Inherited cardiac arrhythmias

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Abstract | The main inherited cardiac arrhythmias are long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia and Brugada syndrome. These rare diseases are often the underlying cause of sudden cardiac death in young individuals and result from mutations in several genes encoding ion channels or proteins involved in their regulation. The genetic defects lead to alterations in the ionic currents that determine the morphology and duration of the cardiac action potential, and individuals with these disorders often present with syncope or a life-threatening arrhythmic episode. The diagnosis is based on clinical presentation and history, the characteristics of the electrocardiographic recording at rest and during exercise and genetic analyses. Management relies on pharmacological therapy, mostly β-adrenergic receptor blockers (specifically, propranolol and nadolol) and sodium and transient outward current blockers (such as quinidine), or surgical interventions, including left cardiac sympathetic denervation and implantation of a cardioverter–defibrillator. All these arrhythmias are potentially life-threatening and have substantial negative effects on the quality of life of patients. Future research should focus on the identification of genes associated with the diseases and other risk factors, improved risk stratification and, in particular for Brugada syndrome, effective therapies.

The field of inherited arrhythmic disorders is bursting with novel information and data, ranging from genetic findings to advances in diagnosis and risk stratification to progress in personalized — even gene-specific — management. Currently, the greatest interest and challenge concerns the so-called ion channelopathies — inherited conditions related to primary electrical disorders in the setting of a structurally normal heart. These diseases are caused by mutations in genes encoding ion channels. Of note, other types of inherited arrhythmias exist, such as hereditary atrial fibrillation and arrhythmogenic right ventricular cardiomyopathy. This Primer focuses on the four major channelopathies: long QT syndrome (LQTS), short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome (BrS). These four clinical entities share several features: they have an overall low prevalence, their diagnosis is not always simple and they can be fatal. The fact that all these diseases have the potential to trigger life-threatening arrhythmias increases the responsibilities and the concerns of the clinicians who see patients with these conditions only occasionally owing to their rarity, and are, therefore, often ill at ease in taking clinical decisions that may be difficult or impossible to reverse.

Following a brief overview of epidemiology, genetics and underlying electrophysiological mechanisms, this Primer focuses on the clinical aspects of diagnosis,

risk stratification and therapy, including — whenever appropriate — gene-specific management. The pregnancy-associated risks are considered, as well as the effects of these diseases on the quality of life of the patients. Finally, a large reference section provides the interested readers with the sources for the statements presented in this document.

Epidemiology

Studies investigating sudden cardiac death (SCD) in young individuals (of <35 years of age), conducted in the USA, Denmark and the Netherlands[1–3], have estimated an incidence in this age group of 1.3–3.2 per 100,000 person-years. A 2016 3-year, prospective, population-based study of SCD among persons of 1 to 35 years of age in Australia and New Zealand uncovered a higher prevalence of SCD in males than females and found that SCD occurred predominantly during sleep (38%) or at rest (27%)[4]. At autopsy, a structurally normal heart was found in 40% of cases, suggesting a possible primary electrical disorder caused by ion channel dysfunction, such as LQTS, SQTS and CPVT, as the cause of death[4]. Coronary artery disease and inherited cardiomyopathies were established as probable cause of death in 24% and 16% of cases, respectively[4]. The incidence of SCD in this age group (<35 years) is much lower than that observed in the general population. Studies in the USA and the Netherlands have reported

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a yearly incidence of 0.6 to >1.4 per 1,000 individuals in the general population[5,6]. At the general population level, the average age at SCD is 65 years, around 75% of individuals are male[7], and coronary artery disease and its consequences, including acute myocardial ischaemia and heart failure, are the cause of SCD in about 80% of cases[8].

The cardiac channelopathies that can be associated with SCD are rare, especially SQTS. Systematic population-based studies are lacking, and the real prevalence of these disorders is largely unknown, with the notable exception of LQTS. As a consequence, the numbers reported in articles and reviews, including guidelines (for example, the figure of 1 per 10,000 individuals for CPVT[9]), are at best educated guesses. Regarding LQTS, a prospective electrocardiogram (ECG) study was performed in 44,596 infants of 15–25 days of age (of whom 43,080 were white individuals)[10]. Whenever the first corrected QT (QTc) interval measured exceeded 450 ms, a second ECG was repeated within 1–2 weeks. If QT prolongation was confirmed and QTc exceeded 470 ms (at the beginning of the study) or 460 ms (towards the end of the study, when the cut-off threshold for genetic tests was lowered), genetic analysis was performed. Disease-causing mutations were identified in 29% of the infants with a QTc between 451 and 460 ms and in 49% of those with a QTc >470 ms. Overall, 17 of 43,080 white infants were diagnosed with LQTS, demonstrating a prevalence of at least 1 in 2,534 apparently healthy live births (95% CI, 1 in 1,583 to 1 in 4,350). As genetic analyses were not performed for infants with a QTc between 450 and 470 ms, it was suggested that the actual prevalence of LQTS with a positive ECG phenotype is at least 1 in 2,000 individuals[10].

Founder mutations causing primary electrical disorders have been described in certain geographical regions. For example, LQTS founder mutations have been reported in Finland[11], South Africa[12], Canada[13], the Netherlands[14] and Sweden[15]. In such regions, the prevalence of the disorder is expected to be higher than in other areas. Knowledge concerning ethnic differences

in the prevalence of these arrhythmias is limited, as most of the patient cohorts studied originated from the Western world and, to a lesser extent, from Asian countries. Ethnic differences have been observed for BrS, as ECG studies showed that the prevalence is higher among Asians (0.0–0.94%) and Japanese–Americans (0.15%) than in Europeans (0.0–0.02%) and North Americans (0.005–0.1%)[16]. However, complete figures regarding precise estimates of BrS are lacking, as in individuals with suspected BrS but without a spontaneous type I ECG, the diagnosis cannot be confirmed without additional investigations (such as, for example, drug challenge during ECG recording)[17] (see Diagnosis, screening and prevention).

Mechanisms/pathophysiology

The great majority of genes identified to date as being associated with the primary electrical disorders encode the crucial cardiac ion channel pore-forming α-subunits or proteins that interact with and regulate ion channels (also known as channel-interacting proteins or ChIPs) (FIG. 1; TABLE 1).

LQTS genetics

LQTS is most commonly inherited as an autosomal dominant disorder (initially known as Romano–Ward syndrome). Inherited genetic variations in one of the three major LQTS susceptibility genes underlie the disorder in ~90% of patients in whom a causative mutation was identified. Type 1 LQTS (LQT1), caused by genetic variants in *KCNQ1* (REF.[18]) encoding the subunit $K_V7.1$ of the voltage-gated potassium channel that is responsible for the outward potassium current I_{Ks}, accounts for ~30–35% of cases[19]. LQT2, caused by genetic variants in *KCNH2* encoding the pore-forming α-subunit $K_V11.1$ of the voltage-gated potassium channel responsible for the inward rectifying potassium current I_{Kr}[20], accounts for ~25–40% of cases. LQT3 is caused by genetic variants in *SCN5A*[21] encoding the subunit-α $Na_V1.5$ of the voltage-gated sodium channel responsible for the inward sodium current I_{Na} and represents ~5–10% of cases of LQTS. Approximately 15–20% of patients with a definite clinical diagnosis of LQTS remain genotype-negative after extensive genetic testing[22]. Single-nucleotide variants, small insertions or small deletions are the most commonly encountered disease-causing variations in these genes[19]. However, large gene rearrangements have also been described[23]. About 5% to 10% of patients with LQTS host multiple mutations in these genes, and symptoms typically present at a younger age and with a more severe phenotype in these patients than in patients with a single mutation[24–26].

Genotype–phenotype correlations. Genotype–phenotype studies in the *KCNQ1* and *KCNH2* genetic subtypes have identified relationships between the severity of the disorder and the type of mutation, the location of the mutation and the extent of functional derangement of the ion channel. Studies conducted in patients with *KCNQ1* defects have identified that variants at sequences encoding transmembrane regions of the $K_V7.1$ channel are associated with a higher risk of cardiac events than
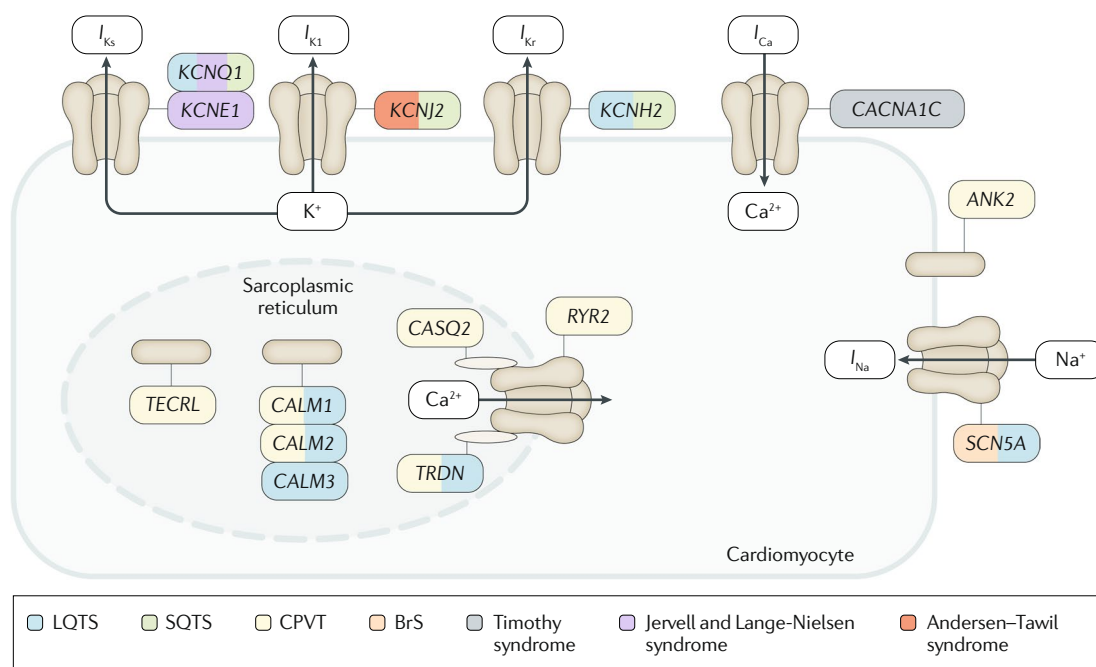
Fig. 1 | **Genes and proteins involved in the pathogenesis of inherited cardiac arrhythmias.** The figure shows the transmembrane ionic channels that are responsible for the potassium (I_{Ks}, I_{K1} and I_{Kr}), calcium (I_{Ca}) and sodium (I_{Na}) currents that contribute to the cardiac action potential. Proteins of the sarcoplasmic reticulum that are involved in calcium handling (encoded by *CASQ2*, *RYR2*, *CALM1*, *CALM2*, *CALM3* and *TRDN*) are also shown. Other proteins that can be mutant in inherited cardiac arrhythmias are encoded by *ANK2* and *TECRL*. The genes that encode all these proteins or their subunits are coloured according to the disease with which they have been associated. BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; SQTS, short QT syndrome.

variants in sequences encoding the carboxy terminus, and variants that result in a severe reduction of channel function due to a dominant-negative effect are also associated with a higher risk of cardiac events than variants that result in haploinsufficiency[25]. In patients with *KCNH2* defects, missense variants in the sequence encoding the pore region of the $K_V11.1$ channel have been associated with more severe clinical manifestations and higher cardiac event rates than those associated with mutations[27] localized outside the pore-coding sequence.

Other LQTS-associated genes. Several other genes encoding either ion channel subunits (*KCNE1*, *KCNE2*, *KCNJ5* and *SCN4B*) or proteins that regulate ion channel function (*CALM1*, *CALM2*, *CALM3*, *AKAP9*, *CAV3*, *ANK2*, *SNTA1* and *TRDN*) have also been implicated in LQTS causality[28]. However, it should be noted that most of these genes have been implicated using a hypothesis-driven, candidate gene approach, and, therefore, the strength of evidence supporting their causality varies widely[28]. In fact, some of these genes received a disputed-evidence (*KCNE2*, *KCNJ5*, *SCN4B*, *SNTA1*, *AKAP9* and *ANK2*) or limited-evidence (*CAV3*, *KCNE1* and *KCNJ2*) gene designation on application of the gene-disease association framework of the Clinical Genome (ClinGen) Resource[28–30]. By contrast, *CALM1*, *CALM2*, *CALM3* and *TRDN* were found to have strong (*TRDN*) or definitive (*CALM1*, *CALM2* and *CALM3*) evidence.
   Patients with LQTS harbouring variants in *CALM1*, *CALM2* or *CALM3* (encoding calmodulin 1, calmodulin

2 and calmodulin 3, respectively) present symptoms early in life with profound QTc interval prolongation, which may be accompanied by 2:1 atrioventricular block and a high predisposition for cardiac arrest and sudden death[31,32]. Calmodulin is a calcium-sensing, signal-transducing protein that regulates many calcium-dependent processes and modulates the function of several cardiac ion channels. *CALM1*, *CALM2* and *CALM3* are located on distinct chromosomes, have a nucleotide sequence homology of 85%, and yet code for a completely identical, 149 amino acid calmodulin protein. Despite this high redundancy, one mutant allele out of six is sufficient to cause LQTS. Relevant information is provided by the International Calmodulinopathy Registry[33] on 74 patients. In a series of 29 patients whose family members were genetically screened, the culprit *CALM* variant occurred de novo in 93% of cases, and in the remaining cases germline mosaicism was present in one of the parents[33]. Patients with homozygous or compound heterozygous pathogenetic variants in *TRDN* may manifest either a predominant LQTS or CPVT phenotype[34,35].

Extracardiac manifestations. Three clinical variants of LQTS manifest with extracardiac features besides QT interval prolongation. The autosomal recessive Jervell and Lange-Nielsen syndrome, characterized by sensorineural deafness and high arrhythmic risk, is caused by homozygous or compound heterozygous mutations in *KCNQ1* (REF.[36]) or *KCNE1* (REF.[37]); *KCNE1* mutations

Table 1 | **Genes frequently associated with inherited cardiac arrhythmias**

Gene	Protein	Function	Associated disorder	Inheritance
KCNQ1	Potassium voltage-gated channel subfamily KQT member 1 (also known as K$_V$7.1)	Subunit of the voltage-gated potassium channel responsible for the I_{Ks} current	LQTS (LQT1)	AD
			Jervell and Lange-Nielsen syndrome	AR
			SQTS (SQT2)	AD
KCNH2	Potassium voltage-gated channel subfamily H member 2 (also known as K$_V$11.1)	Pore-forming subunit of the voltage-gated potassium channel responsible for the I_{Kr} current	LQTS (LQT2) and SQTS (SQT1)	AD
KCNE1	Potassium voltage-gated channel subfamily E member 1	Subunit of the potassium channel responsible for the I_{Ks} current	Jervell and Lange-Nielsen syndrome	AR
KCNJ2	Inward rectifier potassium channel 2 (Kir2.1)	Potassium channel responsible for the I_{K1} current	Andersen–Tawil syndrome and SQTS (SQT3)	AD
SCN5A	Sodium channel protein type 5 subunit-α (also known as Na$_V$1.5)	Subunit of the voltage-gated sodium channel responsible for the I_{Na} current	LQTS (LQT3)	AD
			BrS	Complex inheritance
CALM1	Calmodulin 1	Calcium-binding protein	LQTS and CPVT	AD
CALM2	Calmodulin 2	Calcium-binding protein	LQTS and CPVT	AD
CALM3	Calmodulin 3	Calcium-binding protein	LQTS	AD
ANK2	Ankyrin B	Protein involved in the localization and membrane stabilization of ion transporters and ion channels	CPVT	AD
TRDN	Triadin	Sarcoplasmic reticulum component of the calcium release unit	LQTS and CPVT	AR
CACNA1C	Voltage-dependent L-type calcium channel subunit α1C (also known as Ca$_V$1.2)	Pore-forming subunit of the calcium channel responsible for L-type calcium currents	Timothy syndrome	AD
RYR2	Ryanodine receptor 2	Sarcoplasmic reticulum calcium channel	CPVT	AD
CASQ2	Calsequestrin 2	Component of the sarcoplasmic reticulum calcium release unit	CPVT	AR
TECRL	Trans-2,3-enoyl-CoA reductase-like	Endoplasmic reticulum protein	CPVT	AR

AD, autosomal dominant; AR, autosomal recessive; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQT1, type 1 long QT syndrome; LQTS, long QT syndrome; SQT1, type 1 short QT syndrome; SQTS, short QT syndrome.

are associated with a less severe phenotype than *KCNQ1* mutations[38]. Timothy syndrome presents with multiorgan dysfunction including webbing of fingers and toes, congenital heart defects, immune deficiency, hypoglycaemia, cognitive abnormalities and autism[39]. The same recurrent sporadic de novo missense mutation in *CACNA1C* (encoding the pore-forming subunit-α Ca$_V$1.2 of the voltage-gated cardiac calcium channel that is responsible for long-lasting (L-type) calcium currents), which results in the G406R amino acid substitution, accounts for many of the cases reported to date[40], although other missense mutations in this gene have also been reported. However, mutations in *CACNA1C* have also been described for autosomal dominant LQTS in the absence of extracardiac features[41]. The Andersen–Tawil syndrome, which presents with facial dysmorphism and hypokalaemic periodic paralysis, is caused by dominantly inherited loss-of-function mutations in *KCNJ2*, which encodes the inward rectifier potassium channel Kir2.1 (which is responsible for the I_{K1} current)[42]. Although Andersen–Tawil syndrome was initially presented as part of the LQTS spectrum, it has been argued that the QT interval prolongation in this disorder is erroneously diagnosed by the inclusion of the prominent U wave abnormality in the QTc calculations[28]; accordingly, this arrhythmic syndrome should not be regarded as part of LQTS[28].

U wave
A small deflection immediately following the T wave and usually in the same direction.

SQTS genetics
SQTS is inherited as an autosomal dominant disorder. Mutations in three genes encoding potassium channels, namely, *KCNH2* (REF.[43]), *KCNQ1* (REF.[44]) and *KCNJ2* (REF.[45]), have been implicated in the disorder and are associated with its subtypes SQT1, SQT2 and SQT3, respectively. In contrast to loss-of-function variants associated with LQTS, SQTS-causing variants in *KCNH2*, *KCNQ1* and *KCNJ2* lead to a gain-of-function defect of the affected potassium channel. Mutations in the L-type calcium channel subunit genes *CACNA1C*, *CACNB2* and *CACNA2D1* (REF.[46]) have been described in patients presenting with a shorter than normal QTc or an overlapping phenotype that combines an abbreviated QTc and a BrS ECG phenotype[47], yet evidence for their causality is limited. These mutations are expected to cause a loss of channel function, thereby also abbreviating the action potential (AP). The same missense mutation in *SLC4A3*, encoding the anion exchange protein 3 (also known as solute carrier family 4 member 3), has been described in a large family with SQTS and a smaller, unrelated family[48].

CPVT genetics
CPVT is commonly inherited in an autosomal dominant manner. In 65% of CPVT probands, the disorder is caused by a mutation in *RYR2*, which encodes

the ryanodine receptor 2 (RYR2), a calcium release channel located on the sarcoplasmic reticulum (SR) of cardiomyocytes[49–51], and these individuals have CPVT type 1. *RYR2* mutations are typically missense and cluster predominantly at sequences encoding specific regions of RYR2, although some mutations still occur outside these clusters[52,53]. Mutations in *CASQ2*, which encodes calsequestrin 2, a protein that binds to free calcium inside the SR, cause CPVT type 2, a much rarer but more severe autosomal recessive form of CPVT[54]. Other genes involved in calcium homeostasis, namely *CALM1* (REF.[55]) and *TRDN*[56], have also been implicated as a cause of CPVT. Mutations in *CALM2* have been described in patients with overlapping features of LQTS and CPVT[57]. Mutations in *ANK2* and *KCNJ2* that also cause, respectively, Ankyrin B syndrome (initially called LQT4) and Andersen–Tawil syndrome have been described in a few patients with normal QTc and exercise-induced arrhythmias[58,59]. Furthermore, recessive mutations in *TECRL*, encoding the *trans*-2,3-enoyl-CoA reductase-like protein expressed in the endoplasmic reticulum, have been associated with a clinical phenotype that has overlapping features of LQTS and CPVT[60]. The CPVT genetic test panel should include at least examination of the entire 105 translated exons of *RYR2, CASQ2, KCNJ2, CALM1, CALM2, CALM3, TRDN, TECRL* and *PKP2* (encoding plakophilin 2)[61]. Notably, PKP2-mediated arrhythmogenic right ventricular cardiomyopathy can have a pre-cardiomyopathic electrical phase of the disease that mimics CPVT[62].

BrS genetics

The only gene thus far unequivocally implicated in BrS is *SCN5A*[63,64]. As opposed to LQTS-associated variants, BrS-associated *SCN5A* variants are loss of function. At least 20 other genes have been reported for BrS; however, these genes have almost exclusively been discovered through candidate gene studies in single individuals or small families. Furthermore, the recent reappraisal of all reported BrS susceptibility genes (either by testing for an increased burden of rare genetic variants in patients with BrS compared with controls[65] or by the application of the ClinGen evidence-based gene curation framework[64]) supports only the involvement of rare variations in *SCN5A*, which are found in ~20% of probands[65]. The largely sporadic presentation of the disorder and the low disease penetrance in families with rare variants in *SCN5A*, as well as the observation of phenotype-positive genotype-negative individuals in such families, has suggested that BrS is a disorder with an inheritance more complex than the Mendelian inheritance that was previously considered[66]. A genome-wide association study that identified common small-effect susceptibility variants in the vicinity of *SCN5A* and *HEY2* provided evidence in support of this complex inheritance[67].

Genetic modifiers

As for most Mendelian disorders, the management of patients with Mendelian primary electrical disorders is complicated by the variability in clinical severity among patients, even those carrying the same mutation. Such variability within families is evidenced by low disease

penetrance (the proportion of individuals carrying a variant who show phenotypic effects), variable expressivity (different severity observed among individuals carrying the familial genetic defect) and pleiotropy (the phenomenon of a single gene affecting several phenotypic traits). Variability is observed both in the extent of the ECG abnormality and in the occurrence of arrhythmic events. Cascade screening and genotyping[68,69] has disclosed that variability in clinical manifestations can be profound, even between siblings with the same mutations, ranging from a normal ECG and no symptoms to a full-blown phenotype with life-threatening arrhythmias. An example is the large variability in QTc duration among individuals harbouring the A341V founder mutation in *KCNQ1* causing LQTS[12] (FIG. 2). A study showed a large spectrum of QTc values in a population of individuals carrying this mutation, including some values within the physiological range; if QTc prolongation were determined only by the A341V mutation, the QTc values should be uniformly prolonged with modest variability[12]. This observation points to the presence of additional factors affecting ventricular repolarization.

Factors that modify the clinical expression of Mendelian primary electrical disorders can be non-genetic, such as age, sex[70] and, according to some studies, features of the cardiac tissues, such as, for example, fibrosis. In addition to non-genetic factors, the inheritance of other genetic variants, commonly referred to as genetic modifiers, contributes to the variability in the phenotype[71]. Genetic modifiers may exacerbate or temper the effect of the disease-causing mutation, and the net effect of the mutation and genetic and non-genetic modifiers determines the severity of the ECG defect and/or occurrence of arrhythmias.

Research into genetic modifiers in these primary electrical disorders is still in its infancy, yet some associations have started to emerge[71], primarily in LQTS[71]. Moreover, the mechanism of action of modifier genes is beginning to be unravelled[72]. The identification of these associations has been in part facilitated by the availability of large founder populations, wherein the presence of the same disease-causing mutation favours the identification of modulatory variants, as it enables the exclusion of interindividual variation stemming from different primary genetic defects[73–76]. As more modulatory variants are identified, combined genotyping for disease-causing mutations as well as for modifiers may enable more refined risk stratification.

Pathophysiology of the individual arrhythmias

Characteristics of the cardiac AP. The cardiac cell, similar to all excitable cells, maintains a voltage difference between the exterior and interior of the cell — the membrane potential — of typically −60 to −90 mV, depending on the cell type. Thus, the interior of the cell has a negative voltage relative to the exterior. When the voltage-gated sodium (in atrial and ventricular cardiomyocytes) or calcium channels (in nodal cardiac cells) open, the membrane depolarizes (the membrane potential becomes more positive), giving rise to an AP. The cardiac AP has a key role in coordinating the contraction of the heart. The cardiac cells of the sinoatrial
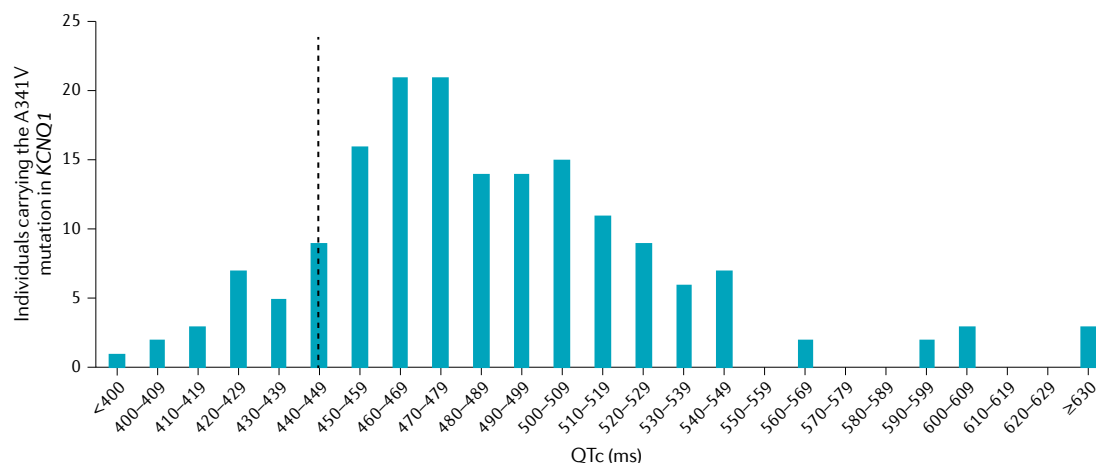
Fig. 2 | **Variability in baseline QTc.** Distribution of the duration of heart rate corrected QT interval (QTc) in individuals who carry the same *KCNQ1* mutation and who belong to a LQT1 South African founder population. The vertical dashed line represents the upper limit of normal values for men (440 ms). If the QTc prolongation were determined only by the A341V mutation, the QTc values should be uniformly prolonged with modest variability. The large spectrum of QTc values points to the presence of additional variants affecting ventricular repolarization. Data from REF.[12].

node provide the pacemaker potential, which determines the heart rate. The APs of these cells propagate through the atria to the atrioventricular node, which is normally the only conduction pathway between the atria and the ventricles. APs from the atrioventricular node travel through the bundle of His and then to the Purkinje fibres system to activate the ventricles in an orderly fashion. Abnormalities in the cardiac AP (due to congenital mutations, exposure to toxins or drugs or injury) can lead to the development of cardiac arrhythmias.

There are four phases to the cardiac AP in the contracting atrial or ventricular cardiac cells (FIG. 3). The sharp depolarization (phase 0) is due to inward movement of sodium ions, whereas repolarizations (phases 1 and 3) are principally due to outward movement of potassium ions. During the phase 2 plateau period, the cells are maintained in a depolarized state achieved through a balance between the inward movement of calcium ions and the outward movement of potassium ions.

SDR as a common link in arrhythmogenesis. The four channelopathies thus far discussed differ with respect to the characteristics of the QT interval. In LQTS and in SQTS, the QT interval prolongs or shortens, respectively, as a result of the disease, whereas in BrS and early repolarization the QT interval remains largely unchanged or abbreviates. However, these four syndromes have in common an amplification of the spatial dispersion of repolarization (SDR)[77], which results in the development of polymorphic ventricular tachycardia (VT) and fibrillation when dispersion of repolarization and refractoriness reach the threshold for reentry. When polymorphic VT occurs in the setting of long QT, it is referred to as Torsades de Pointes according to its specific morphology. The threshold for reentry decreases as the AP duration and refractoriness are reduced and the conduction path length required for establishing a reentrant depolarization wave is progressively reduced[77]. Of note, the conduction path length required for establishing reentry is also importantly influenced by conduction velocity, such

that reentry is facilitated when conduction is slowed. It has to be said that the hypothesis supporting a major role of SDR has largely originated from experiments in canine wedge preparations[78], with interpretations that are not uniform; indeed, several electrophysiologists have different views as to the arrhythmic substrate in some of these conditions[79].

LQTS. In LQTS[80–82], a reduction of net repolarizing current secondary to loss of function of outward potassium channel currents or gain of function of inward currents underlies the prolongation of the myocardial AP and QT interval that attend both congenital and acquired LQTS[83–85]. Acquired LQTS is most of the time secondary to drugs that have an I_{Kr}-blocking effect[86]. Accentuation of SDR and refractoriness within the ventricular myocardium, secondary to exaggerated trans-septal or transmural dispersion of repolarization, has been identified as the principal arrhythmogenic substrate in LQTS[87,88]. This exaggerated intrinsic heterogeneity together with early afterdepolarization-induced triggered activity, both caused by a reduction in net repolarizing current, underlie the substrate and trigger the development of Torsades de Pointes observed in LQTS[87]. The mechanism underlying Torsades de Pointes has been a matter of debate for many years. In addition to reentrant activity, early afterdepolarization-mediated focal activity has been proposed. Although short episodes of Torsades de Pointes may be due to focal activity, longer and non-terminating episodes are always maintained by reentrant activity[89].

SDR is further exaggerated by sympathetic influences, especially in LQT1 and LQT2, accounting for the great sensitivity of these patients to adrenergic stimuli. It is important to keep in mind that neurally mediated sympathetic activation acts through release of noradrenaline at the neural terminals in the ventricles, which has consequences different from those produced by blood-borne catecholamines, and the effects of noradrenaline as a neurotransmitter are different from those produced by circulating catecholamines. Locally

released noradrenaline increases the heterogeneity of repolarization and facilitates ventricular fibrillation[90]; this effect is very different from that of adrenaline and, experimentally, of isoprenaline (a β-adrenergic receptor agonist).

SQTS. SQTS is an extremely rare channelopathy, characterized by pathologically accelerated repolarization resulting in very short QT intervals and the appearance of tall peaked T waves on the ECG. The augmented T_{peak}–T_{end} interval associated with this ECG feature suggests that SDR underlies the arrhythmogenic substrate in the ventricles. Experimental studies suggest that the abbreviation of AP duration in SQTS is heterogeneous, owing to preferential abbreviation in the epicardium and resulting in an increase in SDR. Dispersion of repolarization and refractoriness serve as substrate for reentry, as they promote unidirectional conduction block. Marked abbreviation of wavelength is an additional factor promoting the maintenance of reentry. Abbreviation of AP duration and effective refractory period and amplification of SDR also predispose to the development of atrial fibrillation by creating the substrate for reentry[91].

Recent studies involving computational modelling of SQTS[92], induced pluripotent stem cell cardiomyocytes (iPS-CMs) isolated from patients with SQTS that recapitulate the SQTS cellular phenotype[93–96] and data from a transgenic rabbit model of SQT1 have provided useful insights into arrhythmogenesis and arrhythmia

substrates in SQTS consistent with previous findings. Nevertheless, there is no clear understanding of the mechanism underlying the premature ventricular contractions (PVCs) that precipitate polymorphic VT in SQTS.

CPVT. Mutations in RYR2, calsequestrin 2 (a calcium-binding protein that acts as a calcium buffer within the SR), calmodulin and triadin, which underlie CPVT, all lead to abnormal regulation of cellular calcium homeostasis[97,98]. This disruption leads to excessive calcium accumulation (overload) in the SR and spontaneous release of calcium from the SR in the cytoplasm, causing augmentation of transient inward current and the development of delayed afterdepolarizations. Several lines of evidence point to delayed afterdepolarization-induced triggered activity as the mechanism underlying monomorphic or bidirectional VT in patients with CPVT. Sympathetic influences greatly amplify the calcium dysregulation, leading to precipitation of episodes of CPVT during exercise and accounting for the responsiveness of patients to β-adrenergic receptor blockade and sympathetic denervation[99,100].

Several studies have reported that abnormal calcium handling can result from missense mutations or post-translational modification, including oxidation and *S*-nitrosylation, and several plausible mechanisms have been proposed — for example, defective RYR2 interaction with peptidyl-prolyl *cis–trans* isomerase (FKBP) proteins owing to phosphorylation of RYR2 at serine 2808 by cAMP-dependent protein kinase A, phosphorylation of RYR2 at serine 2814 by calcium/calmodulin-dependent protein kinase type II, store overload-induced Ca^{2+} release, defective intrasubunit domain interaction in RYR2 (domain unzipping) or disruptions in calsequestrin 2 (REF.[53]). Finally, defective calmodulin binding to RYR2 has also been shown to be crucial to induce CPVT[101–103].

The ectopic activity originating from the epicardium is associated with an increased T_{peak}–T_{end} interval and augmented SDR due to reversal of the normal activation sequence across the ventricular wall. The increased SDR in turn creates the substrate for reentry, permitting the induction of polymorphic VT[104]. Propranolol (a β-adrenergic receptor blocker) and verapamil (an L-type calcium channel blocker) suppressed all arrhythmic activity in experimental wedge preparations[104]. Thus, an accentuation of SDR may play a key part in the transition of bidirectional VT to polymorphic VT and ventricular fibrillation in the setting of CPVT. However, a different conclusion comes from a study in transgenic mice, which provided evidence that the His–Purkinje system can be an important source of delayed afterdepolarization-induced triggered activity giving rise to focal arrhythmias in CPVT[98,105]. Currently, we are left with these two hypotheses.

BrS. Prominent J waves in the ECG are associated with BrS and early repolarization. The electrocardiographic J wave is the result of a transmural voltage gradient created by the presence of a transient outward potassium current (I_{to}) mediated by the potassium voltage-gated channel
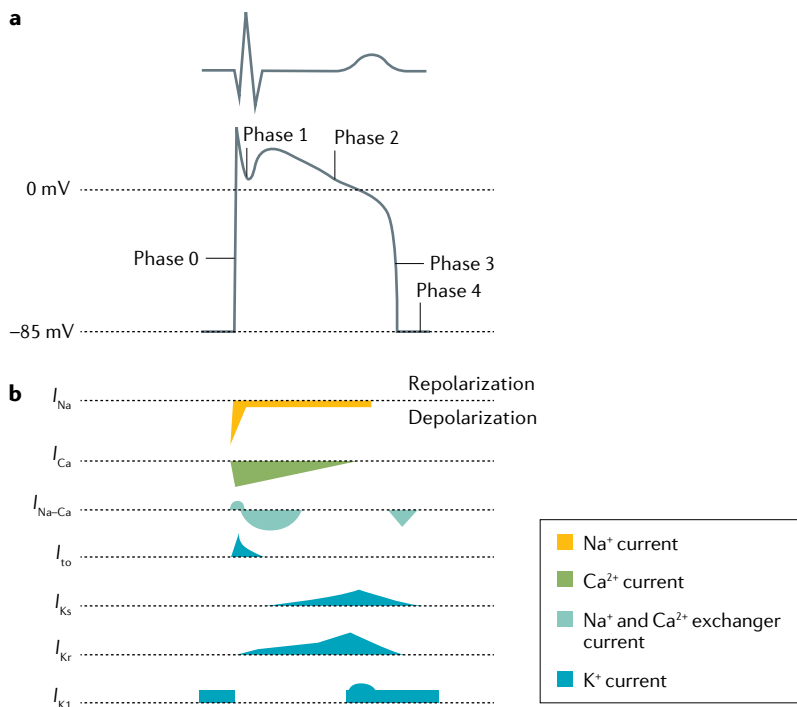
Fig. 3 | **Ventricular action potential and ionic currents. a** | Schematic showing a normal electrocardiogram trace and the corresponding phases of the ventricular action potential (0, 1, 2, 3 and 4) that determine the shape of the trace. **b** | The major transmembrane ionic currents that generate the ventricular action potential. Inward currents that contribute to depolarization are oriented downwards, and outward currents that contribute to repolarization are oriented upwards; the shapes of the currents indicate their relative intensity. I_{to}, transient outward potassium current.

Legend for b:
- Na⁺ current
- Ca²⁺ current
- Na⁺ and Ca²⁺ exchanger current
- K⁺ current

Labels in a: Phase 0, Phase 1, Phase 2, Phase 3, Phase 4, 0 mV, −85 mV

Labels in b: I_{Na}, I_{Ca}, $I_{Na–Ca}$, I_{to}, I_{Ks}, I_{Kr}, I_{K1}, Repolarization, Depolarization

subfamily D member 3 (also known as $K_V4.3$) creates a notch in the shape of the AP — that is, in the first part of phase 2, in the ventricular epicardium but not the endocardium[106–108] (FIG. 4). The transmural gradient and associated J wave is much greater in the right ventricle than in the left ventricle, particularly in the region of the right ventricular outflow tract (RVOT), because of a more prominent I_{to}-mediated AP notch in the right ventricular epicardium[109]. This distinction explains why BrS is a right ventricular disease. The RVOT origin of BrS could also be attributed to the reduced expression of gap junctions and sodium channels[110]. By contrast, in the left ventricle, I_{to} is most prominent in the inferior wall, accounting for why early repolarization occurs in the left ventricle, with the most prominent J point elevation appearing in the inferior ECG leads[111]. The cellular mechanism underlying early repolarization is similar to that of BrS[111]. The principal difference is the region most involved in generating the arrhythmogenic substrate: the epicardial cells in the left ventricular inferior wall are most susceptible to early repolarization owing to a high density of $K_V4.3$ channels[111]. Using ECG imaging techniques, a study demonstrated markedly abbreviated activation–recovery intervals and marked dispersion of repolarization in the inferior and lateral regions of the left ventricle in patients with early repolarization[112]. However, recent epicardial mapping data demonstrate abnormal conduction (fractionated epicardial signals

— that is, multiple deflections in the QRS complex) in 75% of the patients with early repolarization[79]. The authors concluded that these data demonstrate that two distinct substrates — delayed depolarization and abnormal early repolarization — underlie inferolateral J wave syndromes (A.A.M.W.). This interpretation is challenged by data showing that, in experimental models of the J wave syndromes, fractionated ECGs giving rise to J waves are due to delayed repolarization, as discussed below (by C.A.).

The ionic and cellular mechanisms underlying BrS have long been a matter of debate[113,114]. Two principal hypotheses have been proposed, the repolarization hypothesis and the depolarization hypothesis. These two hypotheses are next presented by their two proponents, respectively C.A. and A.A.M.W. These arguments and observations notwithstanding, it stands to reason that the repolarization and depolarization hypotheses are not mutually exclusive and may indeed be synergistic. The repolarization hypothesis, also alluded to in the previous paragraph, asserts that an outward shift in the balance of currents at the end of phase 1 of the right ventricular epicardial AP, due to genetic mutations in genes encoding ion channels, generates the BrS ECG phenotype and the underlying repolarization abnormalities (that is, a heterogeneous loss of the epicardial AP dome) responsible for the development of both the epicardium to endocardium gradient and transmural SDR. These repolarization
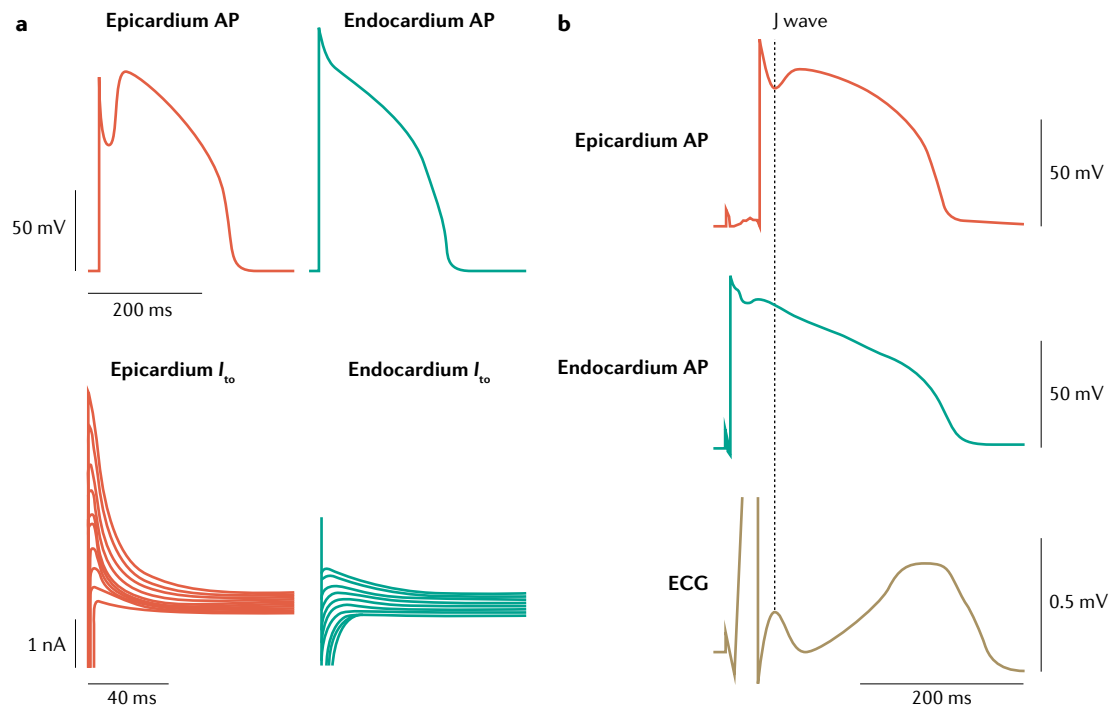
Fig. 4 | **Spatial dispersion of repolarization. a** | A prominent transient outward current (I_{to}) is responsible for phase 1 of the action potential (AP), giving rise to a prominent AP notch in the epicardium but not in the endocardium, where this current is relatively small. **b** | The presence of a prominent notch in the epicardium but not the endocardium gives rise to a transmembrane voltage gradient. Heterogeneous transmural distribution of the I_{to}-mediated AP notch is responsible for the inscription of the J wave on the electrocardiogram (ECG). Part **a** adapted from REF.[253], Liu, D. W., Gintant, G. A. & Antzelevitch, C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. *Circ. Res.* **72**(3), 671–687 (https://www.ahajournals.org/journal/res). Part **b** adapted from REF.[108], Yan G. X. & Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* **93**(2), 372–379 (https://www.ahajournals.org/journal/circ).

abnormalities could lead to the development of reentry during phase 2 of the AP, thereby generating closely coupled premature beats, which can trigger polymorphic VT or ventricular fibrillation. By contrast, the depolarization hypothesis maintains that fibrosis and reduced expression of gap junction α1 protein (also known as connexin 43) and sodium channels in the RVOT[110] lead to discontinuities in conduction that are responsible for the development of the ECG and arrhythmic manifestations of BrS.

C.A. In BrS, the amplitude of J waves, typically appearing as type I ST segment elevation, diminishes at fast heart rates, owing to reduced availability of I_{to}, consistent with the repolarization hypothesis[113,115]. The ability of agents such as quinidine (a sodium channel blocker and a blocker of I_{to}) to reduce ST segment elevation and exert an ameliorative effect in BrS is likewise attributable to a reduction in I_{to}. These observations lend support to the repolarization hypothesis, as does the demonstration of a lack of conduction delay in the RVOT in a whole heart experimental model of BrS[116] and the demonstration of an ameliorative effect following radiofrequency ablation of RVOT, a procedure that destroys the epicardial cells with the most prominent I_{to}-mediated AP notch[117–119].

A.A.M.W. In every debate on the pathophysiological substrate of the ST segment elevation in the right precordial ECG leads, the ability of quinidine to reduce ST segment elevation is prominently mentioned (see also the previous paragraph). This argument seems valid, given that the sodium blocking activity of quinidine is expected to be detrimental (that is, increasing the level of ST segment elevation), but it is also important to consider that the AP morphology is a crucial determinant for the safety of conduction. This factor is particularly relevant in areas where conduction is potentially hampered — for example, in areas with substantial fibrosis (such as the RVOT in patients with BrS)[119] and in Purkinje–ventricular junctions. Hence, every intervention that alters the AP morphology (for example, decreases in I_{to} or any other early potassium current or an increase in I_{Ca}, among others) can improve the safety of conduction[120,121] and, therefore, can be compatible with the depolarization hypothesis. Quinidine blocks I_{to} and, therefore, can increase the safety of conduction in regions in which conduction is compromised.

Diagnosis, screening and prevention
Clinical manifestations
LQTS. Patients with LQTS may remain without symptoms throughout their life or may become symptomatic. Most symptomatic patients have their first arrhythmic event during the first 20 years of life, individuals with LQT1 or Jervell and Lange-Nielsen syndrome earlier than those with LQT2 or LQT3; at variance with males, females remain at risk throughout life[122] . The main clinical manifestations are syncopal episodes, cardiac arrest and SCD[123,124]. These events are due to Torsades de Pointes VT, which often degenerates in ventricular fibrillation. The occurrence or absence of arrhythmic events in a patient with a disease-causing mutation does not

predict what may happen in their offspring[125], with the exceptions of specific genetic variants that are associated with very high[126] or very low[127] clinical severity.

Most symptomatic patients show a distinct prolongation of the QT interval, which is often accompanied by a bizarre morphology of the T wave[128,129]. The arrhythmic risk increases significantly when QTc is >500 ms (REF.[70]) and especially when episodes of T wave alternans are observed[130]. Specific triggers for arrhythmic events in patients with LQTS have been identified; namely, swimming, running, unexpected noises (such as the telephone ringing, an alarm clock and thunder) or being frightened[131]. The identification of the LQTS-associated genes has revealed that, at variance with all other channelopathies, there is a strong genotype–phenotype correlation in the three LQTS subtypes, a correlation that is especially important for the recognition of the conditions that may trigger the arrhythmias[122]. Patients with LQT1 are at increased risk whenever sympathetic activity increases, as during emotional or physical stresses, especially swimming[122,132]. Patients with LQT2 are at increased risk when exposed to sudden noises, especially if they are at rest or asleep and are woken up abruptly; of note, sleep is not a homogeneously quiet state, as during rapid eye movement sleep there are bursts of both vagal and sympathetic activity that can be quite arrhythmogenic. Individuals with LQT2 are also very sensitive to low plasma levels of potassium, and female patients are at high risk during the postpartum period[133,134], probably because of sleep disruption. Finally, patients with LQT3 are at risk primarily when they are at rest or asleep. Independently of the genotype, infants who have a cardiac event in the first year of life are at an especially high risk of mortality and often are not protected by the traditional therapies[135]. LQTS, as well as all other channelopathies, can contribute to sudden death in infancy. Almost 10% of infants who die suddenly in the first year of life carry LQTS-causing mutations[136,137], and a prolonged QT interval in newborn babies increases the risk for sudden death[138]. It is evident that, without genetic testing, an infant who died suddenly in the first months of life would be labelled as a case of sudden infant death syndrome[139,140]. These data have conceptual implications. On one hand, they strengthen the rationale for widespread ECG screening in the first month of life[10,138], with the objective to identify infants with LQTS who are at risk of dying in the first year of life or later[141]; on the other hand, they call for great restraint before assuming that recurrent sudden deaths in infancy always imply infanticide.

SQTS. To date, just over 200 patients have been reported to have SQTS, and most clinical data come from two relatively large studies[142,143]. In both studies, a male predominance was reported, but the risk of cardiac arrest was similar in both sexes. Although the majority of patients with SQTS are symptomatic, SQTS may also be diagnosed in asymptomatic patients during family screening or as an incidental finding during routine ECG or during sport pre-participation screening. One study[142] reported the long-term outcome of 53 patients with SQTS from the European Short QT registry (75% male, median

T wave alternans
Beat-to-beat variation in the polarity or amplitude of T waves; this phenomenon indicates an unevenness in the refractoriness of the myocardium and points to elevated cardiac electrical instability.

age 23 years, follow-up period 64 ± 27 months); 62% of patients were symptomatic at presentation. The most common presenting symptom was cardiac arrest (33%). Most cardiac arrest events (>90%) occurred between 14 and 40 years of age in male patients. Thirteen patients (24%) had palpitations, and in six of these patients atrial fibrillation or atrial flutter were documented; eight patients (15%) had syncope. Atrial fibrillation was noted already in newborn babies and young children.

The second study[143] included 73 patients with SQTS (84% male; mean age 26 ± 15 years, follow-up 60 ± 41 months); 53% of patients (n = 39) were symptomatic at presentation, and SCD or non-fatal sudden cardiac arrest (40%) were the most common presenting symptoms[143]. The second most common symptom was syncope (19%). The rate of cardiac arrest was 4% in the first year of life. The annual event rate was 1.3% between 20 and 40 years of age, and 40% of patients experienced a cardiac arrest by 40 years of age (cumulative probability of an annual event rate 0.9%). There was no reported trigger of cardiac arrest, and in 83% of patients cardiac arrest occurred during rest.

CPVT. Phenotypically, CPVT most closely mimics LQT1, with adrenergic-triggered syncopes, seizures, sudden cardiac arrest or SCD. In fact, many patients with CPVT had been previously misdiagnosed with either atypical LQTS or exercise-triggered epilepsy[49,99]. Although CPVT can manifest at any time, sentinel events are most likely to occur during the first two decades of life and are uncommon after 40 years of age. Thus, CPVT should be suspected in any patient with a structurally normal heart and a normal resting ECG with a normal QT interval who experiences a sudden faint, seizure or cardiac arrest during exercise, exertion or emotional stress (positive or negative). In fact, in these settings, CPVT would be more plausible as the root cause than LQT1 with a normal QT interval.

Although it has been reported, CPVT is rarely the cause of sudden infant death syndrome[136,137,144]. By contrast, CPVT is one of the most common genetically identifiable explanations for sudden unexplained death in individuals of 1–35 years of age in whom autopsy results did not show structural heart defects, especially if the death occurred during exertional activity, particularly swimming[145,146]. In an otherwise unexplained drowning or near drowning, CPVT should be explored as a possibility. In addition, CPVT should be investigated in patients diagnosed previously with an exertion-triggered generalized seizure disorder, especially if the epilepsy diagnosis had been accompanied by a normal electroencephalogram. CPVT also contributes to idiopathic ventricular fibrillation as shown in a genetic study in 76 survivors that documented that disease-causing mutations were present in 7% of cases[147].

BrS. The most frequent clinical manifestations of BrS include a type 1 ECG (see Diagnosis) and malignant ventricular arrhythmias[148,149], more specifically rapid polymorphic VT or ventricular fibrillation, typically initiated by extrasystoles from the RVOT region. Rarely, isolated ectopic beats (most commonly with a left bundle branch block or inferior axis deviation morphology on the ECG) or non-sustained ventricular arrhythmias are observed. However, some patients with BrS may report syncopal events, which are probably caused by self-terminating arrhythmias and lead to an increased risk of malignant arrhythmias (see below). Arrhythmic events occur typically during the night[150]. Supraventricular arrhythmias, most often atrial fibrillation, have been recognized as part of the BrS phenotype since they were first described as a separate clinical entity[148]. The prevalence of atrial fibrillation may be as high as almost 40% in certain cohorts[151]. The first symptoms typically occur in the third to fourth decade of life (both in men and women); however, they can also occur in children and in individuals of >50 years of age[152]. Fever is a specific trigger for symptoms, particularly in the paediatric subgroup[153,154]. Males are more frequently affected than females, as shown by every study.

Three morphologies of the BrS ECG pattern have been described. Type 1 is characterized by a high J point with a coved-type ST segment in the right precordial ECG leads, often followed by a terminal negative T wave. Type 2 ECG has a saddle-back-shaped ST segment, with an elevation of ≥2 mm, and type 3 has a saddle-back type or a coved ST segment with an elevation of <2 mm. Another characteristic ECG feature is the presence of minor conduction delay at all cardiac levels, manifested by slight PR prolongation, QRS widening (fractionation) and an abnormal electrical axis, which can be either leftward (manifesting with a wide "S" in lead I) or rightward. Conduction delay occurs in particular in the presence of a loss-of-function sodium channel mutation[155], which underlies the disease in approximately 20% of cases[156].

Risk stratification in asymptomatic patients with BrS is ill defined. Most studies are retrospective in nature, and no single parameter, with the exception of a spontaneous (that is, not induced by administration of sodium channel blockers or fever) type 1 ECG, has consistently been shown to predict risk of malignant arrhythmias[157]. An asymptomatic patient with a spontaneous type 1 ECG has a yearly risk of ~1% to present with malignant arrhythmias, and such risk may or may not be considered sufficient to warrant the implant of an implantable cardioverter–defibrillator (ICD), whereas the risk in symptomatic patients is ~3–7% per year, depending on the presenting symptom. Probably the most reliable risk factor is a (progressive) fractionated ECG in the right precordial leads[157]. Programmed electrophysiological stimulation (that is, stimulation of the heart by intracardiac catheters following a predesigned stimulation protocol) may help to estimate the risk, provided a low-intensity protocol is used[158].

Diagnosis

LQTS. The diagnosis of typical cases (such as a youngster who experienced a syncope during emotional or physical stress and has a prolonged QT interval) is quite straightforward. The upper limits of normal QTc (with Bazett's correction) are 440 ms for males and 460 ms for females. The normal mean QTc is 400 ± 20 ms. Accidental diagnoses are often triggered

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Electrical axis
The net direction of the depolarization activity, resulting from the sum of all the electrical vectors on ECG.

Box 1 | **1993–2011 long QT syndrome diagnostic criteria**

ECG findings

Electrocardiogram (ECG) findings can be included in the score in the absence of medications or disorders known to affect ECG features. Corrected QT (QTc) is calculated by Bazett's formula, in which $QTc = QT/\sqrt{RR}$.

- QTc 450–459 ms (in male individuals) (1 point)
- QTc 460–479 ms (2 points)
- QTc ≥480 ms (3 points)
- QTc on fourth minute of recovery from exercise stress test ≥480 ms (1 point)
- Torsades de Pointes (2 points)
- T wave alternans (1 point)
- Notched T wave in three leads (1 point)
- Resting heart rate below the second percentile for the patient's age (0.5 point)

Clinical history

- Syncope[a] with stress (2 points)
- Syncope[a] without stress (1 point)
- Congenital deafness (0.5 point)

Family history

- Family members with definite long QT syndrome (LQTS) diagnosis[b] (1 point)
- Unexplained sudden cardiac death before 30 years of age among first-degree relatives[b] (0.5 point)

  A score of ≤1 point indicates a low probability of LQTS, a score of 1.5–3 points indicates an intermediate probability of LQTS, and a score of ≥3.5 points indicates a high probability of LQTS.

[a]Mutually exclusive. [b]Mutually exclusive. Adapted from REF.[160], Schwartz P. J. & Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. *Circulation* **124**(20), 2181–2184 (https://www.ahajournals.org/journal/circ).

by medical visits and ECG ahead of participation in sports, especially in countries such as Italy where these visits are mandatory by law. In asymptomatic individuals, especially when the QT interval is only modestly prolonged, the diagnosis is more complex and requires experience and additional tests. To help clinicians, a diagnostic score has been developed and upgraded over the years[80,124,159,160] (BOX 1). The accurate measurement of the QTc duration at rest is most informative both for diagnosis and prognosis. More and more frequently the so-called tangent method is used, on the basis that it facilitates the identification of the point where the descending limb of the T wave crosses the baseline. However, this method is actually misleading whenever the descending limb of the T wave has a slow component, which happens often when there is an impairment of I_{Ks} and I_{Kr}. The tangent method can, therefore, lead to an underestimation of the QT interval and should not be used when there is a suspicion of LQTS. The morphology of the T wave is also indicative, especially in the precordial leads, and often suggests the probable underlying genotype (FIG. 5). The exercise stress test almost never induces arrhythmias, at striking variance with CPVT, but can provide three important pieces of information about QT interval adaptation (or lack of it) to R–R interval shortening, T wave changes in the first minutes of recovery[161,162] — both useful parameters to support the diagnosis of LQTS — and the rapidity of the reduction in heart rate during the first minute following cessation of exercise[163], which is important

for risk stratification. The 24-h, 12-lead Holter ECG recording provides almost invaluable information, especially about cardiac activity during the night, because it is typical of LQTS to present even gross, albeit sudden and brief, changes in T wave morphology. Finally, in several patients, there are specific mechanical alterations, which can be identified by echocardiography[164–169].

Since the late 1990s, genetic testing has not only aided the diagnosis of LQTS but has also enabled the identification of the specific genotype and family members of patients who also carry the causative mutation (and are therefore at risk) but have a borderline QT interval duration and would probably escape diagnosis and not receive protective measures. Of course, the results of genetic tests must be interpreted correctly, and physicians who care for these patients should know the difference between a disease-causing mutation and a variant of uncertain significance[170]. Once the disease-causing mutation has been identified in the proband, the entire family should undergo cascade genetic screening, which, within 2–3 weeks, can identify the relatives who are genotype-positive and those who are genotype-negative[68,69].

SQTS. The hallmark of SQTS is a very short QT interval. SQTS was initially recognized in patients with a QTc <300 ms. Subsequently, patients with slightly or moderately shortened QT intervals (≤360 ms) and similar clinical presentations were also described[47,142,171,172]. Several population and cohort studies showed that the prevalence of individuals with QTc <360 ms is very low. In a large Finnish cohort, the prevalence of patients with a QTc <340 ms was 0.4%, and that of patients with a QTc <320 ms was 0.1%[173]. In a paediatric population, the prevalence of QTc ≤340 ms was 0.05%[174]. These studies revealed that short QT interval alone was not associated with increased risk of arrhythmic events. Thus, the cut-off value of QT interval for defining SQTS remains a matter of debate, as there is an overlap between healthy individuals and patients with SQTS. In the 2015 guidelines of the European Society of Cardiology[175], a cut-off value of QTc ≤340 ms was recommended for the diagnosis of SQTS (class I, level of evidence C). SQTS should be also considered in patients with QTc ≤360 ms in the presence of one or more of the following factors: a confirmed pathogenetic mutation; a family history of SQTS; a family history of sudden death before 40 years of age; and non-fatal VT or ventricular fibrillation episodes in the absence of structural heart disease (class IIa, level of evidence C).

Owing to the impaired QT adaptation to heart rate changes in patients with SQTS, experts recommend measuring the QT interval on ECG with a heart rate between 50 and 70 beats per min. Other prevalent ECG patterns that could be helpful in establishing the diagnosis of SQTS include PQ segment deviation (observed in 81% of patients with SQTS), a pattern of tall and symmetrical T waves with a very short or missing ST segment, early repolarization (in 65% of patients with SQTS), frequent presence of apparent U waves (especially in precordial leads) and impaired adaptation of the QT interval during exercise[176–180]. Furthermore,
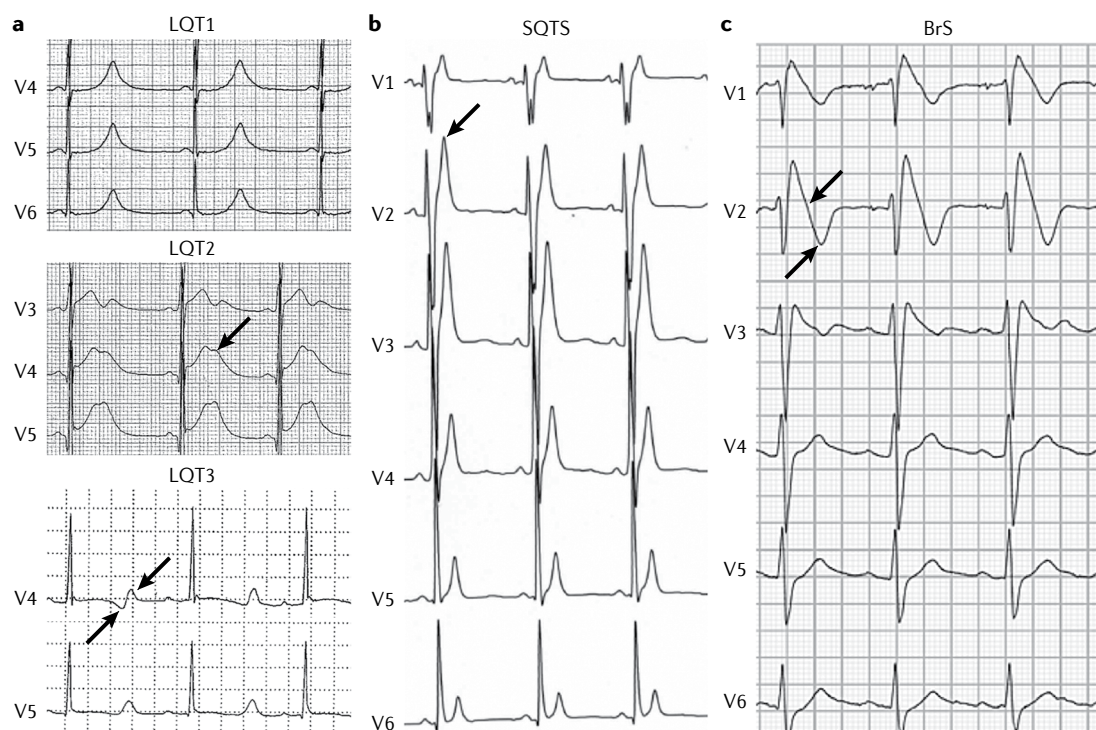
Fig. 5 | **Examples of ECG traces. a** | Example of electrocardiogram (ECG) traces of patients with long QT syndrome (LQTS). In LQTS type 1 (LQT1), the QT interval is extremely prolonged, with a tall peaked T wave. In LQT2, a very prolonged QT interval is present, with a clear and typical notch on the T wave (arrow). In LQT3, a very prolonged QT interval is followed by a late-onset diphasic (arrows) T wave. **b** | In a patient with short QT syndrome (SQTS), the QT interval is extremely short, with a tall peaked T wave (arrow). **c** | A patient with Brugada syndrome (BrS) has an ECG trace with a typical type 1 pattern. There is a coved-type ST segment (arrow) in the right precordial leads followed by a terminal negative T wave (arrow).

overlapping syndromes have been described in patients who had non-fatal sudden cardiac arrest and presented with a BrS-like ECG pattern and a shorter than normal QT interval. As in LQTS, genetic testing is recommended for patients with suspected SQTS. However, similarly to BrS, a causative mutation is identified only in ~20% of cases and, therefore, genetic test results must be interpreted very carefully.

CPVT. In a child, adolescent or young adult with the clinical manifestation described earlier, CPVT should always be considered. In CPVT, the heart is virtually always structurally normal, and, in fact, identification of a structural abnormality should rule out a CPVT diagnosis. Similarly, the 12-lead ECG at rest is essentially normal in CPVT[99,181]. The diagnosis of CPVT is established in a clinically symptomatic patient who has a structurally normal heart by cardiac imaging and a normal ECG at rest but an abnormal exercise stress test (FIG. 6). The appearance during exercise of bidirectional VT is regarded as pathognomonic for CPVT. Although bidirectional VT provoked in this setting is extremely specific for CPVT, it is seen only rarely.

The characteristic stress test profile of most patients with CPVT involves normal sinus rhythm at rest, with the onset of single ventricular extrasystoles (PVCs) starting when the sinus heart rate reaches ~110–130 beats per minute. As the heart rate increases, the single

PVCs (which often originate from the RVOT) increase in frequency and then progress to PVCs in bigeminy. Next, the bigeminal pattern gives way to PVC couplets, including bidirectional couplets, and then occasionally non-sustained VT, polymorphic VT and, rarely, bidirectional VT at higher heart rates. Sometimes, the arrhythmic pattern that manifests during exercise often ceases at the highest heart rates, and normal sinus rhythm then persists throughout the recovery phase, or, if arrhythmia persisted at the highest heart rates, the arrhythmia ceases almost immediately in the recovery phase. Accordingly, in the patient with a history consistent with CPVT and normal echocardiography and ECG, the presence of exercise-induced arrhythmia in the pattern described that culminates in bidirectional PVC couplets means that the diagnosis of CPVT is very likely to be correct, even though bidirectional VT did not occur.

In a patient with suspected CPVT on the basis of clinical manifestations and cardiological testing, CPVT genetic testing is indicated[22]. The vast majority of CPVT cases stem from pathogenetic missense variants in *RYR2*, and a rare missense variant can be identified in 60–70% of patients with a robust clinical diagnosis of CPVT[52]. Of note, a rare missense variant in *RYR2* can also be found in 3% of healthy, asymptomatic individuals[52]. In other words, when the clinical evidence for a CPVT diagnosis is compelling, identification of a rare missense

Bigeminy
Heart rhythm characterized by two beats close together with a pause following each pair of beats; the first beat in the pair is the sinus beat, whereas the second one is a premature contraction. Bigeminy rhythm is often associated with the sensation of the heart skipping a beat.

PVC couplets
Two premature ventricular contractions (PVCs) in consecutive heart beats.

variant in *RYR2* has at least a 20:1 chance of being the pathogenetic mutation of CPVT type 1. In accordance with the 2013 HRS/EHRA/APHRS guidelines, the identification of a CPVT type 1 causative mutation is deemed equivalent to a clinical diagnosis of CPVT that should compel cascade, variant-specific genetic testing of all appropriate relatives and the possible initiation of prophylactic β-adrenergic receptor blocker therapy even in asymptomatic family members with a normal stress test who are positive for the variant[9].

BrS. BrS is diagnosed in the presence of a characteristic ECG pattern including a spontaneous type 1 pattern with a coved ST segment elevation in one or both of the right precordial leads V1 and V2, positioned in the second, third or fourth intercostal space[17]. A type 1 ECG is mandatory for the diagnosis; only when a type 2 or type 3 ECG converts into a type 1 pattern (that is, with a drug test) can the diagnosis of BrS be made. As described earlier, type 1 morphology reflects a coved-type ST elevation of ≥2 mm (0.2 mV) in the right precordial leads followed by a negative terminal ST segment[182] (FIG. 5). In the absence of a spontaneous abnormal ECG with the V1 and V2 leads in the standard positions, the diagnostic
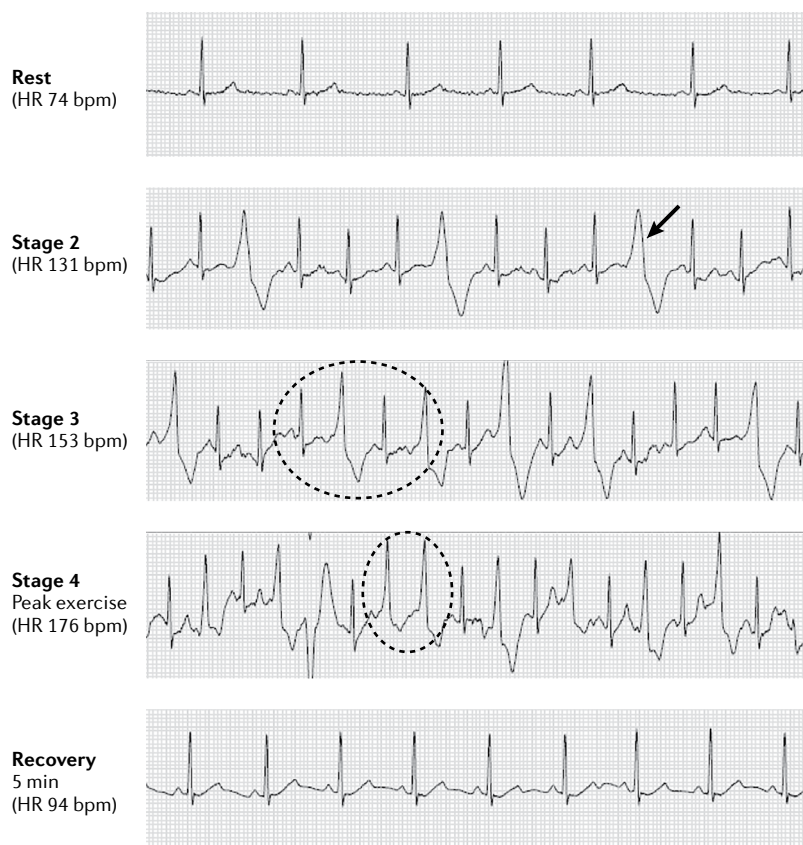
sensitivity of the ECG can be increased by placing the right precordial leads higher, administering a sodium channel blocker (the drug challenge test, with ajmaline being the most effective drug, although the sensitivity and specificity of these tests is unknown) or increasing the vagal tone (that is, by recording the ECG after the patient has had a meal or exercised)[183]. These procedures (preferably a drug challenge test or, alternatively, a 'heavy meal test' or exercise test) should be performed in any patient with a reasonable suspicion of BrS with a non-diagnostic baseline ECG. Additional clinical criteria are required to reach the diagnosis in cases in which a type 1 ECG is only observed after drug challenge test or during fever[17], and a 12-lead 24-h Holter ECG recording performed at regular intervals can be useful. Of note, several differential diagnoses are possible even when the ECG shows the typical type 1 form[184].

Management
Pharmacological therapy
LQTS. The pharmacological therapy of LQTS is rather straightforward. With very few exceptions (see below), β-adrenergic receptor blockers should be given to every diagnosed patient, because the risk of a fatal first event is high. The only two β-adrenergic receptor blockers that are effective beyond doubt are propranolol and nadolol[124]. Metoprolol should not be used[185], as it is not effective; concerns about efficacy exist also for atenolol[186], and available data about the other β-adrenergic receptor blockers are insufficient. There is no justification to risk the patients' lives with drugs of uncertain efficacy. The few patients in whom not starting β-adrenergic receptor blocker therapy may be considered are asymptomatic males with LQT1 off therapy by 25 years of age[122] and genotype-positive but phenotype-negative (that is, with a normal QTc) individuals. Incorrect considerations have led for several years to the misconception that β-adrenergic receptor blockers would not be useful, and potentially dangerous, for patients with LQT3; it is now evident that these drugs are very effective also for these patients[135,187].

The understanding of the mechanism of action of *SCN5A* mutations has led to the proposal of using the sodium channel blocker mexiletine to shorten the QT interval in patients with LQT3 (REF.[188]). This first example of gene-specific therapy was successful and was confirmed by recent studies[189]. Whenever mexiletine shortens the QTc by >40 ms in patients with a baseline QTc >500 ms, this drug should be added to therapy as recommended in 2005 (REF.[190]) and also by the HRS/EHRA/APHRS guidelines[9]. Very recently, groups in the Mayo Clinic and Milan have observed that mexiletine effectively shortens QTc also in a small series of patients with LQT2, and this assessment has now become routine in these two large referral centres[191]. A practical point to be kept in mind is the simplicity and rapidity by which it is possible to determine whether or not mexiletine is effective in a patient, even without knowing the functional characteristics of the mutation that the patient carries. Indeed, the therapeutic plasma concentration is reached within 90–120 minutes from administration of half of the daily oral dose, and, by monitoring the ECG for 2 hours, it is evident whether or not QTc shortens by

Rest
(HR 74 bpm)

Stage 2
(HR 131 bpm)

Stage 3
(HR 153 bpm)

Stage 4
Peak exercise
(HR 176 bpm)

Recovery
5 min
(HR 94 bpm)

Fig. 6 | **Catecholaminergic polymorphic ventricular tachycardia exercise test.** Exercise stress test in a patient with catecholaminergic polymorphic ventricular tachycardia as confirmed by genetic analysis. Sinus rhythm was normal at rest, with ectopy increasing with exercise. The patient demonstrated single premature ventricular contractions (PVCs) (arrow) with increasing frequency as the heart rate (HR) progressively increased, transitioning to PVCs in bigeminy (dotted circle in stage 3) with couplets (dotted circle in stage 4) and triplets at peak exercise. Ectopy disappears after 5 min of recovery, and normal sinus rhythm is restored. bpm, beats per minute.

at least 40 ms; if the QTc does shorten, the patient is considered a responder, and mexiletine can be added to the therapeutic regimen. Despite high hopes, there are insufficient data about the efficacy of ranolazine and other new sodium channel blockers to recommend their use.

Finally, data on patient-specific iPS-CMs raise the possibility that the lumacaftor–ivacaftor combination (a drug that corrects trafficking defects and is used clinically for cystic fibrosis) might be useful in patients with LQT2 with mutations causing trafficking defects[192]. Indeed, the initial clinical data in the same patients whose iPS-CMs responded to lumacaftor seem to support the experimental observation[193].

SQTS. The main predictor for recurrent arrhythmic events in patients with SQTS is a non-fatal cardiac arrest event. Asymptomatic patients with QTc 300–360 ms should be monitored and followed up without any prophylactic medication[194]. Patients with markedly shortened QTc (≤300 ms) may be at increased risk of SCD, especially during sleep or rest. The only pharmacological therapy that leads to lengthening of the QTc and reduction of arrhythmic events is quinidine. Quinidine should be considered on a case-by-case basis in patients with increased risk of SCD and strong family history of SCD as a primary prevention (class IIb, level of evidence C)[175]. In patients with SQTS and recurrent ICD shocks, quinidine has been shown to prevent further ICD discharges[142]. Finally, emergency isoprenaline infusion can be effective in patients with an electrical storm or refractory ventricular fibrillation to restore and maintain sinus rhythm[164].

CPVT. β-Adrenergic receptor blocker therapy is the standard, first-line therapy in all patients with symptomatic CPVT who manifested self-limiting syncope or seizures as their sentinel event[9,194]. Nadolol is the preferred β-adrenergic receptor blocker in CPVT[195,196]. Preliminary evidence suggests that carvedilol may be a suitable alternative, but only if nadolol is either not available or not tolerated[197]. Combination drug therapy with a β-adrenergic receptor blocker and flecainide is increasingly utilized. In addition to its sodium channel blocker activity, flecainide may help to reduce diastolic calcium SR overload by stabilizing the 'leaky' RYR2s that stem from *RYR2* defects[198,199]. A small, randomized, placebo-controlled trial confirmed the ability of flecainide to decrease the burden of exercise-triggered ventricular ectopy and arrhythmias[200].

In general, among the largest CPVT centres throughout the world, the proxy to therapeutic success is the normalization of the patient's stress test, with general tolerance for the occasional presence of PVCs in bigeminy that persist on therapy. If bidirectional PVC couplets or worse arrhythmias persist during follow-up stress testing, medication doses are increased, combination drug therapy is initiated[201] or additional non-pharmacological therapies are considered.

BrS. The options for pharmacological therapy are limited in BrS. Antiarrhythmic drugs can be life-saving in the acute phase of an arrhythmic storm. Intravenous isoprenaline is the most effective treatment, with an immediate effect on the arrhythmia burden and the ECG pattern, which may normalize. The drug that has received the greatest interest so far and on which multiple retrospective studies have yielded encouraging reports is quinidine[202]. Cilostazol and milrinone (inotropic agents) are other drugs with reported beneficial effects in some patients with BrS with arrhythmias[17]. Importantly, there is a long list of drugs that have to be avoided in patients with BrS[203] (Brugadadrugs.org), including virtually all cardiac sodium channel blockers except quinidine.

Non-pharmacological therapy

LQTS. Left cardiac sympathetic denervation (LCSD) and ICD are the two established non-pharmacological therapies that are the pillars for the management of LQTS, and genetic progress has enabled gene-specific management. Family members of patients with LQTS should receive cardiopulmonary resuscitation training, and, in particular, they should be taught the importance of precordial thump, as this manoeuvre, if correctly performed within 1 minute from the onset of loss of consciousness, almost invariably restores sinus rhythm. For children with LQTS, the acquisition of an automatic external defibrillator may be considered[204].

Since the early 1970s, patients in whom β-adrenergic receptor blockers are not sufficient to prevent arrhythmic events have benefited from LCSD[123,205–207]. The rationale for this surgical intervention is well understood[208] and largely hinges on the interruption of the release of noradrenaline from the left cardiac sympathetic nerves, which are quantitatively dominant at the ventricular level, and on the increase in the ventricular fibrillation threshold, which means that it is more difficult for a VT to degenerate into ventricular fibrillation[209]. As LCSD is a preganglionic denervation, there is no reinnervation or postdenervation supersensitivity[210]. The currently preferred surgical approach is by thoracoscopy[124,211–213], which is simpler and less invasive than the traditional retropleural approach[214]. As LCSD has few to no contraindications, it is performed increasingly often. The main indication remains for patients not protected by β-adrenergic receptor blockers; however, LCSD is also indicated in primary prevention when a patient, albeit asymptomatic on β-adrenergic receptor blockers, keeps showing signs of high risk, such as a QTc >500 ms or T wave alternans[207]. LCSD is also effective in preventing multiple shocks in patients with an ICD[207] and in low-risk patients who are intolerant to β-adrenergic receptor blockers. In the few cases of LCSD failure, it is recommended to proceed with right cardiac sympathetic denervation to obtain a complete bilateral sympathectomy. This sequential approach has been used with success since the late 1980s[206,207]. There is no justification for performing a bilateral cardiac sympathectomy in patients with LQTS or CPVT without having first assessed whether unilateral LCSD has failed; otherwise, the patients would undergo a longer and unnecessary surgery, doubling the risk of complications, and would be deprived without reason of an important component of the adrenergic control

of their cardiac function. Importantly, the most common reason for post-LCSD breakthrough events is a suboptimal surgical procedure whereby only the left stellate ganglion is removed[100,207]. Indeed, to be effective, LCSD requires section of the lower half of the left stellate ganglion together with the first four thoracic ganglia[208].

As a general rule, an ICD should be implanted whenever a patient has survived a cardiac arrest. However, as per the 2013 guidelines[9], after a careful assessment, young patients with LQT1 who experienced a cardiac arrest while not on β-adrenergic receptor blocker therapy could be treated only with β-adrenergic receptor blockers and/or LCSD[215]. In all other patients, the pros and cons of ICDs should be very carefully considered, and the alternative option of LCSD should always be presented to the patients and their families[216,217]. The largest study on ICDs in LQTS has shown that a staggering 31% of patients have adverse events (for example, infection, lead dislodgement and tricuspid valve insufficiency) within 5 years from the implant, and the younger the patient, the higher the number of ICD substitutions that will be required over time[218]. A correct strategy is often to use both approaches — LCSD to prevent arrhythmic episodes and the ICD as a safety net.

Finally, the understanding of gene-specific triggers for arrhythmic events has led to gene-specific management for LQTS[190]. Patients with LQT1 should limit exposure to physical and, if possible, emotional stress; they should be allowed to swim but under the supervision of an adult who can swim. Their sport participation is questionable, depends on the local laws, and different views coexist[219–222]. Patients with LQT2 are at risk especially when exposed to sudden noises when they are at rest or asleep; alarm clocks and telephones should be avoided in their bedrooms. These individuals are also very sensitive to decreases in their plasma potassium levels. Potassium supplements should be given after repeated episodes of diarrhoea and potassium-sparing agents to patients with chronically low potassium levels. Women with LQT2 are at increased risk in the postpartum period and should avoid sleep deprivation, if at all possible. Their partners should take care of feeding the infant during the night-time, when breast-feeding can be avoided. The indications for patients with LQT3 are more uncertain, as arrhythmic events in these patients tend to occur at night. As night-time deaths in both LQT2 and LQT3 are often not silent[223], it is recommended to have an intercom in the room if the patient is a child, and that adults sleep with another adult, as these measures would enable recognition of gasping noises and prompt intervention.

SQTS. Patients with SQTS with a history of cardiac arrest or with documented spontaneous sustained VT are at increased risk of recurrent arrhythmic events (with an estimated risk of recurrent cardiac arrest of 10% per year) and, therefore, should receive an ICD for secondary prevention. Quinidine is recommended to reduce the number of ICD shocks. In patients who refuse ICD implantation, treatment with quinidine may be considered[9,176].

CPVT. The most rational and recommended non-pharmacological therapeutic option for CPVT is videoscopic LCSD surgery[100,211,224]. The LCSD surgical procedure is the same previously reported for LQTS. LCSD is indicated as a treatment intensification option for patients with recurrent sustained VT during stress testing or recurrent syncope despite receiving adequate or maximally tolerated β-adrenergic receptor blocker therapy[194] or combination therapy.

The other option is the placement of an ICD. Because CPVT has a higher lethality per cardiac event than LQTS, the management of both symptomatic and asymptomatic patients with CPVT tends to be more aggressive, with increased ICD use. However, CPVT is the only entity in which ICD itself may contribute to not only morbidity but also mortality[225–227]. Indeed, ICD-associated comorbidities are far more severe than those of either pharmacological therapy or LCSD, and inappropriate shocks are an inherent painful and stressful experience that may elicit a lethal arrhythmic storm. In such situations, an initial inciting shock occurs inappropriately owing to sinus tachycardia or atrial fibrillation and activates the CPVT substrate, thereby precipitating a severe and ultimately fatal electrical storm[225–227]. The most recent analysis of the effect of ICD implants in patients with CPVT has concluded that ICD use should be limited as much as possible and LCSD should be favoured[228]. Presently, the largest and more experienced CPVT centres throughout the world increasingly aim to reserve ICD only for patients with CPVT with a clinical manifestation of sudden cardiac arrest that required external defibrillation resuscitation. However, even in these centres, if the sentinel event of sudden cardiac arrest occurred while the individual was undiagnosed and, therefore, untreated, it may still be possible to successfully implement a non-ICD treatment programme with triple therapy (nadolol, flecainide and LCSD) that may confer the same survival benefit as an ICD but without its comorbidities.

BrS. Non-pharmacological therapy options consist of ICD implant and, more recently, epicardial ablation of the arrhythmogenic substrate (that is, areas that generate fractionated ECG) in the RVOT area. Patients who have survived a cardiac arrest or who have demonstrated ventricular arrhythmias have a class I indication for an ICD implant[9]. Epicardial ablation of the RVOT was first performed in nine severely symptomatic patients; after ablation of an area with abnormal low amplitude QRS voltages and late to very late (>200 ms) fractionated activity, in eight patients the ECG normalized, and recurrence of arrhythmic events was successfully prevented[229]. This epicardial approach was investigated in a larger cohort, which also included asymptomatic patients; the ECG manifestations disappeared after the procedure and could no longer be elicited by ajmaline or flecainide exposure, and in the 39 symptomatic patients no arrhythmia recurred in the short (10 months) follow-up period[230]. The exact role for epicardial ablation has to be established; of note, given the potential complications of this procedure (for example, tamponade or damage to the coronary arteries) and the relatively low

event rate in asymptomatic patients with BrS with a type 1 ECG, a prophylactic epicardial ablation in asymptomatic patients raises major ethical questions and should be discouraged at present[231].

Pregnancy-associated risk

This section focuses primarily on LQTS, as this channelopathy is the only one with adequate studies during pregnancy. The only study in CPVT to date indicates no augmented maternal risk during or after pregnancy[232]. Similarly, arrhythmic event rates in women with BrS do not seem to be elevated during pregancy[233]; thus, the management of BrS in pregnancy is limited to aggressive fever management and avoidance of medications that may provoke arrhythmias.

Maternal risk of adverse events. Surveillance during pregnancy in women with channelopathies focuses on primary arrhythmia prevention with adequate β-adrenergic receptor blockade, monitoring for breakthrough arrhythmias and identification of high-risk women (that is, those with a history of syncope or cardiac arrest). There are abundant data supporting the safety of commonly used β-adrenergic receptor blockers in pregnancy[134,234,235]. The β-adrenergic receptor blockers with proven efficacy in LQTS are nadolol and propranolol. Atenolol should not be used in pregnancy, as it is associated with significant intrauterine growth restriction (pregnancy class D)[236]. The genetic subtype is also an important modulator of pregnancy-related arrhythmia risk. Postpartum cardiac event rates are <1% in LQT1 but reach 16% in patients with LQT2 (REF.[133]), and this observation mandates specific cautionary measures as described; there are no data for LQT3 (REF.[133]). Recent studies have also shown that the risks of miscarriage and stillbirth are increased in LQTS pregnancies, and the probability of fetal death is greater if the mother, rather than the father, carries the pathogenetic mutation (or mutations) (24.4% and 3.4%, respectively)[237].

Labour and delivery management. The management plan for labour and delivery should be individualized. Low-risk women (with no previous arrhythmic events) who are adequately treated with β-adrenergic receptor blockers can safely proceed with spontaneous vaginal delivery unless there are maternal or fetal indications for assisted or Caesarean delivery. Although active pushing increases the maximal heart rate, the heart rate response is expected to be blunted in a woman with adequate β-adrenergic receptor blockade. In pregnant women with LQTS, intrapartum rhythm monitoring is not necessary, as event rates are extremely low. However, cardiac telemetry is advisable during labour in women with CPVT, as arrhythmia can occur and progress from isolated PVCs to more complex and unstable ventricular arrhythmias. Caesarean delivery with maternal telemetry should be considered in pregnant women with poorly controlled arrhythmias or a history of cardiac arrest[238].

Any pharmacological therapy in women with LQTS or BrS should be reviewed[239]. Oxytocin, commonly used during labour and delivery, has some potential for QT prolongation[240], but this effect should not preclude the use of oxytocin when indicated[241]. A reasonable approach to oxytocin use is to optimize serum potassium and magnesium levels and to obtain an ECG at baseline and 1–2 h after oxytocin is initiated. The drug should be discontinued if the QTc exceeds 500 ms or increases beyond 60 ms from baseline[86]. Decisions regarding analgesia, including neuronal axial blockade, should be made according to maternal preference and estimated obstetric risk.

Management of the newborn baby. Neonatal genetic screening for the familial pathogenetic variant should be performed. Because the QT interval is often prolonged in healthy newborn babies for the first 7–10 days[242,243], 12-lead ECG screening of the neonate who is at risk of LQTS is unreliable for the diagnosis of LQTS until after the second week of life[10], unless QTc of the newborn baby exceeds 500 ms. The Bazett method to calculate QTc is valid and useful also in infants[244]. Until the genetic test results are available, or if a variant of unknown significance is detected, ongoing clinical follow-up is recommended.

Pregnancy and risk of disease transmission. When one of the parents is affected by a channelopathy and the disease-causing mutation is known, the cardiologist is often asked whether it is possible to prevent transmission of this potentially life-threatening disorder to the offspring. The cardiologist has the responsibility of providing the essential information on in vitro fertilization and pre-implantation genetic screening of the embryo, as this approach allows the possibility of favouring the development of the embryo without the mutation, thereby ensuring the offspring will not have the disease present in the family[245–247].

Quality of life

The quality of life of the patients should be a primary concern for their doctors. For channelopathies, there are three main aspects to consider: the negative effects of certain therapies (mainly ICDs), the effect on sports participation and the specific concerns of patients with BrS.

ICDs are undoubtedly life-saving devices but, in these disorders, when physicians opt for an ICD they might be influenced to some extent by their own wish to avoid possible negligence investigations. ICDs often have a very negative effect on the quality of life, especially in young patients. In particular, patients with LQTS or CPVT are very sensitive to catecholamines, and the pain and fear generated by every ICD shock often contribute to initiate a vicious cycle of recurrent VT and/or ventricular fibrillation, which can result in an electrical storm with multiple ICD shocks. Experienced investigators limit the use of ICDs as much as possible in these patients[124], and, barring a previous cardiac arrest, whenever feasible they use LCSD instead. Indeed, LCSD has been associated with a documented improvement in quality of life[248,249].

For a youngster involved in competitive sports, having to stop practising following the diagnosis of a channelopathy is a major negative event with substantial

psychological effects. Physician recommendation on whether it is appropriate to continue the sporting activity should take into account the local legislature (as in some regions the law forbids competitive sports for individuals with these diseases), the type of sports and the specific characteristics of the individual patient[250]. Owing to the pressure to perform by the other players, team sports are more dangerous than individual sports in which players may decide how much to push themselves. Phenotypic and genotypic features should also be considered (for example, patients with LQT2 or LQT3 are at somewhat lower risk than individuals with LQT1). The European Society of Cardiology is updating its previous consensus document[251], which provided different perspectives compared with the more recent and more liberal consensus document by the American Heart Association and the American College of Cardiology[250].

Asymptomatic patients with BrS and a spontaneous type 1 ECG have a unique problem, as they are usually told that their major risk is to die suddenly at night, and their options are limited to implanting an ICD, which would potentially be used in ~1% of them yearly, whereas the others would remain without cardiac events. Such a situation causes anxiety in these patients and their families. Thus, the mildly encouraging data with quinidine are welcome, as they enable doctors to encourage and reassure patients. A future therapeutic option could be prophylactic ablation of the RVOT area with abnormal QRS complexes. However, a multicentre randomized trial to demonstrate that the benefits outweigh the complication rate of the ablation procedure in patients who are still asymptomatic is mandatory before this procedure enters regular clinical practice.

Outlook
LQTS

The current approach to LQTS management is overall very satisfactory, and sudden death among properly treated patients is rare nowadays, with the exception of infants presenting with cardiac events in the first year of life because of their poor response to therapy. However, too many patients who would benefit from LCSD do not receive it, as even in large centres there are few surgeons capable of performing LCSD or else this option is not offered to the patient. This same problem occurs in CPVT.

Two areas of ongoing active research have the potential of providing a very useful clinical fallout and, therefore, should be expanded. One is the field investigating genetic modifiers[71], as increased knowledge of these factors could help to improve risk stratification, and understanding their mechanisms of action[72] might lead to novel therapies. The second area involves the use of patient-specific iPS-CMs, as recent data[193,252] raise the possibility that they might represent a useful tool to identify drugs that are effective against mutation-specific arrhythmogenic mechanisms.

SQTS

Patients with SQTS are very rare, as <200 cases have been reported; accordingly, data on risk stratification are lacking. The European Short QT registry should be expanded to better understand the natural course of this disease. Furthermore, we have only limited information on overlap syndromes such as the combination of a shorter than normal QT and BrS. Data on long-term treatment with quinidine are also lacking, and adherence to and tolerability of quinidine therapy remain a problem. Perhaps in the future the use of iPS-CM research will help to identify effective patient-specific drugs that can restore the functions of ion channels.

CPVT

Numerous advances are needed in the diagnosis, prognosis and therapy of CPVT. In one-third of individuals with a clinical diagnosis of CPVT, a pathogenetic defect cannot be identified, suggesting that some CPVT-associated genes have not yet been identified. In addition, long delays persist in the diagnosis of CPVT. In particular, young patients presenting with a sentinel event of sudden cardiac arrest are often recommended ICD implantation as a secondary prevention measure after completing a cardiological evaluation to rule out both structural and arrhythmic causes of SCD. However, such evaluation often fails to include an exercise stress test, thereby failing to test for possible CPVT. This must change.

The identification of patients who are at negligible risk remains difficult, and, therefore, universal β-adrenergic receptor blocker therapy remains the general recommendation. Nevertheless, treating all patients with CPVT with lifelong prophylactic β-adrenergic receptor blocker therapy on the basis solely of a positive CPVT genetic test is wholly unsatisfying, and much progress is needed in risk stratification. In addition, there is substantial heterogeneity throughout the world in the treatment of patients with previously symptomatic CPVT, ranging from β-adrenergic receptor blocker therapy only, to combination drug therapy with β-adrenergic receptor blockers and flecainide, combination therapy and LCSD, and ICD therapy only. We must increase awareness that, among these options for symptomatic patients, β-adrenergic receptor blockade monotherapy is probably insufficient and ICD monotherapy should never be recommended[228]. In the future, perhaps a patient who presents with sudden cardiac arrest and is subsequently diagnosed with CPVT may be effectively treated with combination drug therapy and LCSD rather than with ICD. Finally, regarding quality of life, continued observational studies are needed to determine whether, akin to some cases of LQTS, sports participation in a well-treated patient with CPVT might be a reasonable consideration.

BrS

BrS is probably one of the disease entities with the most controversial issues and open questions. The most pressing questions concern the pathogenesis (including the role of genetics), risk stratification and the best treatment options. Thus, future research should be directed towards these areas. Large patient registries, with detailed clinical data, will be needed to ultimately identify the clinical parameters that contribute to risk and to quantify the risk of individual patients, in particular asymptomatic patients. To date, conflicting data exist on

most proposed risk factors[157], and a pooled analysis of all BrS registries may be the way forwards. When combined with genetic data, such analysis could also identify genetic factors that contribute to risk stratification. The presence of more than four (out of six) risk alleles, identified through genome-wide association studies, is more likely to result in a type 1 ECG pattern[67]. This dataset is currently being expanded, and, in a much larger set of patients, additional risk alleles might be identified and more statistical power might be present to successfully associate the number of risk alleles with the risk of cardiac events.

Finally, the role of targeted epicardial ablation should be studied through multicentre randomized trials before individual centres start performing epicardial ablation of RVOT in asymptomatic patients. Invasive ablation procedures should be performed by very experienced clinicians in high-capacity centres and should also be used to gain more insight into the electrophysiological mechanisms of the ECG characteristics. Specific pacing protocols may be one way to provide this much needed insight.

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1. Meyer, L. et al. Incidence, causes, and survival trends from cardiovascular-related sudden cardiac arrest in children and young adults 0 to 35 years of age: a 30-year review. Circulation 126, 1363–1372 (2012).
2. Winkel, B. G. et al. Nationwide study of sudden cardiac death in persons aged 1–35 years. Eur. Heart J. 32, 983–990 (2011).
3. Bardai, A. et al. Incidence, causes, and outcomes of out-of-hospital cardiac arrest in children. A comprehensive, prospective, population-based study in the Netherlands. J. Am. Coll. Cardiol. 57, 1822–1828 (2011).
4. Bagnall, R. D. et al. A prospective study of sudden cardiac death among children and young adults. N. Engl. J. Med. 374, 2441–2452 (2016).
5. Kong, M. H. et al. Systematic review of the incidence of sudden cardiac death in the United States. J. Am. Coll. Cardiol. 57, 794–801 (2011).
6. De Vreede-Swagemakers, J. J. M. et al. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. J. Am. Coll. Cardiol. 30, 1500–1505 (1997).
7. Bardai, A. et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. PLoS One 7, e42749 (2012).
8. Huikuri, H. V., Castellanos, A. & Myerburg, R. J. Sudden death due to cardiac arrhythmias. N. Engl. J. Med. 345, 1473–1482 (2001).
9. Priori, S. G. et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 10, 1932–1963 (2013).
   An important consensus document on genetic arrhythmias.
10. Schwartz, P. J. et al. Prevalence of the congenital long-QT syndrome. Circulation 120, 1761–1767 (2009).
    This is the study that provided the data-based prevalence of LQTS.
11. Piippo, K. et al. A founder mutation of the potassium channel KCNQ1 in long QT syndrome: implications for estimation of disease prevalence and molecular diagnostics. J. Am. Coll. Cardiol. 37, 562–568 (2001).
12. Brink, P. A. et al. Phenotypic variability and unusual clinical severity of congenital long-QT syndrome in a founder population. Circulation. 112, 2602–2610 (2005).
13. Arbour, L. et al. A KCNQ1 V205M missense mutation causes a high rate of long QT syndrome in a first nations community of northern British Columbia: a community-based approach to understanding the impact. Genet. Med. 10, 545–550 (2008).
14. Postema, P. G. et al. Founder mutations in the Netherlands: SCN5a 1795insD, the first described arrhythmia overlap syndrome and one of the largest and best characterised families worldwide. Neth. Heart J. 17, 422–428 (2009).
15. Winbo, A. et al. Origin of the Swedish long QT syndrome Y111C/KCNQ1 founder mutation. Heart Rhythm. 8, 541–547 (2011).
16. Refaat, M. M., Hotait, M. & Scheinman, M. Brugada syndrome. Card. Electrophysiol. Clin. 8, 239–245 (2016).
17. Antzelevitch, C. et al. J-wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. Heart Rhythm. 13, e295–e324 (2016).
    A 'must read' report on J wave syndromes.

18. Wang, Q. et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat. Genet. 12, 17–23 (1996).
19. Tester, D. J., Will, M. L., Haglund, C. M. & Ackerman, M. J. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm. 2, 507–517 (2005).
20. Curran, M. E. et al. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell. 80, 795–803 (1995).
21. Wang, Q. et al. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. Hum. Mol. Genet. 4, 1603–1607 (1995).
22. Ackerman, M. J. et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm. 8, 1308–1339 (2011).
23. Koopmann, T. T. et al. Long QT syndrome caused by a large duplication in the KCNH2 (HERG) gene undetectable by current polymerase chain reaction-based exon-scanning methodologies. Heart Rhythm. 3, 52–55 (2006).
24. Schwartz, P. J., Priori, S. G. & Napolitano, C. How really rare are rare diseases? The intriguing case of independent compound mutations in the long-QT syndrome. J. Cardiovasc. Electrophysiol. 14, 1120–1121 (2003).
25. Moss, A. J. et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. Circulation. 115, 2481–2489 (2007).
26. Westenskow, P., Splawski, I., Timothy, K. W., Keating, M. T. & Sanguinetti, M. C. Compound mutations: a common cause of severe long-QT syndrome. Circulation. 109, 1834–1841 (2004).
27. Shimizu, W. et al. Genotype–phenotype aspects of type 2 long-QT syndrome. J. Am. Coll. Cardiol. 54, 2052–2062 (2009).
28. Giudicessi, J. R., Wilde, A. A. M. & Ackerman, M. J. The genetic architecture of long QT syndrome: a critical reappraisal. Trends Cardiovasc. Med. 28, 453–464 (2018).
29. Strande, N. T. et al. Evaluating the clinical validity of gene–disease associations: an evidence-based framework developed by the clinical genome resource. Am. J. Hum. Genet. 100, 895–906 (2017).
30. Adler, A. et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. Circulation 141, 418–428 (2020).
31. Crotti, L. et al. Calmodulin mutations associated with recurrent cardiac arrest in infants. Circulation 127, 1009–1017 (2013).
32. Boczek, N. J. et al. Spectrum and prevalence of CALM1-, CALM2-, and CALM3-encoded calmodulin variants in long QT syndrome and functional characterization of a novel long QT syndrome-associated calmodulin missense variant, E141G. Circ. Cardiovasc. Genet. 9, 136–146 (2016).
33. Crotti, L. et al. Calmodulin mutations and life-threatening cardiac arrhythmias: insights from the International Calmodulinopathy Registry. Eur. Heart J. 40, 2964–2975 (2019).
    The analysis of the genetic and clinical knowledge on the effects of calmodulin mutations.
34. Altmann, H. M. et al. Homozygous/compound heterozygous triadin mutations associated with autosomal-recessive long-QT syndrome and pediatric sudden cardiac arrest: elucidation of the triadin knockout syndrome. Circulation 131, 2051–2060 (2015).

35. Clemens, D. J. et al. International Triadin Knockout Syndrome Registry. Circ. Genom. Precis. Med. 12, e002419 (2019).
36. Neyroud, N. et al. A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardioauditory syndrome. Nat. Genet. 15, 186–189 (1997).
37. Schulze-Bahr, E. et al. KCNE1 mutations cause Jervell and Lange-Nielsen syndrome. Nat. Genet. 17, 267–268 (1997).
38. Schwartz, P. J. et al. The Jervell and Lange-Nielsen syndrome: natural history, molecular basis, and clinical outcome. Circulation 113, 783–790 (2006).
    A comprehensive review of the Jervell and Lange-Nielsen syndrome.
39. Splawski, I. et al. Ca$_V$1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 119, 19–31 (2004).
40. Dufendach, K. A. et al. Clinical outcomes and modes of death in Timothy syndrome: a multicenter international study of a rare disorder. JACC Clin. Electrophysiol. 4, 459–466 (2018).
41. Boczek, N. J. et al. Exome sequencing and systems biology converge to identify novel mutations in the L-type calcium channel, CACNA1C, linked to autosomal dominant long QT syndrome. Circ. Cardiovasc. Genet. 6, 279–289 (2013).
42. Plaster, N. M. et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell 105, 511–519 (2001).
43. Brugada, R. et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 109, 30–35 (2004).
44. Bellocq, C. et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation 109, 2394–2397 (2004).
45. Priori, S. G. et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ. Res. 96, 800–807 (2005).
46. Templin, C. et al. Identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome (SQTS6). Eur. Heart J. 32, 1077–1088 (2011).
47. Antzelevitch, C. et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 115, 442–449 (2007).
48. Thorsen, K. et al. Loss-of-activity-mutation in the cardiac chloride-bicarbonate exchanger AE3 causes short QT syndrome. Nat. Commun. 8, 1696 (2017).
49. Priori, S. G. et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation 103, 196–200 (2001).
50. Lieve, K. V., van der Werf, C. & Wilde, A. A. Catecholaminergic polymorphic ventricular tachycardia. Circ. J. 80, 1285–1291 (2016).
51. Laitinen, P. J. et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. Circulation 103, 485–490 (2001).
52. Medeiros-Domingo, A. et al. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long-QT syndrome: a comprehensive open reading frame mutational analysis. J. Am. Coll. Cardiol. 54, 2065–2074 (2009).
53. Priori, S. G. & Chen, S. R. W. Inherited dysfunction of sarcoplasmic reticulum Ca^{2+} handling and arrhythmogenesis. Circ. Res. 108, 871–883 (2011).

54. Lahat, H., Pras, E. & Eldar, M. A missense mutation in CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. *Ann. Med.* **36**, 87–91 (2004).

55. Nyegaard, M. et al. Mutations in calmodulin cause ventricular tachycardia and sudden cardiac death. *Am. J. Hum. Genet.* **91**, 703–712 (2012).

56. Roux-Buisson, N. et al. Absence of triadin, a protein of the calcium release complex, is responsible for cardiac arrhythmia with sudden death in human. *Hum. Mol. Genet.* **21**, 2759–2767 (2012).

57. Makita, N. et al. Novel calmodulin mutations associated with congenital arrhythmia susceptibility. *Circ. Cardiovasc. Genet.* **7**, 466–474 (2014).

58. Tester, D. J. et al. Genotypic heterogeneity and phenotypic mimicry among unrelated patients referred for catecholaminergic polymorphic ventricular tachycardia genetic testing. *Heart Rhythm.* **3**, 800–805 (2006).

59. Mohler, P. J. et al. A cardiac arrhythmia syndrome caused by loss of ankyrin-B function. *Proc. Natl Acad. Sci. USA* **101**, 9137–9142 (2004).

60. Devalla, H. D. et al. TECRL, a new life-threatening inherited arrhythmia gene associated with overlapping clinical features of both LQTS and CPVT. *EMBO Mol. Med.* **8**, 1390–1408 (2016).

61. Tester, D. J. et al. Plakophilin-2 truncation variants in patients clinically diagnosed with catecholaminergic polymorphic ventricular tachycardia and decedents with exercise-associated autopsy negative sudden unexplained death in the young. *JACC Clin. Electrophysiol.* **5**, 120–127 (2019).

62. Cerrone, M. et al. Plakophilin-2 is required for transcription of genes that control calcium cycling and cardiac rhythm. *Nat. Commun.* **8**, 106 (2017).

63. Chen, Q. et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* **392**, 293–296 (1998).

64. Hosseini, S. M. et al. Reappraisal of reported genes for sudden arrhythmic death. *Circulation* **138**, 1195–1205 (2018).

65. Le Scouarnec, S. et al. Testing the burden of rare variation in arrhythmia-susceptibility genes provides new insights into molecular diagnosis for Brugada syndrome. *Hum. Mol. Genet.* **24**, 2757–2763 (2015).

66. Probst, V. et al. SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome. *Circ. Cardiovasc. Genet.* **2**, 552–557 (2009).

67. Bezzina, C. R. et al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nat. Genet.* **45**, 1044–1049 (2013).
Novel insights on the complexity of the genetics of BrS.

68. Hofman, N., Tan, H. L., Alders, M., van Langen, I. M. & Wilde, A. A. M. Active cascade screening in primary inherited arrhythmia syndromes. Does it lead to prophylactic treatment? *J. Am. Coll. Cardiol.* **55**, 2570–2576 (2010).

69. Schwartz, P. J. Cascades or waterfalls, the cataracts of genetic screening are being opened on clinical cardiology. *J. Am. Coll. Cardiol.* **55**, 2577–2579 (2010).

70. Priori, S. G. et al. Risk stratification in the long-QT syndrome. *N. Engl. J. Med.* **348**, 1866–1874 (2003).

71. Schwartz, P. J., Crotti, L. & George, A. L. Modifier genes for sudden cardiac death. *Eur. Heart J.* **39**, 3925–3931 (2018).
A comprehensive review on modifier genes associated with sudden death.

72. Lee Y.-K. et al. MTMR4 SNVs modulate ion channel degradation and clinical severity in congenital long QT syndrome: insights in the mechanism of action of protective modifier genes. *Cardiovasc. Res.* https://doi.org/10.1093/cvr/cvaa019 (2020).

73. Schwartz, P. J. Sudden cardiac death, founder populations, and mushrooms: what is the link with gold mines and modifier genes? *Heart Rhythm.* **8**, 548–550 (2011).

74. Crotti, L. et al. KCNH2-K897T is a genetic modifier of latent congenital long-QT syndrome. *Circulation* **112**, 1251–1258 (2005).

75. Crotti, L. et al. NOS1AP is a genetic modifier of the long-QT syndrome. *Circulation* **120**, 1657–1663 (2009).

76. de Villiers, C. P. et al. AKAP9 is a genetic modifier of congenital long-QT syndrome type 1. *Circ. Cardiovasc. Genet.* **7**, 599–606 (2014).

77. Antzelevitch, C. & Oliva, A. Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT, short QT and Brugada syndromes. *J. Intern. Med.* **259**, 48–58 (2006).

78. Ueda, N., Zipes, D. P. & Wu, J. Prior ischemia enhances arrhythmogenicity in isolated canine ventricular wedge model of long QT 3. *Cardiovasc. Res.* **63**, 69–76 (2004).

79. Haïssaguerre, M. et al. Depolarization versus repolarization abnormality underlying inferolateral J-wave syndromes: new concepts in sudden cardiac death with apparently normal hearts. *Heart Rhythm.* **16**, 781–790 (2014).

80. Schwartz, P. J. Idiopathic long QT syndrome: progress and questions. *Am. Heart J.* **109**, 399–411 (1985).

81. Moss, A. J. et al. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation* **84**, 1136–1144 (1991).

82. Zipes, D. P. The long QT interval syndrome. A Rosetta stone for sympathetic related ventricular tachyarrhythmias. *Circulation* **84**, 1414–1419 (1991).

83. Dumaine, R. & Antzelevitch, C. Molecular mechanisms underlying the long QT syndrome. *Curr. Opin. Cardiol.* **17**, 36–42 (2002).

84. Roden, D. M. Drug-induced prolongation of the QT interval. *N. Engl. J. Med.* **350**, 1013–1022 (2004).
A comprehensive review on drug-induced LQTS.

85. Itoh, H. et al. The genetics underlying acquired long QT syndrome: impact for genetic screening. *Eur. Heart J.* **37**, 1456–1464 (2016).

86. Schwartz, P. J. & Woosley, R. L. Predicting the unpredictable: drug-induced QT prolongation and Torsades de Pointes. *J. Am. Coll. Cardiol.* **67**, 1639–1650 (2016).

87. Antzelevitch, C. & Shimizu, W. Cellular mechanisms underlying the long QT syndrome. *Curr. Opin. Cardiol.* **17**, 43–51 (2002).

88. Sicouri, S., Glass, A., Ferreiro, M. & Antzelevitch, C. Transseptal dispersion of repolarization and its role in the development of Torsade de Pointes arrhythmias. *J. Cardiovasc. Electrophysiol.* **21**, 441–447 (2010).

89. Vandersickel, N. et al. Short-lasting episodes of Torsade de Pointes in the chronic atrioventricular block dog model have a focal mechanism, while longer-lasting episodes are maintained by re-entry. *JACC Clin. Electrophysiol.* **3**, 1565–1576 (2017).

90. Han, J. & Moe, G. K. Nonuniform recovery of excitability in ventricular muscle. *Circ. Res.* **14**, 44–60 (1964).

91. Nof, E., Burashnikov, A. & Antzelevitch, C. Cellular basis for atrial fibrillation in an experimental model of short QT1: implications for a pharmacological approach to therapy. *Heart Rhythm.* **7**, 251–257 (2010).

92. Whittaker, D. G., Colman, M. A., Ni, H., Hancox, J. C. & Zhang, H. Human atrial arrhythmogenesis and sinus bradycardia in KCNQ1-linked short QT syndrome: insights from computational modelling. *Front. Physiol.* **9**, 1402 (2018).

93. Guo, F. et al. Patient-specific and gene-corrected induced pluripotent stem cell-derived cardiomyocytes elucidate single-cell phenotype of short QT syndrome. *Circ. Res.* **124**, 66–78 (2019).

94. Shinnawi, R. et al. Modeling reentry in the short QT syndrome with human-induced pluripotent stem cell-derived cardiac cell sheets. *J. Am. Coll. Cardiol.* **73**, 2310–2324 (2019).

95. El-Battrawy, I. et al. Modeling short QT syndrome using human-induced pluripotent stem cell-derived cardiomyocytes. *J. Am. Heart Assoc.* **7**, e007394 (2018).

96. Odening, K. E. et al. Transgenic short-QT syndrome 1 rabbits mimic the human disease phenotype with QT/action potential duration shortening in the atria and ventricles and increased ventricular tachycardia/ventricular fibrillation inducibility. *Eur. Heart J.* **40**, 842–853 (2019).

97. Wehrens, X. H. T. The molecular basis of catecholaminergic polymorphic ventricular tachycardia: what are the different hypotheses regarding mechanisms? *Heart Rhythm.* **4**, 794–797 (2007).

98. Cerrone, M., Napolitano, C. & Priori, S. G. Catecholaminergic polymorphic ventricular tachycardia: a paradigm to understand mechanisms of arrhythmias associated to impaired Ca^{2+} regulation. *Heart Rhythm.* **6**, 1652–1659 (2009).

99. Hayashi, M. et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation* **119**, 2426–2434 (2009).
A thorough analysis of the clinical manifestations of CPVT.

100. De Ferrari, G. M. et al. Clinical management of catecholaminergic polymorphic ventricular tachycardia: the role of left cardiac sympathetic denervation. *Circulation* **131**, 2185–2193 (2015).
The definite evidence for the role of left cardiac sympathetic denervation in CPVT.

101. Nakamura, Y. et al. Ryanodine receptor-bound calmodulin is essential to protect against catecholaminergic polymorphic ventricular tachycardia. *JCI insight* **4**, e126112 (2019).

102. Xu, X. et al. Defective calmodulin binding to the cardiac ryanodine receptor plays a key role in CPVT-associated channel dysfunction. *Biochem. Biophys. Res. Commun.* **394**, 660–666 (2010).

103. Klipp, R. C. et al. EL20, a potent antiarrhythmic compound, selectively inhibits calmodulin-deficient ryanodine receptor type 2. *Heart Rhythm.* **15**, 578–586 (2018).

104. Nam, G.-B., Burashnikov, A. & Antzelevitch, C. Cellular mechanisms underlying the development of catecholaminergic ventricular tachycardia. *Circulation.* **111**, 2727–2733 (2005).

105. Cerrone, M. et al. Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia. *Circ. Res.* **101**, 1039–1048 (2007).

106. Litovsky, S. H. & Antzelevitch, C. Transient outward current prominent in canine ventricular epicardium but not endocardium. *Circ. Res.* **62**, 116–126 (1988).

107. Litovsky, S. H. & Antzelevitch, C. Differences in the electrophysiology of ventricular epicardium and endocardium as the basis for the Osborne wave. *Circulation* **80**, II–129 (1989).

108. Yan, G. X. & Antzelevitch, C. Cellular basis for the electrocardiographic J wave. *Circulation* **93**, 372–379 (1996).

109. Di Diego, J. M., Sun, Z. Q. & Antzelevitch, C. I(to) and action potential notch are smaller in left vs. right canine ventricular epicardium. *Am. J. Physiol.* **271**, H548–H561 (1996).

110. Boukens, B. J. et al. Reduced sodium channel function unmasks residual embryonic slow conduction in the adult right ventricular outflow tract. *Circ. Res.* **113**, 137–141 (2013).

111. Koncz, I. et al. Mechanisms underlying the development of the electrocardiographic and arrhythmic manifestations of early repolarization syndrome. *J. Mol. Cell Cardiol.* **68**, 20–28 (2014).

112. Ghosh, S. et al. Early repolarization associated with sudden death: insights from noninvasive electrocardiographic imaging. *Heart Rhythm.* **7**, 534–537 (2010).

113. Wilde, A. A. M. et al. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. *J. Mol. Cell Cardiol.* **49**, 543–553 (2010).
A thorough analysis of the pathophysiology of BrS.

114. Morita, H., Zipes, D. P. & Wu, J. Brugada syndrome: insights of ST elevation, arrhythmogenicity, and risk stratification from experimental observations. *Heart Rhythm.* **6**, S34–S43 (2009).

115. Antzelevitch, C. & Yan, G.-X. J-wave syndromes: Brugada and early repolarization syndromes. *Heart Rhythm.* **12**, 1852–1866 (2015).

116. Di Diego, J. et al. In a whole-heart model of the Brugada syndrome, delayed conduction in the RVOT "does not" contribute to inscription of the electrocardiographic J wave/ST segment elevation. *Heart Rhythm.* **15**, S242 (2018).

117. Brugada, J. et al. Brugada syndrome phenotype elimination by epicardial substrate ablation. *Circ. Arrhythmia Electrophysiol.* **8**, 1373–1381 (2015).

118. Szél, T. & Antzelevitch, C. Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of Brugada syndrome. *J. Am. Coll. Cardiol.* **63**, 2037–2045 (2014).

119. Nademanee, K. et al. Fibrosis, connexin-43, and conduction abnormalities in the Brugada syndrome. *J. Am. Coll. Cardiol.* **66**, 1976–1986 (2015).

120. Rohr, S. & Kucera, J. P. Involvement of the calcium inward current in cardiac impulse propagation: induction of unidirectional conduction block by nifedipine and reversal by Bay K 8644. *Biophys. J.* **72**, 754–766 (1997).

121. Huelsing, D. J., Spitzer, K. W., Cordeiro, J. M. & Pollard, A. E. Conduction between isolated rabbit Purkinje and ventricular myocytes coupled by a variable resistance. *Am. J. Physiol.* **274**, H1163–H1173 (1998).

122. Schwartz, P. J. et al. Genotype–phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* **103**, 89–95 (2001).
The evidence for the importance of the genotype in the triggering of arrhythmic events in LQTS.

123. Schwartz, P. J., Periti, M. & Malliani, A. The long Q-T syndrome. *Am. Heart J.* **89**, 378–390 (1975).

124. Schwartz, P. J. & Ackerman, M. J. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur. Heart J.* **34**, 3109–3116 (2013).
An updated view on the clinical management of LQTS.

125. Kimbrough, J. et al. Clinical implications for affected parents and siblings of probands with long-QT syndrome. *Circulation* **104**, 557–562 (2001).

126. Crotti, L. et al. The common long-QT syndrome mutation KCNQ1/A341V causes unusually severe clinical manifestations in patients with different ethnic backgrounds: toward a mutation-specific risk stratification. *Circulation* **116**, 2366–2375 (2007).

127. Lim, E. T. et al. Distribution and medical impact of loss-of-function variants in the Finnish founder population. *PLoS Genet.* **10**, e1004494 (2014).

128. Jervell, A. & Lange-Nielsen, F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval, and sudden death. *Am. Heart J.* **54**, 59–68 (1957).

129. Schwartz, P. J. & Priori, S. G. in *Cardiac electrophysiology. From cell to bedside* 4th edn (eds Zipes, D. P. & Jalife, J.) 711–719 (Saunders, 2004).

130. Schwartz, P. J. & Malliani, A. Electrical alternation of the T-wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T syndrome. *Am. Heart J.* **89**, 45–50 (1975).

131. Schwartz, P. J., Zaza, A., Locati, E. & Moss, A. J. Stress and sudden death. The case of the long QT syndrome. *Circulation* **83**, II71–II80 (1991).

132. Ackerman, M. J., Tester, D. J. & Porter, C. J. Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. *Mayo Clin. Proc.* **74**, 1088–1094 (1999).

133. Khositseth, A., Tester, D. J., Will, M. L., Bell, C. M. & Ackerman, M. J. Identification of a common genetic substrate underlying postpartum cardiac events in congenital long QT syndrome. *Heart Rhythm.* **1**, 60–64 (2004).

134. Seth, R. et al. Long QT syndrome and pregnancy. *J. Am. Coll. Cardiol.* **49**, 1092–1098 (2007).

135. Schwartz, P. J., Spazzolini, C. & Crotti, L. All LQT3 patients need an ICD: true or false? *Heart Rhythm.* **6**, 113–120 (2009).

136. Arnestad, M. et al. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation* **115**, 361–367 (2007).

137. Tester, D. J. et al. Cardiac genetic predisposition in sudden infant death syndrome. *J. Am. Coll. Cardiol.* **71**, 1217–1227 (2018).

138. Schwartz, P. J. et al. Prolongation of the QT interval and the sudden infant death syndrome. *N. Engl. J. Med.* **338**, 1709–1714 (1998).

139. Schwartz, P. J. et al. A molecular link between the sudden infant death syndrome and the long-QT syndrome. *N. Engl. J. Med.* **343**, 262–267 (2000).

140. Schwartz, P. J. Molecular diagnosis in a child with sudden infant death syndrome. *Lancet* **358**, 1342–1343 (2001).

141. Saul, J. P. et al. Rationale and objectives for ECG screening in infancy. *Heart Rhythm* **11**, 2316–2321 (2014).

142. Giustetto, C. et al. Long-term follow-up of patients with short QT syndrome. *J. Am. Coll. Cardiol.* **58**, 587–595 (2011).

143. Mazzanti, A. et al. Novel insight into the natural history of short QT syndrome. *J. Am. Coll. Cardiol.* **63**, 1300–1308 (2014).

144. Tester, D. J. et al. A mechanism for sudden infant death syndrome (SIDS): stress-induced leak via ryanodine receptors. *Heart Rhythm.* **4**, 733–739 (2007).

145. Choi, G. et al. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. *Circulation* **110**, 2119–2124 (2004).

146. Tester, D. J., Medeiros-Domingo, A., Will, M. L., Haglund, C. M. & Ackerman, M. J. Cardiac channel molecular autopsy: insights from 173 consecutive cases of autopsy-negative sudden unexplained death referred for postmortem genetic testing. *Mayo Clin. Proc.* **87**, 524–539 (2012).

147. Leinonen, J. T. et al. The genetics underlying idiopathic ventricular fibrillation: a special role for catecholaminergic polymorphic ventricular tachycardia? *Int. J. Cardiol.* **250**, 139–145 (2018).

148. Brugada, P. & Brugada, J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J. Am. Coll. Cardiol.* **20**, 1391–1396 (1992).
The original description of BrS.

149. Mizusawa, Y. & Wilde, A. A. M. Brugada syndrome. *Circ. Arrhythmia Electrophysiol.* **5**, 606–616 (2012).

150. Matsuo, K. et al. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. *Eur. Heart J.* **20**, 465–470 (1999).

151. Morita, H. et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J. Am. Coll. Cardiol.* **40**, 1437–1444 (2002).

152. Milman, A. et al. Age of first arrhythmic event in Brugada syndrome: data from the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 patients. *Circ. Arrhythm. Electrophysiol.* **10**, e005222 (2017).

153. Michowitz, Y. et al. Fever-related arrhythmic events in the multicenter survey on arrhythmic events in Brugada syndrome. *Heart Rhythm.* **15**, 1394–1401 (2018).

154. Mizusawa, Y. et al. Prognostic significance of fever-induced Brugada syndrome. *Heart Rhythm.* **13**, 1515–1520 (2016).

155. Smits, J. P. P. et al. Genotype–phenotype relationship in Brugada syndrome: electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. *J. Am. Coll. Cardiol.* **40**, 350–356 (2002).

156. Kapplinger, J. D. et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm.* **7**, 33–46 (2010).

157. Adler, A. et al. Risk stratification in Brugada syndrome: clinical characteristics, electrocardiographic parameters, and auxiliary testing. *Heart Rhythm.* **13**, 299–310 (2016).

158. Sroubek, J. et al. Programmed ventricular stimulation for risk stratification in the Brugada syndrome: a pooled analysis. *Circulation* **133**, 622–630 (2016).

159. Schwartz, P. J., Moss, A. J., Vincent, G. M. & Crampton, R. S. Diagnostic criteria for the long QT syndrome. An update. *Circulation* **88**, 782–784 (1993).

160. Schwartz, P. J. & Crotti, L. QTc behavior during exercise and genetic testing for the long-QT syndrome. *Circulation* **124**, 2181–2184 (2011).

161. Schwartz, P. J. & Crotti, L. in *Cardiac Electrophysiology. From Cell to Bedside* 7th edn. (eds Zipes, D. P. & Jalife, J.) 893–904 (Elsevier, 2009).

162. Horner, J. M., Horner, M. M. & Ackerman, M. J. The diagnostic utility of recovery phase QTc during treadmill exercise stress testing in the evaluation of long QT syndrome. *Heart Rhythm.* **8**, 1698–1704 (2011).

163. Crotti, L. et al. Vagal reflexes following an exercise stress test: a simple clinical tool for gene-specific risk stratification in the long QT syndrome. *J. Am. Coll. Cardiol.* **60**, 2515–2524 (2012).

164. Nador, F. et al. Unsuspected echocardiographic abnormality in the long QT syndrome. Diagnostic, prognostic, and pathogenetic implications. *Circulation* **84**, 1530–1542 (1991).
The first evidence for a mechanical abnormality in LQTS.

165. De Ferrari, G. M. et al. Effect of calcium channel block on the wall motion abnormality of the idiopathic long QT syndrome. *Circulation* **89**, 2126–2132 (1994).

166. De Ferrari, G. M. & Schwartz, P. J. Vox clamantis in deserto. We spoke but nobody was listening: echocardiography can help risk stratification of the long-QT syndrome. *Eur. Heart J.* **36**, 148–150 (2015).

167. Ter Bekke, R. M. A. et al. Electromechanical window negativity in genotyped long-QT syndrome patients: relation to arrhythmia risk. *Eur. Heart J.* **36**, 179–186 (2015).

168. Haugaa, K. H. et al. Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome. *Eur. Heart J.* **30**, 330–337 (2009).

169. De Ferrari, G. M. & Schwartz, P. J. Long QT syndrome, a purely electrical disease? Not anymore. *Eur. Heart J.* **30**, 253–255 (2009).

170. Ackerman, M. J. Genetic purgatory and the cardiac channelopathies: exposing the variants of uncertain/unknown significance issue. *Heart Rhythm.* **12**, 2325–2331 (2015).
A practical and insightful view of the complexities of the genetics of channelopathies.

171. Viskin, S. et al. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. *Heart Rhythm.* **1**, 587–591 (2004).

172. Schimpf, R., Wolpert, C., Gaita, F., Giustetto, C. & Borggrefe, M. Short QT syndrome. *Cardiovasc. Res.* **67**, 357–366 (2005).
An expert review on SQTS.

173. Anttonen, O. et al. Prevalence and prognostic significance of short QT interval in a middle-aged Finnish population. *Circulation* **116**, 714–720 (2007).

174. Guerrier, K. et al. Short QT interval prevalence and clinical outcomes in a pediatric population. *Circ. Arrhythm. Electrophysiol.* **8**, 1460–1464 (2015).

175. Priori, S. G. & Blomström-Lundqvist, C. 2015 European Society of Cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur. Heart J.* **36**, 2757–2759 (2015).

176. Wolpert, C. et al. Further insights into the effect of quinidine in short QT syndrome caused by a mutation in HERG. *J. Cardiovasc. Electrophysiol.* **16**, 54–58 (2005).

177. Anttonen, O. et al. Differences in twelve-lead electrocardiogram between symptomatic and asymptomatic subjects with short QT interval. *Heart Rhythm.* **6**, 267–271 (2009).

178. Schimpf, R. et al. Electromechanical coupling in patients with the short QT syndrome: further insights into the mechanoelectrical hypothesis of the U wave. *Heart Rhythm.* **5**, 241–245 (2008).

179. Tülümen, E. et al. PQ segment depression in patients with short QT syndrome: a novel marker for diagnosing short QT syndrome? *Heart Rhythm.* **11**, 1024–1030 (2014).

180. Watanabe, H. et al. High prevalence of early repolarization in short QT syndrome. *Heart Rhythm.* **7**, 647–652 (2010).

181. Postma, A. V. et al. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. *J. Med. Genet.* **42**, 863–870 (2005).

182. Wilde, A. A. M. et al. Proposed diagnostic criteria for the Brugada syndrome. *Eur. Heart J.* **23**, 1648–1654 (2002).

183. Makimoto, H. et al. Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. *J. Am. Coll. Cardiol.* **56**, 1576–1584 (2010).

184. Baranchuk, A. et al. Brugada phenocopy: new terminology and proposed classification. *Ann. Noninvasive Electrocardiol.* **17**, 299–314 (2012).

185. Chockalingam, P. et al. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. *J. Am. Coll. Cardiol.* **60**, 2092–2099 (2012).

186. Chatrath, R., Bell, C. M. & Ackerman, M. J. Beta-blocker therapy failures in symptomatic probands with genotyped long-QT syndrome. *Pediatr. Cardiol.* **25**, 459–465 (2004).

187. Wilde, A. A. M. et al. Clinical aspects of type 3 long-QT syndrome: an international multicenter study. *Circulation* **134**, 872–882 (2016).
The study that proved that β-adrenergic receptor blockers are effective also for patients with LQT3.

188. Schwartz, P. J. et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na⁺ channel blockade and to increases in heart rate. Implications for gene-specific therapy. *Circulation.* **92**, 3381–3386 (1995).
The first suggestion for gene-specific therapy.

189. Mazzanti, A. et al. Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. *J. Am. Coll. Cardiol.* **67**, 1053–1058 (2016).

190. Schwartz, P. J. Management of long QT syndrome. *Nat. Clin. Pract. Cardiovasc. Med.* **2**, 346–351 (2005).

191. Bos, J. M. et al. Mexiletine shortens the QT interval in patients with potassium channel-mediated type 2 long QT syndrome. *Circ. Arrhythm. Electrophysiol.* **12**, e007280 (2019).

192. Mehta, A. et al. Identification of a targeted and testable antiarrhythmic therapy for long-QT syndrome type 2 using a patient-specific cellular model. *Eur. Heart J.* **39**, 1446–1455 (2018).

193. Schwartz, P. J. et al. From patient-specific induced pluripotent stem cells to clinical translation in long QT syndrome type 2. *Eur. Heart J.* **40**, 1832–1836 (2019).
The first attempt to verify clinically the responses to drugs made in iPS-CMs from patients with LQTS.

194. Al-Khatib, S. M. et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary. *J. Am. Coll. Cardiol.* **138**, e210–e271 (2018).

195. Ackerman, M. J. et al. Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: are all beta-blockers equivalent? *Heart Rhythm.* **14**, e41–e44 (2017).

196. Leren, I. S. et al. Nadolol decreases the incidence and severity of ventricular arrhythmias during exercise stress testing compared with β1-selective β-blockers in patients with catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* **13**, 432–440 (2016).

197. Zhou, Q. et al. Carvedilol and its new analogs suppress arrhythmogenic store overload-induced Ca^{2+} release. *Nat. Med.* **17**, 1003–1009 (2011).

198. Watanabe, H. et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nat. Med.* **15**, 380–383 (2009).

199. van der Werf, C. et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. *J. Am. Coll. Cardiol.* **57**, 2244–2254 (2011).

200. Kannankeril, P. J. et al. Efficacy of flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia: a randomized clinical trial. *JAMA Cardiol.* **2**, 759–766 (2017).

201. Watanabe, H. et al. Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* **10**, 542–547 (2013).

202. Belhassen, B. Management of Brugada syndrome 2016: should all high risk patients receive an ICD? Alternatives to implantable cardiac defibrillator therapy for Brugada syndrome. *Circ. Arrhythm. Electrophysiol.* **9**, e004185 (2016).

203. Postema, P. G. et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). *Heart Rhythm.* **6**, 1335–1341 (2009).

204. Pundi, K. N., Bos, J. M., Cannon, B. C. & Ackerman, M. J. Automated external defibrillator rescues among children with diagnosed and treated long QT syndrome. *Heart Rhythm.* **12**, 776–781 (2015).

205. Moss, A. J. & McDonald, J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. *N. Engl. J. Med.* **285**, 903–904 (1971).

206. Schwartz, P. J. et al. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome. A worldwide report. *Circulation* **84**, 503–511 (1991).

207. Schwartz, P. J. et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. *Circulation* **109**, 1826–1833 (2004).

208. Schwartz, P. J. Cardiac sympathetic denervation to prevent life-threatening arrhythmias. *Nat. Rev. Cardiol.* **11**, 346–353 (2014).
The updated review on cardiac sympathetic denervation in the prevention of lethal arrhythmias.

209. Schwartz, P. J., Snebold, N. G. & Brown, A. M. Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. *Am. J. Cardiol.* **37**, 1034–1040 (1976).

210. Schwartz, P. J. & Stone, H. L. Left stellectomy and denervation supersensitivity in conscious dogs. *Am. J. Cardiol.* **49**, 1185–1190 (1982).

211. Collura, C. A., Johnson, J. N., Moir, C. & Ackerman, M. J. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Heart Rhythm.* **6**, 752–759 (2009).

212. Bos, J. M., Bos, K. M., Johnson, J. N., Moir, C. & Ackerman, M. J. Left cardiac sympathetic denervation in long QT syndrome: analysis of therapeutic

nonresponders. *Circ. Arrhythm. Electrophysiol.* **6**, 705–711 (2013).

213. Schwartz, P. J., De Ferrari, G. M. & Pugliese, L. Cardiac sympathetic denervation 100 years later: Jonnesco would have never believed it. *Int. J. Cardiol.* **237**, 25–28 (2017).

214. Odero, A., Bozzani, A., De Ferrari, G. M. & Schwartz, P. J. Left cardiac sympathetic denervation for the prevention of life-threatening arrhythmias: the surgical supraclavicular approach to cervicothoracic sympathectomy. *Heart Rhythm.* **7**, 1161–1165 (2010).

215. Vincent, G. M. et al. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment "failures". *Circulation* **119**, 215–221 (2009).

216. Horner, J. M. et al. Implantable cardioverter defibrillator therapy for congenital long QT syndrome: a single-center experience. *Heart Rhythm.* **7**, 1616–1622 (2010).

217. Schwartz, P. J. Efficacy of left cardiac sympathetic denervation has an unforeseen side effect: medicolegal complications. *Heart Rhythm.* **7**, 1330–1332 (2010).

218. Schwartz, P. J. et al. Who are the long-QT syndrome patients who receive an implantable cardioverter–defibrillator and what happens to them? Data from the European Long-QT Syndrome Implantable Cardioverter–Defibrillator (LQTS ICD) registry. *Circulation* **122**, 1272–1282 (2010).

219. Johnson, J. N. & Ackerman, M. J. Competitive sports participation in athletes with congenital long QT syndrome. *JAMA* **308**, 764–765 (2012).

220. Johnson, J. N. & Ackerman, M. J. Return to play? Athletes with congenital long QT syndrome. *Br. J. Sports Med.* **47**, 28–33 (2013).

221. Pelliccia, A. Long QT syndrome, implantable cardioverter defibrillator (ICD) and competitive sport participation: when science overcomes ethics. *Br. J. Sports Med.* **48**, 1135–1136 (2014).

222. Schwartz, P. J. in *Exercise and Sport Cardiology* Vol. 3 (eds Thompson, P. & Fernandez, A.) 269–278 (World Scientific Publishing Europe, 2018).

223. Schwartz, P. J. The congenital long QT syndromes from genotype to phenotype: clinical implications. *J. Intern. Med.* **259**, 39–47 (2006).

224. Wilde, A. A. M. et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N. Engl. J. Med.* **358**, 2024–2029 (2008).

225. Miyake, C. Y. et al. Efficacy of implantable cardioverter defibrillators in young patients with catecholaminergic polymorphic ventricular tachycardia: success depends on substrate. *Circ. Arrhythm. Electrophysiol.* **6**, 579–587 (2013).

226. Roses-Noguer, F., Jarman, J. W. E., Clague, J. R. & Till, J. Outcomes of defibrillator therapy in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* **11**, 58–66 (2014).

227. Roston, T. M. et al. Implantable cardioverter–defibrillator use in catecholaminergic polymorphic ventricular tachycardia: a systematic review. *Heart Rhythm.* **15**, 1791–1799 (2018).

228. van der Werf, C. et al. Implantable cardioverter–defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. *Eur. Heart J.* **40**, 2953–2961 (2019).
A large study on the disquieting consequences of the ICDs in patients with CPVT.

229. Nademanee, K. et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation* **123**, 1270–1279 (2011).

230. Pappone, C. et al. Electrical substrate elimination in 135 consecutive patients with Brugada syndrome. *Circ. Arrhythmia Electrophysiol.* **10**, 1–13 (2017).

231. Viskin, S. Radiofrequency ablation of asymptomatic Brugada syndrome: don't go burning my heart. *Circulation* **137**, 1883–1884 (2017).

232. Cheung, C. C. et al. Pregnancy in catecholaminergic polymorphic ventricular tachycardia. *JACC Clin. Electrophysiol.* **5**, 387–394 (2019).

233. Rodríguez-Mañero, M. et al. The clinical significance of pregnancy in Brugada syndrome. *Rev. Esp. Cardiol.* **67**, 176–180 (2014).

234. Heradien, M. J. et al. Does pregnancy increase cardiac risk for LQT1 patients with the KCNQ1-A341V mutation? *J. Am. Coll. Cardiol.* **48**, 1410–1415 (2006).

235. Ishibashi, K. et al. Arrhythmia risk and β-blocker therapy in pregnant women with long QT syndrome. *Heart* **103**, 1374–1379 (2017).

236. Duan, L., Ng, A., Chen, W., Spencer, H. T. & Lee, M.-S. Beta-blocker subtypes and risk of low birth weight in newborns. *J. Clin. Hypertens.* **20**, 1603–1609 (2018).

237. Cuneo, B. F. et al. Mothers with long QT syndrome are at increased risk for fetal death: findings from a multicenter international study. *Am. J. Obstet. Gynecol.* **222**, 263.e1–263.e11 (2020).
The risk of fetal death in LQTS families.

238. Vogl, S. E. et al. Mode of delivery is associated with maternal and fetal endocrine stress response. *BJOG* **113**, 441–445 (2006).

239. Fazio, G., Vernuccio, F., Grutta, G. & Re, G. L. Drugs to be avoided in patients with long QT syndrome: focus on the anaesthesiological management. *World J. Cardiol.* **5**, 87–93 (2013).

240. Bodi, I. et al. Postpartum hormones oxytocin and prolactin cause pro-arrhythmic prolongation of cardiac repolarization in long QT syndrome type 2. *Europace* **21**, 1126–1138 (2019).

241. Martillotti, G., Talajic, M., Rey, E. & Leduc, L. Long QT syndrome in pregnancy: are vaginal delivery and use of oxytocin permitted? A case report. *J. Obstet. Gynaecol. Can.* **34**, 1073–1076 (2012).

242. Schwartz, P. J. et al. Guidelines for the interpretation of the neonatal electrocardiogram. A task force of the European Society of Cardiology. *Eur. Heart J.* **23**, 1329–1344 (2002).

243. Walsh, S. Z. Electrocardiographic intervals during the first week of life. *Am. Heart J.* **66**, 36–41 (1963).

244. Stramba-Badiale, M. et al. For neonatal ECG screening there is no reason to relinquish old Bazett's correction. *Eur. Heart J.* **39**, 2888–2895 (2018).

245. Dahdouh, E. M. et al. Technical update: preimplantation genetic diagnosis and screening. *J Obstet. Gynaecol. Can.* **37**, 451–463 (2015).

246. Treff, N. R. & Zimmerman, R. S. Advances in preimplantation genetic testing for monogenic disease and aneuploidy. *Annu. Rev. Genomics Hum. Genet.* **18**, 189–200 (2017).

247. Regitz-Zagrosek, V. et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur. Heart J.* **39**, 3165–3241 (2018).

248. Antiel, R. M. et al. Quality of life after videoscopic left cardiac sympathetic denervation in patients with potentially life-threatening cardiac channelopathies/cardiomyopathies. *Heart Rhythm.* **13**, 62–69 (2016).

249. Schwartz, P. J. When the risk is sudden death, does quality of life matter? *Heart Rhythm.* **13**, 70–71 (2016).

250. Ackerman, M. J., Zipes, D. P., Kovacs, R. J. & Maron, B. J. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 10: the cardiac channelopathies: a scientific statement from the American Heart Association and American College of Cardiology. *J. Am. Coll. Cardiol.* **66**, 2424–2428 (2015).

251. Heidbüchel, H. et al. Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions. Part 2: ventricular arrhythmias, channelopathies, and implantable defibrillators. *Europace* https://doi.org/10.1093/europace/euaa106 (2020).

252. Wu, J. C. et al. Towards precision medicine with human iPSCs for cardiac channelopathies. *Circ. Res.* **125**, 653–658 (2019).

253. Liu, D. W., Gintant, G. A. & Antzelevitch, C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. *Circ. Res.* **72**, 671–687 (1993).

Competing interests
M.J.A. is a consultant for Audentes Therapeutics, Boston Scientific, Gilead Sciences, Invitae, Medtronic, MyoKardia and St. Jude Medical, and holds equity/royalties of AliveCor, Blue Ox Health and StemoniX. C.A. is a consultant for Novartis Institutes for BioMedical Research, Inc. and Trevena, Inc. All other authors declare no competing interests.

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