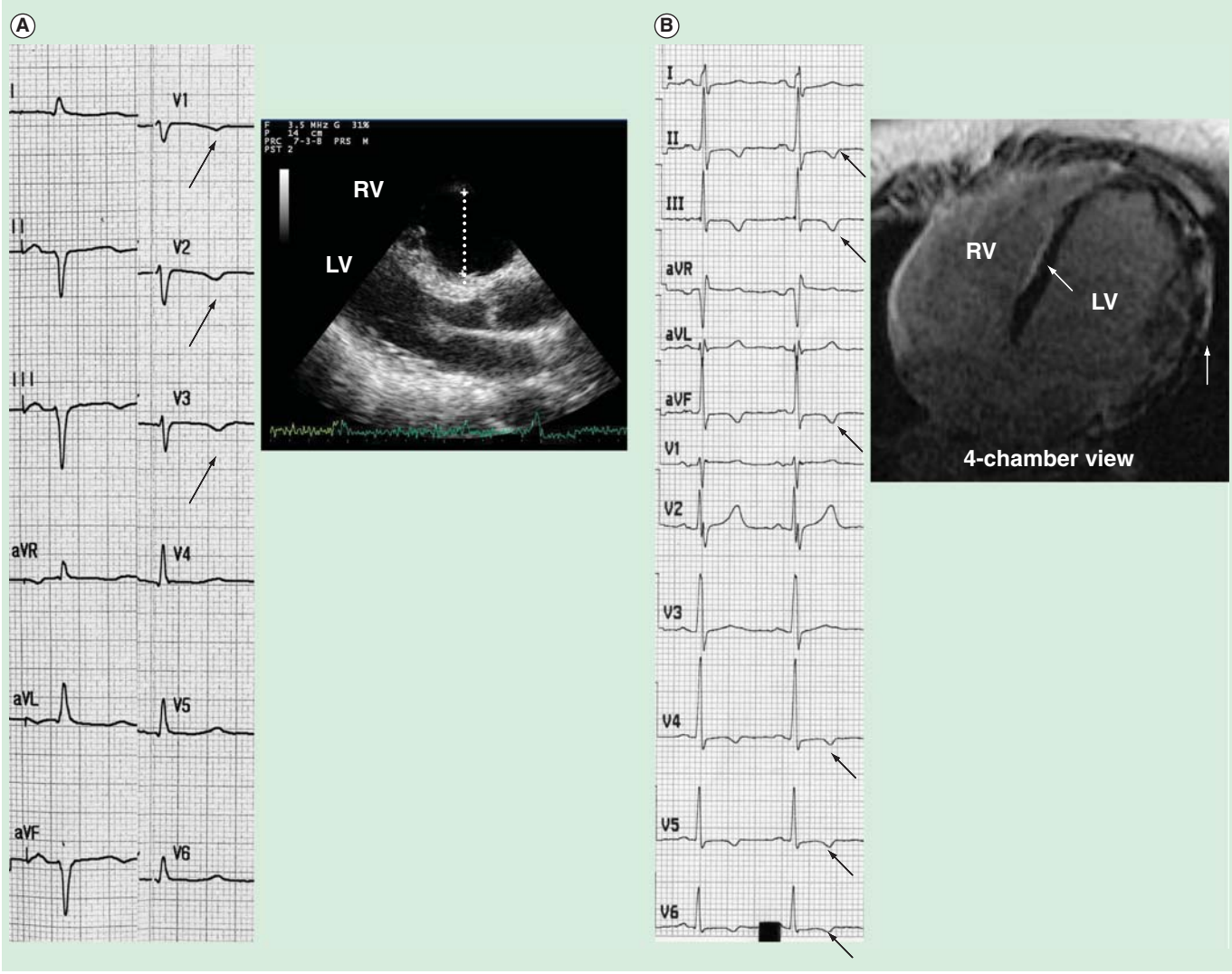

Figure 2. Arrhythmogenic right ventricular cardiomyopathy. (A) 12-lead ECG and trans-thoracic echocardiogram from a 70-year-old man with diagnosis of arrhythmogenic RV cardiomyopathy affecting the right ventricle. The ECG shows negative T waves in the right precordial leads (V1–V3, see black arrows). The echocardiogram (parasternal long-axis view) shows a severely enlarged right ventricle (42 mm or 24 mm/m^2). **(B)** A 12-lead ECG and postgadolinium cardiac MRI from a 24-year-old woman of Greek origin with presyncope, nonsustained polymorphic ventricular tachycardia on Holter recordings and a family history of sudden cardiac death. The ECG shows negative T waves in the lateral and inferior leads, suggestive for a left-dominant form of arrhythmogenic RV cardiomyopathy (see black arrows). The MRI shows extensive subepicardial (i.e., nonischemic) delayed enhancement on both ventricles (see white arrows).
LV: Left ventricle; RV: Right ventricle.

significant LV involvement [81], while plakophilin mutations seem to be associated with early onset arrhythmias [89]. Complex genotypes, including compound heterozygosity (coinheritance of two mutated copies of the same gene) and digenic heterozygosity (co-inheritance of two mutations in different desmosomal genes), are observed in up to one-third of ARVC probands [90], and these have been demonstrated to be a powerful risk factor for lifetime major arrhythmic events and SCD [91].

The clinical manifestations of the disease often appear in the third and fourth decades [65], but earlier presentations are possible and about 10–15% of ARVC deaths occur at the age of 18 or earlier [83] Features of affected individuals in ARVC include isolated electroanatomical abnormalities, ventricular arrhythmias and heart failure symptoms, which may culminate differently in individual patients. Evolution to overt right ventricular or biventricular dysfunction is an uncommon finding [92,93], whereas sustained VTs and SCD may occur at any clinical stage. According to some authors, SCD is the first clinical manifestation of the disease in 20–50% of index cases [92,94,95]. Among the modulators that may explain the variable expressivity of ARVC, exercise has emerged as a key player for the development of ARVC among desmosomal mutation carriers. Initially, Kirchhof *et al.* [96] showed that endurance exercise accelerates the development of RV dysfunction and arrhythmias in a plakoglobin-deficient mouse model. More

recently, James *et al.* [97] found that among a large cohort of patients with desmosomal mutations, athletes were more likely to be at risk of life-threatening arrhythmias and had an increased probability of developing a fully penetrant ARVC phenotype and heart failure compared with non-athletes.

The diagnosis of ARVC relies on a multiparametric score that incorporates anatomical, histological, electrophysiological, arrhythmic and genetic features [54]. Of note, existing guidelines concentrate on the diagnosis of the 'right ventricular variant' (Figure 2A), whereas no clear criteria exist for the left-dominant forms of the disease. We consider that negative T waves in the lateral leads are a sensitive indicator for the left-dominant arrhythmogenic ventricular cardiomyopathy and should always prompt further investigations (Figure 2B).

Patients who survive a CA or experience a hemodynamically unstable sustained VT have an 8–10% per year risk of recurrence and are suitable candidates for ICD implantation. Other risk factors for arrhythmic events include unexplained syncope, severe RV dilation and LV dysfunction, VT on Holter or exercise testing and a younger age at diagnosis [98,99]. While ICD implantation represents the most reliable option for the prevention of SCD [75], antiarrhythmic therapy may have a role in alleviating arrhythmic symptoms. Though trial data are limited, pharmacological agents regarded as safe and with possible efficacy include β-blockers [100], sotalol [101] and amiodarone [102].

Dilated cardiomyopathy

DCM is defined by LV dilatation and systolic dysfunction; right ventricular involvement may be present, but is not necessary for the diagnosis [51]. When DCM occurs in the absence of a detectable cause (such as ischemic heart disease or mitral/aortic regurgitation), it is referred to as 'idiopathic' DCM (iDCM). The estimated prevalence of iDCM is about 1 in 2700 individuals [33]. No morphological or histological findings are specific for iDCM, but a familial presentation may be identifiable in up to half of the cases [103,104]. Most genetic DCM inheritance follows an autosomal-dominant pattern, with characteristic age-dependent penetrance and variable clinical expression. Autosomal recessive, X-linked and mitochondrial forms have been described in a minority of cases [42].

Recent evidence suggests that sporadic iDCM cases may have a genetic cause as frequently as familial forms [105]. More than 30 disease-causing genes encoding for proteins of the sarcolemma, cytoskeleton, sarcomere, mitochondria and proteins forming ion channels have been associated with familial DCM, but none of them individually account for more than 5% of positively genotyped probands. Globally, the yield of molecular screening in unselected familial DCM does not exceed one-quarter of cases [42]. Conversely, there is a subset of patients who present with DCM features associated with cardiac conduction disease and/or skeletal muscle myopathy in which a mutation in the *LMNA* gene may be found in up to 33% of cases [106], and this result bears prognostic implications (Figure 3). Patients harboring a *LMNA* mutation, in fact, may experience SCD in an early phase of the disease, when only mild reduction of systolic function is present. Specific recommendations for the implant of an ICD have been proposed in this setting [107].

The documentation of LV dilation and systolic dysfunction with echocardiography is diagnostic of DCM; cardiac MRI may contribute to the diagnosis providing also noninvasive tissue characterization through LGE. Isolated mild LV enlargement or systolic impairment may represent an initial stage of DCM, especially when seen within the context of a family history [108].

DCM may develop at any age, but it usually presents during adolescence or in young adults [109]. The prognosis of overt DCM is poor, with a 5-year mortality estimated at 20% and with SCD accounting for approximately 30% of deaths [110,111]. Medical therapy with neurohumoral antagonists (β-blockers, ACE inhibitors and aldosterone antagonists) have been shown to reduce the risk of CA in patients with DCM [58,112,113], but ICD therapy provides incremental protection in subjects at the greatest risk, like those who survived a CA or had documented sustained VT [75]. The indication for primary ICD therapy is mainly dependent on the severity of systolic dysfunction [58]. Consensus guidelines recommend ICD placement in patients who have severe systolic dysfunction (LV ejection fraction ≤35%) while receiving optimal medical therapy and have reasonable 1-year survival prospects. Recommendations are strongest for patients with heart failure symptoms (e.g., New York Heart Association classes II and III) [57,75]. Other risk factors for SCD include unexplained syncope, a family history of SCD [75] or the presence of nonsustained ventricular arrhythmias at Holter monitoring [114]. More recently, microvolt T wave alternans and the degree of fibrosis estimated by LGE at cardiac MRI have been suggested as good candidates to improve risk stratification for SD in DCM [115].

Channelopathies

The term 'channelopathies' defines a group of IADs caused by mutations in genes encoding for ion channel proteins or their ancillary subunits. These mutations disrupt the balance of currents in the cardiac action potential, favoring the onset of arrhythmias in the absence of overt structural heart defects, although channelopathies are treated as a subgroup of cardiomyopathies in some classifications [116].

Very recently, the Heart Rhythm Association, the European Heart Rhythm Association and the Asia-Pacific Heart Rhythm Society released new guidelines for the diagnosis and management of patients with 'inherited primary arrhythmia syndromes'. We will refer to this document in our description of the four most common channelopathies [44].

Long QT syndrome

LQTS is characterized by an unusually prolonged ventricular repolarization that facilitates the onset of ventricular arrhythmias [117]. The estimated prevalence of LQTS among most ethnic groups approaches 1 in 2000 for its autosomal-dominant variant, the 'Romano–Ward syndrome' [34]. An autosomal-recessive

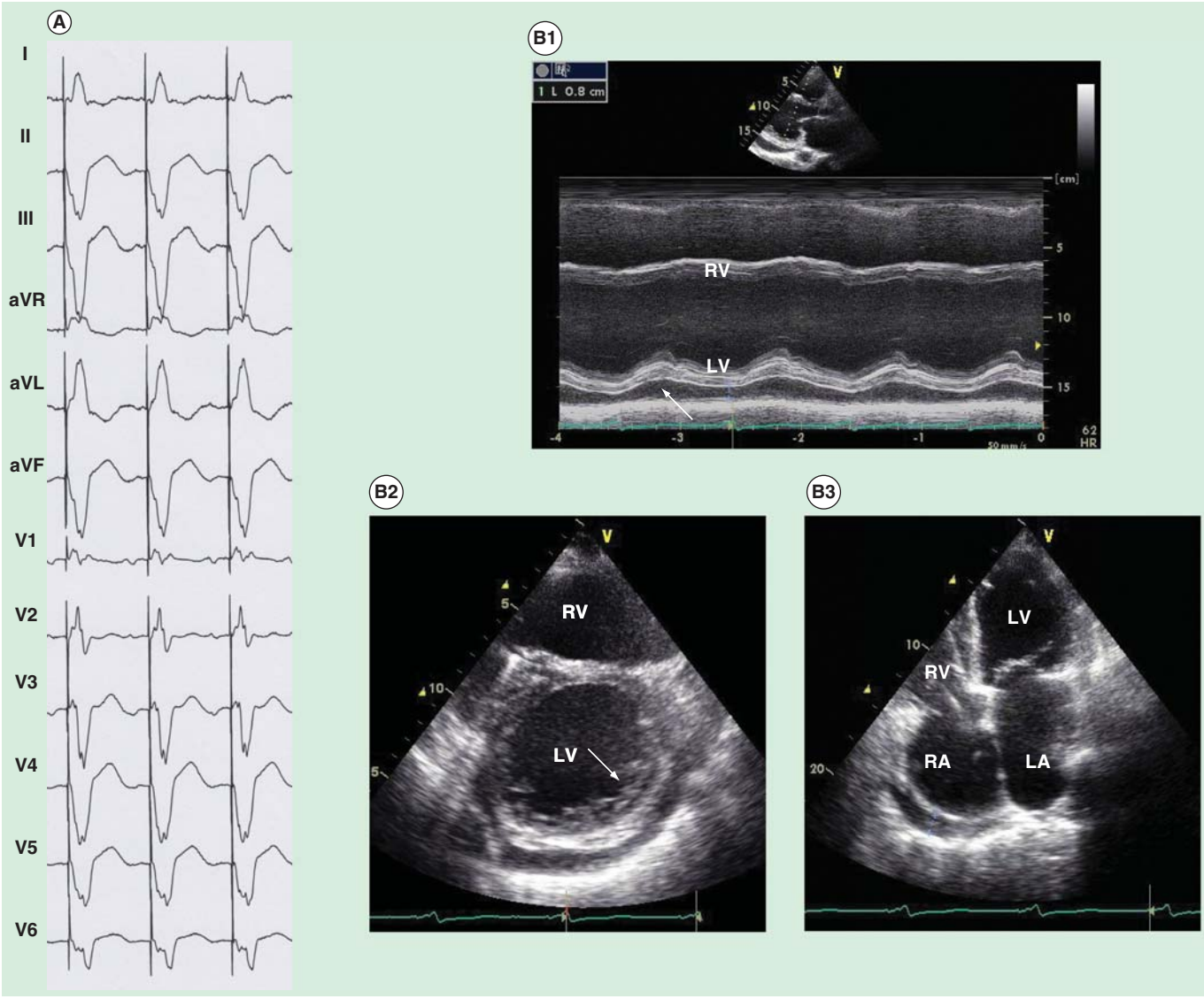

Figure 3. Dilated cardiomyopathy. 12-lead ECG and trans-thoracic echocardiogram of a 67-year-old lady with end-stage dilated cardiomyopathy and a family history of sudden death. A dual-chamber pace maker had been implanted at the age of 57 due to second-degree atrioventricular block, when only a mild left ventricular dysfunction was present. The genetic analysis subsequently revealed a nonsense mutation in the *LMNA* gene. **(A)** The ECG shows sinus rhythm with paced ventricular beats. **(B1)** Monodimensional echocardiogram showing a severely enlarged (end-diastolic diameter of 66 mm) and grossly hypokinetic left ventricle (ejection fraction 25%), with normal wall thickness. A mild posterior pericardial effusion is also evident (arrow). **(B2)** Short axis parasternal view showing an enlarged left ventricle with thin walls and hypertrabeculated myocardium in the inferoposterior aspect of the ventricle (arrow). **(B3)** Apical four-chamber view showing severe biatrial enlargement. Diastolic parameters were significantly elevated, suggesting severe diastolic dysfunction. Pericardial effusion is evident behind the right atrium.
LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle.

form of LQTS also exists, the 'Jervell and Lange-Nielsen syndrome' [118]. This is extremely rare, reaching the highest prevalence among Northern Europeans (1 in 200,000 in Norway [119]) and is characterized by an aggressive arrhythmic behavior and congenital deafness.

At least 13 genes have been associated with the dominant form of LQTS, and most of them encode for subunits of potassium, sodium or calcium voltage-dependent ion channels [44]. Genetic screening of these 13 genes allows identification of a disease-causing mutation in more than 75% of LQTS cases. Interestingly, screening the three first recognized genes alone leads to the identification of more than 90% of the disease-causing mutations. These highly important genes are called *KCNQ1, KCNH2* and *SCN5A* and encode for the potassium channels Kv 7.1, Kv 11.1 and the sodium channel Nav 1.5, respectively [41,42,120,121]. These genes clearly play a very critical role in determining the duration of the cardiac action potential that is reflected by the QT interval on surface ECGs.

The clinical manifestations of LQTS are related to a unique form of VT, termed *torsade des pointes* that was originally described

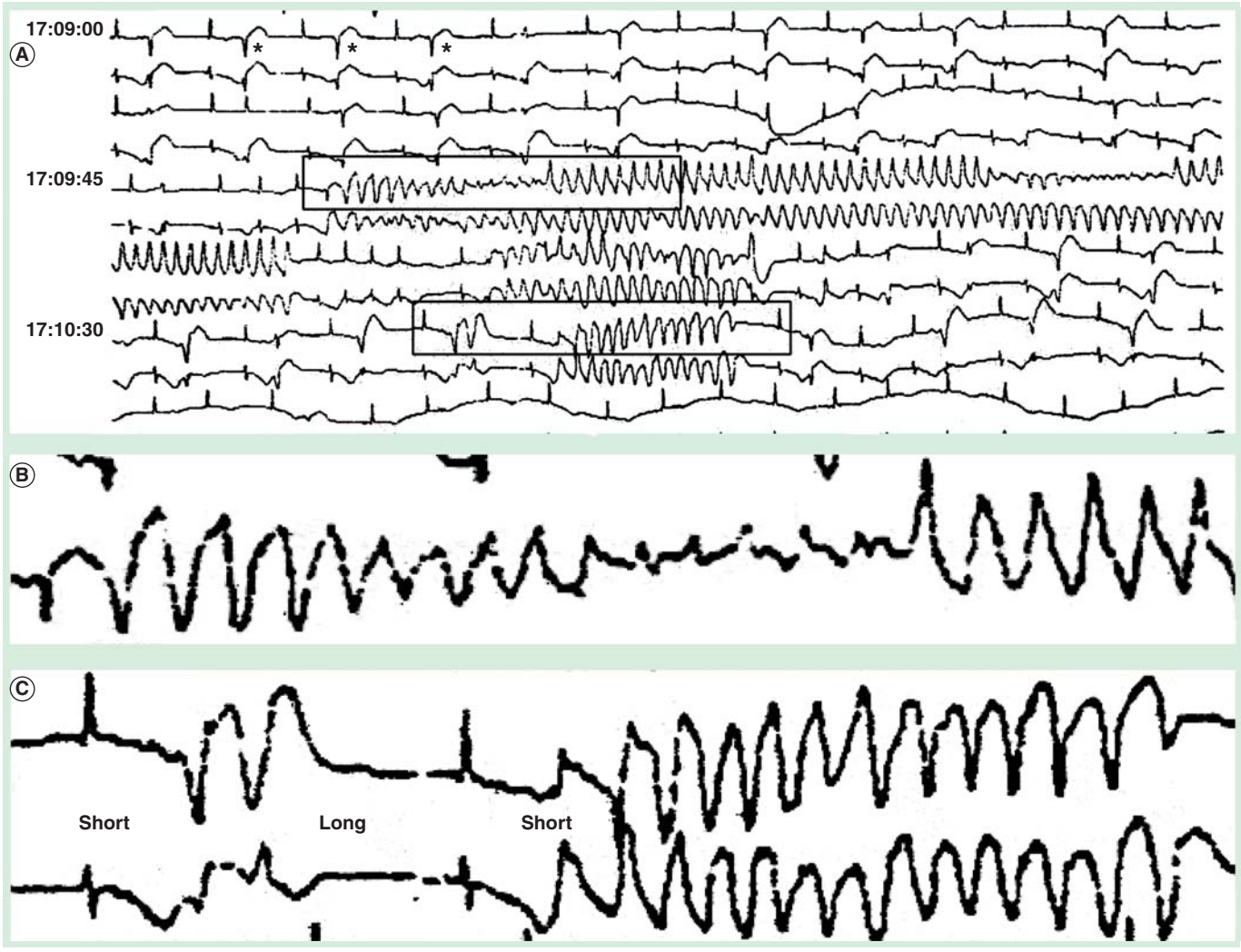

Figure 4. Torsade de pointes in the long QT syndrome. (A) Holter recording showing brief episodes of nonsustained ventricular tachycardia (VT) recorded in a 28-year-old man with Long QT Syndrome (LQT2 with a missense mutation in the *KCNH2* gene) and history of syncope. Bigeminal ventricular beats are evident (*), which trigger the VT (boxed sections). **(B)** Magnification of the sequence highlighted by the first box in figure **(A)**. The ECG trace shows a characteristic 'Torsade de Pointes', with a sequence of consecutive ventricular complexes, the orientation of which reverses direction every few cycles. The amplitude of the QRS complexes varies continuously and progressively around the isoelectric line ([122]). **(C)** Magnification of the sequence highlighted by the second box in figure **(A)**. The ECG trace shows a characteristic 'short–long–short' sequence of extrasystoles that triggers the onset of the VT.

as 'fast bursts of ventricular complexes, twisting by 180° around the isoelectric line' (Figure 4) [122]. Depending on its duration, the arrhythmic episodes may manifest as palpitations, syncopal episodes or CA. Symptoms are commonly triggered by adrenergic stress but, in about 10% of patients, arrhythmias occurs at rest or while sleeping [123]. The mean age of onset of arrhythmic events and syncopal episodes is 14 years [124]: the earlier the onset of arrhythmia, the more severe the prognosis [125,126].

The diagnosis of LQTS is based mainly on the measurement of the QT interval corrected for heart rate (QTc) using Bazett's formula. According to recently released guidelines [44], LQTS may be diagnosed in patients with syncope and QTc more than 480 ms. In the absence of symptoms, a QTc more than 500 ms is required to establish the diagnosis. In cases with less evident QT prolongation, a multiparametric score has been created that combines the age of the patient, the family history, the symptoms and the QTc duration and provides a probability of the diagnosis of LQTS [127].

Interestingly, up to 1/3 of carriers of a pathogenic mutation may fail to show prolongation of QT interval, underscoring the importance of genetic testing for identification of the disease. These individuals, however, continue to have a higher risk of arrhythmic events than the general population [39] and as a result, the use of β-blockers in this subgroup is advocated in the recent guidelines [44].

Clinically, a history of aborted CA or syncope [128] remains the strongest predictor for recurrent arrhythmic events in LQTS. Conversely, in asymptomatic individuals, the QT

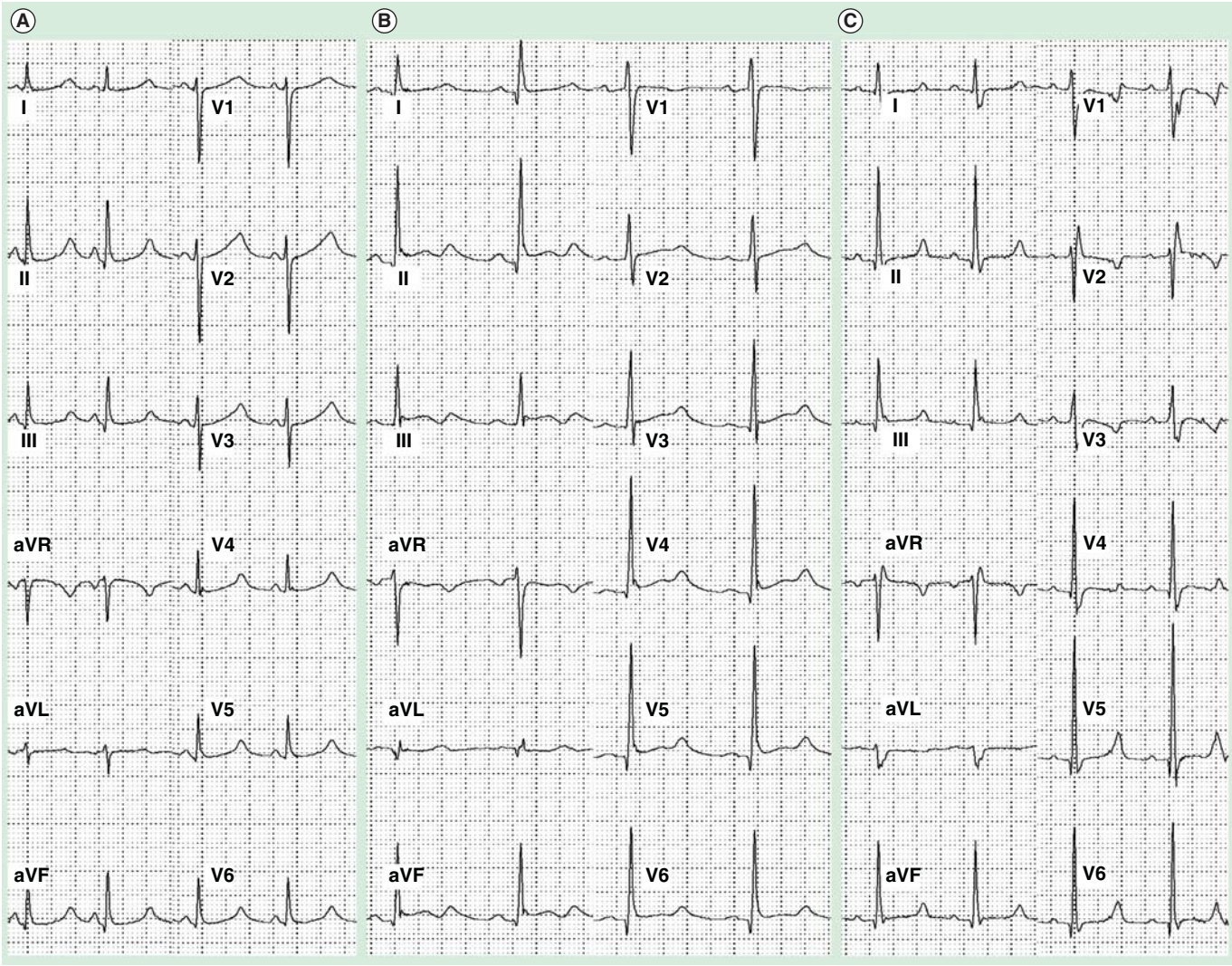

Figure 5. Long QT syndrome. 12-lead ECG patterns of different long QT (LQT) syndrome genotypes. **(A)** LQT1. ECG from a 15-year-old girl with recurrent syncope and a nonsense mutation in the *KCNQ1* gene. RR 730 ms, QT 440 ms, QTc 520 ms. A broad-based, smooth, T wave is present in precordial leads V1–V3. The ascending limb of the T wave is particularly accentuated. In the remaining leads, a late-onset T wave is evident. **(B)** LQT2. ECG from a 62-year-old man with recurrent syncope, coronary artery disease and a missense mutation in the *KCNH2* gene. RR 1100 ms, QT 580 ms, QTc 553 ms. Widespread, low amplitude, bifid T waves are the hallmark of the LQT2 genotype. **(C)** LQT3. ECG from an asymptomatic 9-year-old boy with a missense SCN5A mutation. RR 811 ms, QT 483 ms, QTc 536 ms. A PR interval of 160 ms (upper normal limits for the age) and interventricular conduction delay with right bundle branch block appearance is evident. Late-onset, peaked T waves with a steep upstroke are characteristic of the LQT3 patients.

interval itself is the most important indicator of risk [124], whereby patients presenting with QTc more than 500 ms are considered at high risk for arrhythmias and SCD [39].

The genetic background is also an important indicator of risk. It was initially observed that specific ECG patterns were found in patients with the three most common genetic variants of LQTS (Figure 5) [129]. Subsequently, it was noted that the triggers for CA were specific for each genetic subtype: emotional stress or physical exertion in LQT1 (related to *KCNQ1* mutations), sudden arousal or loud noise in LQT2 (*KCNH2* mutations) and bradycardia in LQT3 (*SCN5A* mutations) [123]. Finally, data emerged to define a gene-specific profile for the risk of SCD [39,130]: LQT1 patients are in the lowest risk category, while LQT2 and LQT3 have significantly higher risk of having cardiac events [39]. Additionally, recent advances in the field have correlated mutations in specific regions of a protein to the severity of the disease [131–134], and even some selected mutations themselves have been identified as highly malignant (e.g., the Ala341Val mutation in the *KCNQ1* gene) [135].

Therapeutic approaches for LQTS patients start from lifestyle modification and extend to drugs (i.e., β-blockers and, in selected patients, sodium channel blockers), cardiac denervation and ICDs [44]. Lifestyle changes include the avoidance of drugs that can prolong the QT interval (an updated list is available on the web at [136]) and the avoidance of triggers for arrhythmias (e.g., intense physical exercise).

β-Blockers have demonstrated their efficacy in protecting most patients from dangerous ventricular arrhythmias and have

dramatically changed the natural history of the disease [125,137]. Genotypic data have also emerged to help personalize therapy. Among the three most common genotypes, β-blockers are maximally effective in LQT1 patients, moderately effective in LQT2 and variably effective in LQT3 patients. As a result, in the latter combination, therapies could be necessary (e.g., with mexiletine, flecainide or ranolazine) [125,138,139].

A minority of LQTS patients continues to present with recurrent symptoms even while on therapy and become candidates for more aggressive therapeutic strategies including left cardiac sympathetic denervation [140] and ICD. Of interest, the 2013 guidelines [44] contraindicate the implantation of an ICD in asymptomatic LQTS patients who are β-blocker therapy naive.

Short QT syndrome

SQTS may be regarded as the antithesis of LQTS, since the former results in an abbreviated duration of cardiac repolarization, constituting both the diagnostic indicator and the substrate for the development of dangerous arrhythmias [49,141–143]. The disease is extremely rare with an estimated prevalence of less than 1 in 10,000.

Five genes encoding for potassium (*KCNH2*, *KCNQ1, KCNJ2*) and calcium (*CACNA1C* and *CACNB2*) conducting channels have been related to SQTS [42]. Interestingly, three of these genes are also associated with three variants of LQTS (LQT1, LQT2 and LQT7). This apparent peculiarity, wherein mutations of the same genes may result in both abnormally prolonged and abnormally shortened repolarization, has actually a fairly straightforward biophysical explanation. Mutations responsible for LQTS cause a decrease (loss of function) in the potassium current conducted by the ion channels encoded by the genes *KCNQ1, KCNH2* and *KCNJ2* (Figure 6). Conversely, mutations responsible for SQTS cause an increase (gain of function) in the current conducted by the same potassium channels, thus shortening repolarization.

Although five genes have been linked to SQTS, the yield of genetic screening is extremely low and each of these genes accounts for less than 5% of SQTS index cases [42,49].

The natural history of SQTS has been recently characterized in greater detail: the disease appears to be highly lethal in all age groups, including children in their first months of life [49,144], and the probability of a first CA by the age of 40 years is greater than 40%. The diagnosis of SQTS relies on the finding of a 'shorter than normal' QT value, but diagnostic thresholds are still debated. In general, QTc values of less than 360 ms combined with symptoms or familial history of SD at a younger age are suggestive for the disease. Individuals with QTc shorter than 340/330 ms should also be considered affected even if asymptomatic [44]. An important caveat is that the QT interval should be measured when the heart rate is close to 60 b.p.m., in order to avoid misdiagnosis related to over or under correction when using the Bazett's formula [145].

Risk stratification in SQTS is not clear at this point. At variance with LQTS, a relation between QT interval shortening and increased susceptibility to arrhythmias has not been demonstrated in the clinical setting [37,49] nor has there been any

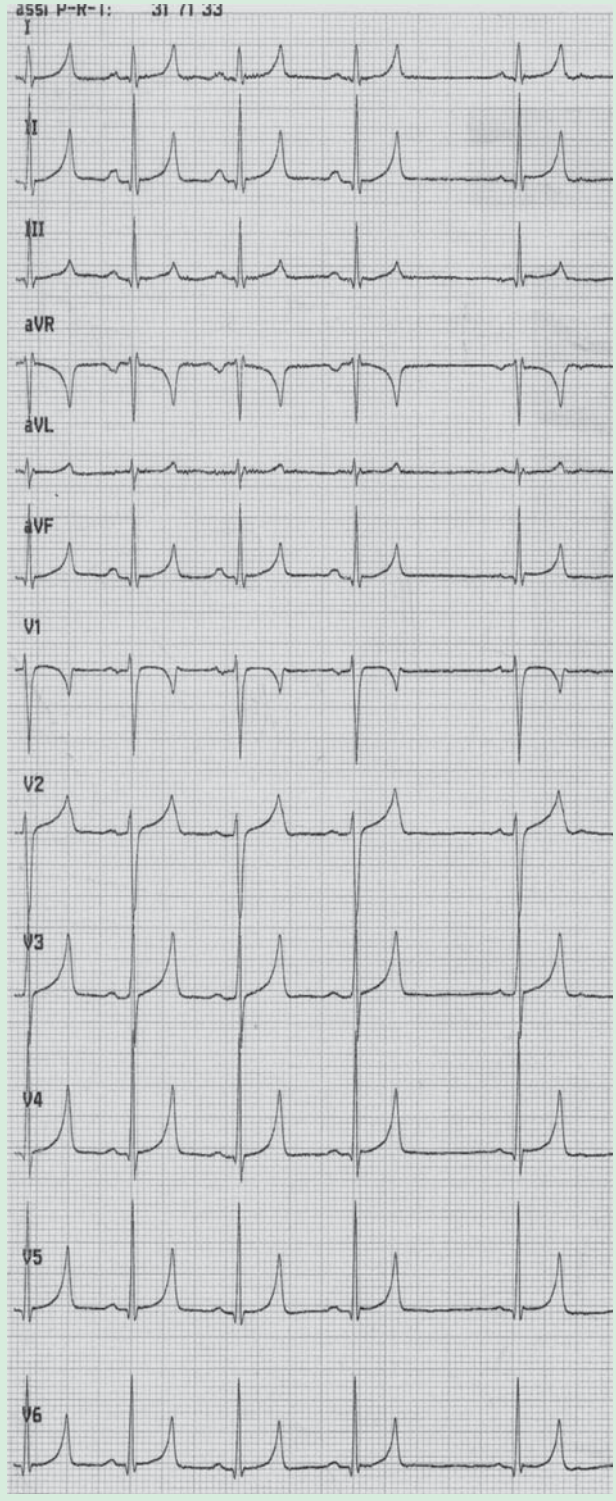

Figure 6. Short QT syndrome. 12-lead ECG from a 16-year-old girl with recurrent palpitations. The genetic screened revealed a missense mutation in the *KCNJ2* gene [183]. RR interval 1000 ms, QT/QTc interval was 330ms. On this trace (variability related to sinus arrhythmia), the T wave was noticeably narrow, peaked and asymmetrical with a rather normal ascending phase and a remarkably rapid terminal phase.

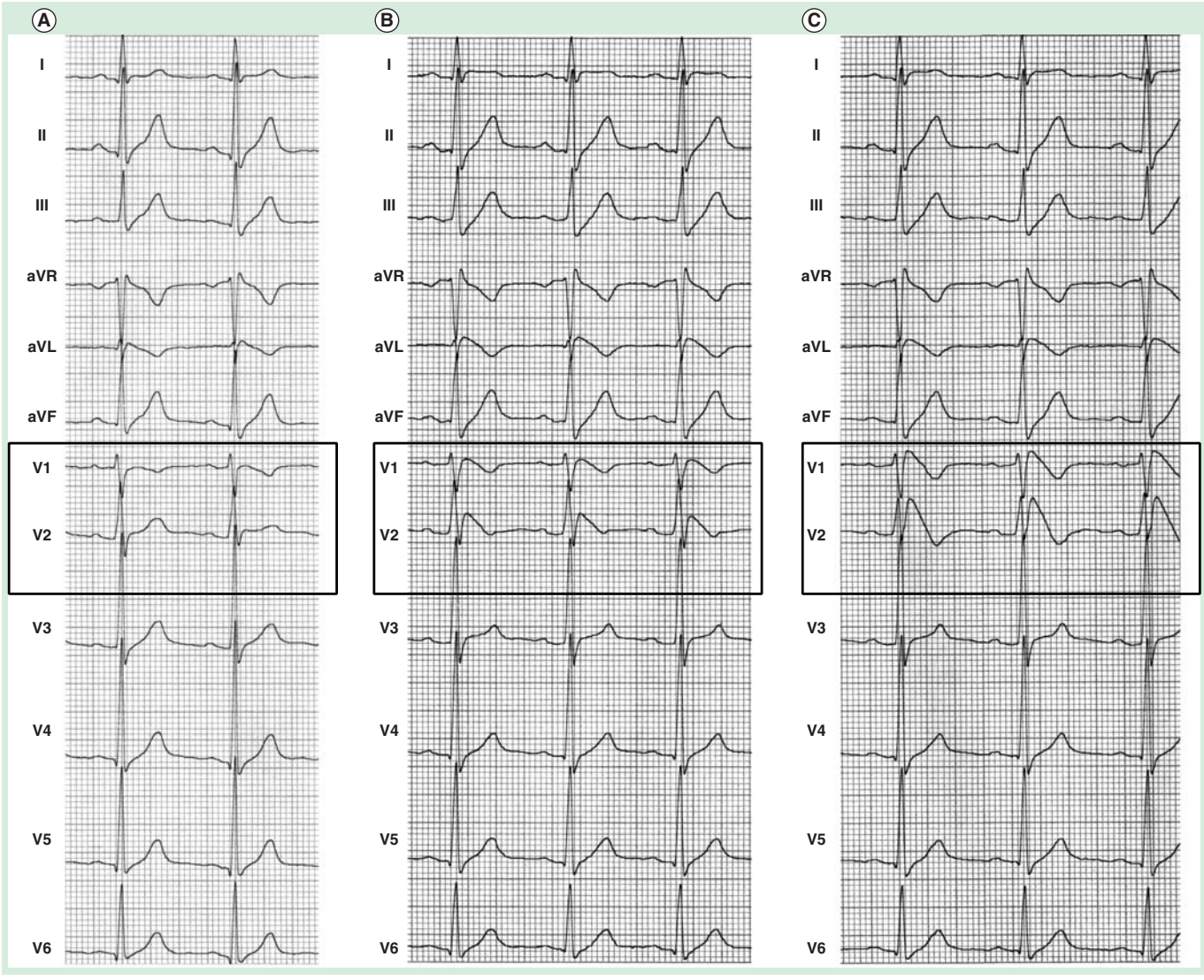

Figure 7. Brugada syndrome. 12-lead ECG from a 35-year-old asymptomatic man with Brugada Syndrome. **(A)** Basal ECG showing negative T wave in lead V1, but no significant ST segment elevation in the right precordial leads (V1 and V2 – Boxed section). **(B)** ECG showing occurrence of coved ST segments in leads V1 and V2 characteristic of type 1 Brugada pattern after infusion of ajmaline 1 mg/kg (Boxed section). **(C)** ECG with altered right precordial lead position (leads V1 and V2 at the second intercostal space) showing more pronounced type 1 Brugada pattern.
Data taken from [44].

data to support the use of genotype to help assess cardiac risk. Furthermore, no clinical predictors of risk have been identified in asymptomatic individuals. SQTS patients at high risk of SCD (e.g., those who survived a previous CA) should receive an ICD for secondary prevention, because the rate of recurrence of CA is approximately 10% per year [49]. Among pharmacological options to reduce the occurrence of life-threatening arrhythmias, quinidine (a class Ia antiarrhythmic) seems particularly promising, because it may normalize the duration of the QT interval (especially in patients with *KCNH2* mutations) and may also reduce ventricular vulnerability in all SQTS individuals, irrespective of the genotype [37]. Further evidence, however, are needed to validate quinidine use in clinical practice.

Brugada syndrome

Brugada syndrome (BrS) was described in 1992 as a disease diagnosed on the basis of a typical electrocardiographic pattern characterized by a 'right bundle branch block and persistent ST segment elevation in precordial leads V1 to V2/V3 not explainable by electrolyte disturbances, ischemia or structural heart disease' [146]. The ST segment elevation as described by Brugada *et al.* has a coved morphology resembling the fin of a shark (Figure 7).

The prevalence of BrS seems to be much higher in South Asia than in Western Countries; however, the worldwide prevalence is estimated to be as high as 1 in 1000 [35].

In BrS, gender has a strong influence on disease penetrance: it is observed that despite the disease being inherited as an

autosomal-dominant condition equally in both males and females, clinical penetrance of the disease is eightfold higher in men than in women [147]. Several genetic modifiers can explain this skewed manifestation [148,149], while there are suggestions that testosterone may have a strong influence on the expression of the phenotype [150].

At least 12 [151] genes have been associated with BrS [42], but to date, molecular screening yields a positive result in only one-third of patients. Furthermore, only mutations in the *SCN5A* and *CACN1Ac* genes, which provoke a reduction in the inward sodium and calcium currents account for more than 5% of positive cases individually [42].

Few factors that predispose to the development of life-threatening arrhythmias in BrS patients are fever, intake of abundant meals and imbibing excessive alcohol [152–154]. On this basis, it has been recommended that prompt reduction of body temperature during febrile illnesses is a lifestyle adjustment that is critical for patients with a diagnosis of BrS. It is also recommended that an ECG be taken during febrile illnesses, especially in children to define whether the increased body temperature worsens the ECG pattern of ST segment elevation. Most cardiac events occur at rest or during sleep [155]. At variance with other channelopathies that are characterized by the appearance of symptoms in early childhood, in BrS, cardiac events appear after the second decade and continue steadily through adult life [46].

The diagnosis of BrS is not always straightforward as the hallmark ECG pattern of a coved ST segment elevation in leads V1, V2 or V3 (termed 'type 1 ECG') may appear intermittently and therefore multiple ECG recordings are required to establish the diagnosis. In order to facilitate the diagnosis, a provocative pharmacological test performed by intravenous infusion of sodium channel blocking agents may be used to unmask an otherwise concealed disease [44].

As for LQTS, several drugs have been related to an increased arrhythmic risk in BrS and should be avoided (an updated list is available at [156]) [44].

Risk stratification in BrS is currently based on clinical parameters. As for all IADs, patients who survived a CA are at high risk of recurrence and should be treated with an ICD [44,157]. The combined presence of a spontaneous type 1 ECG at baseline and a history of syncope identify subjects at risk of CA [46,48]. More recently, the evidence of fragmented QRS on the right precordial leads [48,158] and very short ventricular effective refractory period have also been identified as useful risk indicators [48].

From a genotype perspective, only preliminary correlations between the type of genetic defect in *SCN5A* and the severity of the disease have been made and still require validation. For example, mutations resulting in a truncated or severely dysfunctional Na^+ -channel might be associated with a worse prognosis compared with mutations that cause only slight alterations in protein function [159].

BrS patients who experience arrhythmic storms [160] may be treated with an isoproterenol infusion that has been found effective in a limited series of patients in an attempt to interrupt the VT/ventricular fibrillation. Quinidine has been proposed as preventive therapy in BrS patients based on encouraging data, showing that it could reduce ventricular vulnerability and ICD shocks in symptomatic patients [161–163]. A clinical trial [NCT00789165] with quinidine in asymptomatic BrS patients is currently ongoing [164], but the drug has been discontinued from production in several countries, therefore, reducing its availability [165]. Very recent findings suggest that catheter ablation over the anterior right ventricular outflow tract epicardium may lead to prevention of arrhythmic storms in BrS patients with recurring episodes [166]. Overall, ICDs remain the mainstay in the treatment of the disease. However, due to the restricted number of indicators for SCD, prognostication is limited and therefore an alternative therapy that could reduce the risk of death is strongly needed. Whether quinidine administration or epicardial ablation represents the future management solutions for intermediate-risk BrS patients remain yet to be seen.

Catecholaminergic polymorphic VT

Catecholaminergic polymorphic VT (CPVT) is an arrhythmogenic disease characterized by adrenergically mediated ventricular arrhythmias, which typically occur during exertion or emotional stress [47,167,168]. The prevalence of the disease is poorly defined, with the most commonly quoted figure being 1 in 10,000. However, this may be falsely low because the diagnosis of CPVT is much more difficult than that of all the other IADs, and therefore it is currently impossible to distinguish between low penetrance and diagnostic failure.

Two CPVT genetic variants are known: an autosomal-dominant one related to mutations in the *RyR2* gene encoding for the cardiac ryanodine receptor [169] and an autosomal-recessive form, resulting from mutations in the *CASQ2* gene encoding for cardiac calsequestrin [170].

Approximately 65% of CPVT index cases carry a mutation in the *RYR2* gene, while the prevalence of *CASQ2* mutations is estimated at approximately 3–5%. Genetic defects in both proteins alter calcium homeostasis in cardiac myocytes and facilitate diastolic calcium release that leads to the development of delayed after depolarizations and subsequent triggered activity that may precipitate supraventricular and ventricular arrhythmias [171,172]. As for LQTS, the recessive form of CPVT is more malignant than the dominant variant [173].

Clinical manifestations of CPVT are stress-induced syncope and CA [47,174]. The mean age at onset of symptoms is 8 years, but there are reports of patients experiencing their first syncope after the age of 40 years. The clinical course is extremely severe as approximately 30% of affected individuals experience symptoms before the age of 10 years, and nearly 60% of patients have at least one syncopal episode before the age of 40 years [47].

A highly problematic aspect in the management of CPVT is the latency between onset of symptoms and clinical diagnosis. The complexity of the diagnosis is further compounded by the fact that, unlike the other channelopathies, CPVT does not present with distinguishing ECG diagnostic markers. On the

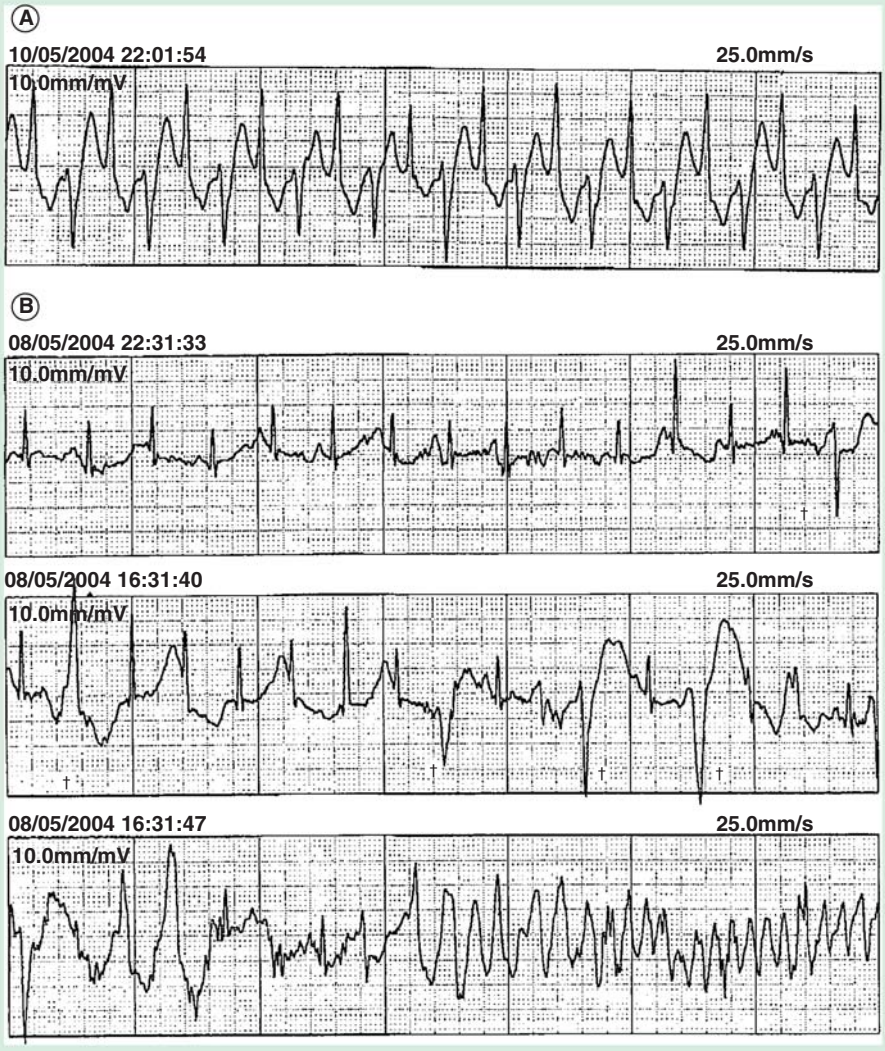

Figure 8. Catecholaminergic polymorphic ventricular tachycardia. Holter recordings from a 16-year-old girl with history of recurrent syncope after emotion and during exercise (swimming) since the age of 10 years. The genetic screening revealed a missense mutation in the *RyR2* gene. **(A)** Trace showing a typical bidirectional ventricular tachycardia, characterized by beat-to-beat alternation of the frontal QRS axis. **(B)** Continuous strips showing sinus tachycardia interrupted by ventricular extrasystolic beats.
†That become more frequent and finally triggering ventricular fibrillation.

contrary, the resting ECG of patients with CPVT is usually normal. Some authors have reported lower-than-normal heart rates [167,175] and prominent U waves in some patients [174,176], but neither finding is sufficiently specific for a diagnosis. Typically, exercise stress testing or strong emotions can elicit a pathognomonic bidirectional or polymorphic VT. The term 'bidirectional' refers to the curious 180° rotation on the frontal plane of the QRS complexes of the ectopic beats (Figure 8) [47,167,174]. Exercise-induced supraventricular tachyarrhythmias are also common in CPVT, ranging from isolated premature atrial contractions to runs of supraventricular tachycardia and bursts of atrial fibrillation [167]. In patients who are unable to exercise, arrhythmias can be reproduced with the infusion of low doses of adrenaline, but there are conflicting results about the sensitivity of this technique [177].

Unfortunately, genetic information has not yet been able to contribute to risk stratification in CPVT patients, but genotype–phenotype correlations are beginning to develop. Current data have shown that relatives with a *RYR2* mutation in the C-terminal channel-forming domain showed an increased risk of nonsustained VT compared with those with N-terminal domain mutations [178].

From the easily demonstrable adrenergic nature of CPVT-related symptoms stems the recognition of β-blockers as the cornerstone of CPVT therapy [174]. After diagnosis, the lack of β-blocker therapy is an independent predictor for arrhythmic events [179]. Discouragingly, despite the appropriate use of β-blockers, up to one-third of CPVT patients experience recurrence of arrhythmic events [47]. In patients who fail to be protected by β-blockers, additional treatments are indicated [47,179]. As in LQTS, left cardiac sympathetic denervation may have a role in some patients, especially in the first few years of life, where implantation of an ICD is associated with a high rate of complications [180]. Additionally, flecainide has been demonstrated as a useful addition to β-blockers to reduce the burden of ventricular arrhythmias. One clinical trial [NCT01117454] [181] is now ongoing to investigate the efficacy of flecainide in addition to standard therapy in patients with an ICD. Until results of the trial become available, ICDs should be considered as the preferred therapy for survivors of CA, patients who continue to experience syncopal episodes despite β-blockers and those who have sustained VT at exercise stress testing. Programming an ICD in CPVT patients requires much care, because all efforts need to be posed in avoiding inappropriate shocks that may have a proarrhythmic effect in this population. Painful shocks by ICD, in fact, can increase the sympathetic tone and trigger further arrhythmias, leading to a malignant cycle of ICD shocks and even death. Because of this, the ICD should be programmed with long delays before shock delivery and high cutoff rates [44].

Expert commentary & five-year view

IADs are a leading cause of SCD that devastates the young and creates great physical and psychological concern for sufferers and their families.

Early recognition of channelopathies and cardiomyopathies allows for the implementation of preventive measures that can dramatically change the clinical course of those affected while providing them and their families the reassurance that they are still able to live fulfilling lives.

A thorough clinical evaluation and a detailed investigation of the family history are the cornerstones that may flag the presence of an IAD. Genetic information, when used rationally, adds important clues to help refine the diagnosis, improve risk stratification in selected cases and also guide therapeutic strategies. The extremely sensitive nature of genetic information, however, requires cautious handling and specifically trained personnel who are able to provide the necessary expertise.

As our knowledge of how genes play a role in the pathogenesis of IADs increases, so will our techniques and methods for identification of causative mutations. The 'holy grail' though continues to be the search for the elusive, 'cure' and therapies aimed at restoring a gene's normal function are likely to represent the next step in the evolution of genetic studies. The future, fortunately, is not as far away as it seems with several promising experimental approaches to 'gene-therapy' currently underway. Results from animal models have been encouraging. One such study, for example, achieved favorable results in the autosomal-recessive form of CPVT related to mutations in the *CASQ2* gene. Our group demonstrated that infection of a viral vector carrying wild-type calsequestrin induces long-term expression of a properly functioning gene in a knockout murine model [182].

One day, diseases like we have described will hopefully become a plague of the past, but till then we need to continue to seek the answers within the walls of our basic building blocks, our DNA.

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Key issues

- Sudden cardiac death in individuals under the age of 40 years have an alarming incidence of up to six events per 100,000 person-years, corresponding to 14,500 deaths in Europe and 10,000 deaths in the USA every year.
- The majority of SCD in the young are due to a group of genetic defects, inherited arrhythmogenic diseases (IADs), which predispose individuals to the development of life-threatening arrhythmias. The genetic nature of IADs implies that when a person is affected, others in the family might be at risk.
- The diagnosis of IADs in the presymptomatic phase is feasible, allowing for preventative measures to be initiated (including lifestyle modifications, medications and devices). Genetic studies may help in uncovering asymptomatic individuals with a concealed phenotype, but who are still at risk of cardiac events.
- Cardiomyopathies are IADs characterized by structural and functional changes in cardiac muscles that enhance the risk for arrhythmias. The most prevalent cardiomyopathies include: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and dilated cardiomyopathy.
- Channelopathies are IADs caused by mutations in genes encoding for ion channel proteins of the cardiomyocytes. These mutations disrupt the balance of currents in the cardiac action potential, favoring the onset of arrhythmias in the absence of structural heart defects. Channelopathies include: long QT Syndrome, short QT Syndrome, Brugada Syndrome and catecholaminergic polymorphic ventricular tachycardia.

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