HHS Public Access

Author manuscript

Nat Rev Dis Primers. Author manuscript; available in PMC 2021 March 06.

Published in final edited form as:

Nat Rev Dis Primers. ; 6(1): 58. doi:10.1038/s41572-020-0188-7.

Inherited cardiac arrhythmias

Peter J. Schwartz[1,2,✉], **Michael J. Ackerman**[3,4,5], **Charles Antzelevitch**[6,7], **Connie R. Bezzina**[2,8], **Martin Borggrefe**[9,10], **Bettina F. Cuneo**[11], **Arthur A. M. Wilde**[2,8,12]

[1]Istituto Auxologico Italiano, IRCCS, Center for Cardiac Arrhythmias of Genetic Origin and Laboratory of Cardiovascular Genetics, Milan, Italy. [2]European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-HEART), Bruxelles, Belgium. [3]Department of Cardiovascular Medicine/Division of Heart Rhythm Services, Mayo Clinic, Rochester, MN, USA. [4]Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology, Mayo Clinic, Rochester, MN, USA. [5]Department of Molecular Pharmacology & Experimental Therapeutics, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA. [6]Lankenau Institute for Medical Research and Lankenau Heart Institute, Wynnewood, PA, USA. [7]Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA. [8]Amsterdam UMC, University of Amsterdam, Heart Center; Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, Netherlands. [9]1st Department of Medicine, University Medical Center Mannheim, Mannheim, Germany. [10]DZHK (German Center for Cardiovascular Research), Partner Site Mannheim, Mannheim, Germany. [11]Department of Pediatrics, Division of Cardiology, Children's Hospital Colorado, Aurora, CO, USA. [12]Columbia University Irving Medical Centre, New York, NY, USA.

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

✉ p.schwartz@auxologico.it.

Author contributions

Introduction (P.J.S.); Epidemiology (P.J.S. and C.R.B.); Mechanisms/pathophysiology (P.J.S., C.R.B., C.A., A.A.M.W., M.B. and M.J.A.); Diagnosis, screening and prevention (P.J.S., A.A.M.W., M.B. and M.J.A.); Management (P.J.S., A.A.M.W., M.B., M.J.A. and B.F.C.); Quality of life (P.J.S., A.A.M.W. and M.J.A.); Outlook (P.J.S., A.A.M.W., M.B. and M.J.A.); Overview of Primer (P.J.S.).

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.

Peer review information

Nature Reviews Disease Primers thanks J. Kanters, R. Kass, H. Morita, S. Nattel, S. Ohno, Y. Rudy, K. Shivkumar, M. Yano and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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 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, demon-strating 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 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 sensori-neural deafness and high arrhythmic risk, is caused by homozygous or compound heterozygous mutations in *KCNQ1* (REF.[36]) or *KCNE1* (REF.[37]); *KCNE1* mutations 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, hypo-glycaemia, cognitive abnormalities and autism[39]. The same recurrent sporadic de novo missense mutation in *CACNA1C* (encoding the pore-forming subunit-α $Ca_V1.2$ 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].

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 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 mono-morphic 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 subfamily D member 3 (also known as $K_V4.3$) that 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 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 wide-spread 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 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 electro-encephalogram. 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 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, 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 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 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 under-stood[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 tele metry 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 out-weigh 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.

Acknowledgements

The authors thank P. De Tomasi (Istituto Auxologico Italiano, IRCCS, Center for Cardiac Arrhythmias of Genetic Origin, Milan, Italy) for an extraordinary editorial support. C.A. acknowledges support from NHLBI (HL47678, HL138103 and HL152201), the W.W. Smith Charitable Trust and the Martha and Wistar Morris Fund; C.R.B., P.J.S. and A.A.M.W. acknowledge the support of ERN GUARD-Heart; C.R.B. and A.A.M.W. acknowledge the support of the Netherlands Heart Foundation (CVON Predict2 project) and Leducq Foundation for Cardiovascular Research grant 17CVD02 “The sodium channel as a therapeutic target for prevention of lethal cardiac arrhythmias”; P.J.S. acknowledges the support of Leducq Foundation for Cardiovascular Research grant 18CVD05 “Towards Precision Medicine with Human iPSCs for Cardiac Channelopathies” and of ESCAPE-NET project (European Union’s Framework Horizon 2020 programme under grant agreement no. 733381). M.B. acknowledges support from the German Center for Cardiovascular Research (DZHK) and Hector Foundation. M.J.A. acknowledges support from the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program.

Glossary

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

Polymorphic ventricular tachycardia
Rapid ventricular rhythm with a continuously varying QRS complex morphology.

Refractoriness
Also known as refractory period. The period of depolarization and repolarization of the cell membrane after excitation during which the cell cannot respond to a second electrical stimulus.

Reentry
A self-sustaining rhythm abnormality that occurs when the propagating electric impulse fails to conclude and the action potential propagates in a closed loop manner.

Torsades de Pointes
A specific form of polymorphic ventricular tachycardia characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line.

Conduction velocity
The speed at which an action potential is distributed throughout the myocardium; conduction velocity is still the primary metric for quantifying the spread of electrical activity in cardiac muscle.

Transmural dispersion of repolarization
The difference between the longest and the shortest repolarization times measured at two points across the cardiac wall.

Early afterdepolarization
Spontaneous diastolic depolarization that occurs during phase 2 and/or phase 3 of the cardiac action potential, thereby delaying repolarization.

Triggered activity
The generation of spontaneous action potentials outside the sinus node as a result of afterdepolarizations.

Focal activity
Abnormal formation of a depolarizing impulse outside the sinus node.

Wavelength
The distance travelled by the excitation wave during its refractory period.

Delayed afterdepolarizations
Spontaneous diastolic depolarizations that occur after repolarization is complete.

Bidirectional VT
A ventricular tachycardia (VT) in which the QRS axis (as seen in the frontal electrocardiogram leads) shifts 180° with each alternate beat.

J waves
Dome-like deflections of the electrocardiogram trace between the QRS complex and the ST segment.

Right ventricular outflow tract
(RVOT). an extension of the infundibulum (a conical pouch of the right ventricle) in the ventricular cavity through which the blood flows towards the pulmonary artery.

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.

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

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.

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RElatED links

Brugadadrugs.org: www.brugadadrugs.org

European Reference Network for rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-HEART): http://guardheart.ern-net.eu

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/√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).

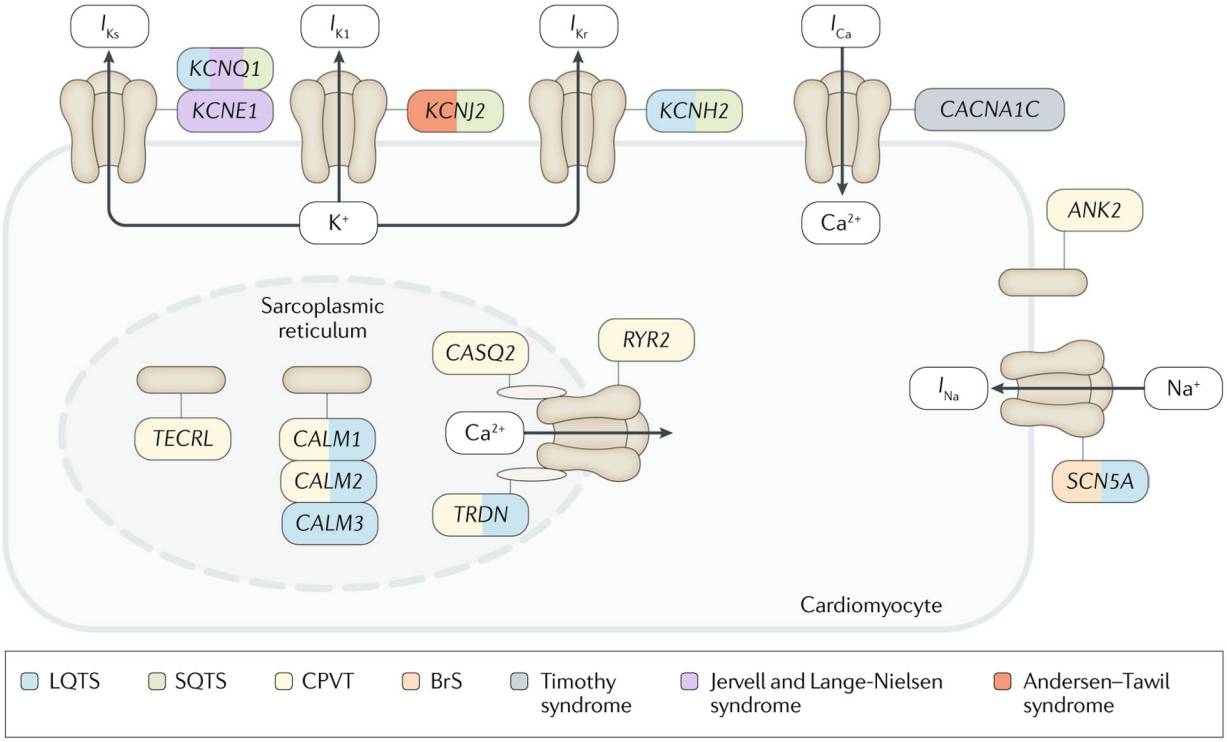

Fig. 1 |. Genes and proteins involved in the pathogenesis of inherited cardiac arrhythmias.
The figure shows the transmembrane ionic channels that are responsible for the potassium (I_{Ks}, I_{K1} and I_{Kr}), calcium (I_{Ca}) and sodium (I_{Na}) currents that contribute to the cardiac action potential. 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.

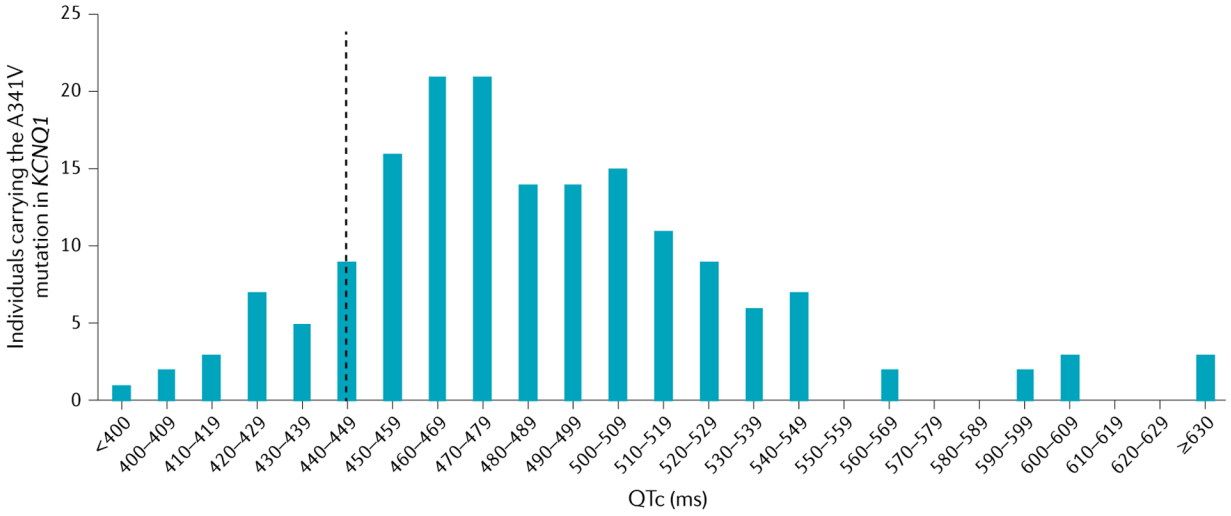

Fig. 2 |. Variability in baseline QTc.

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].

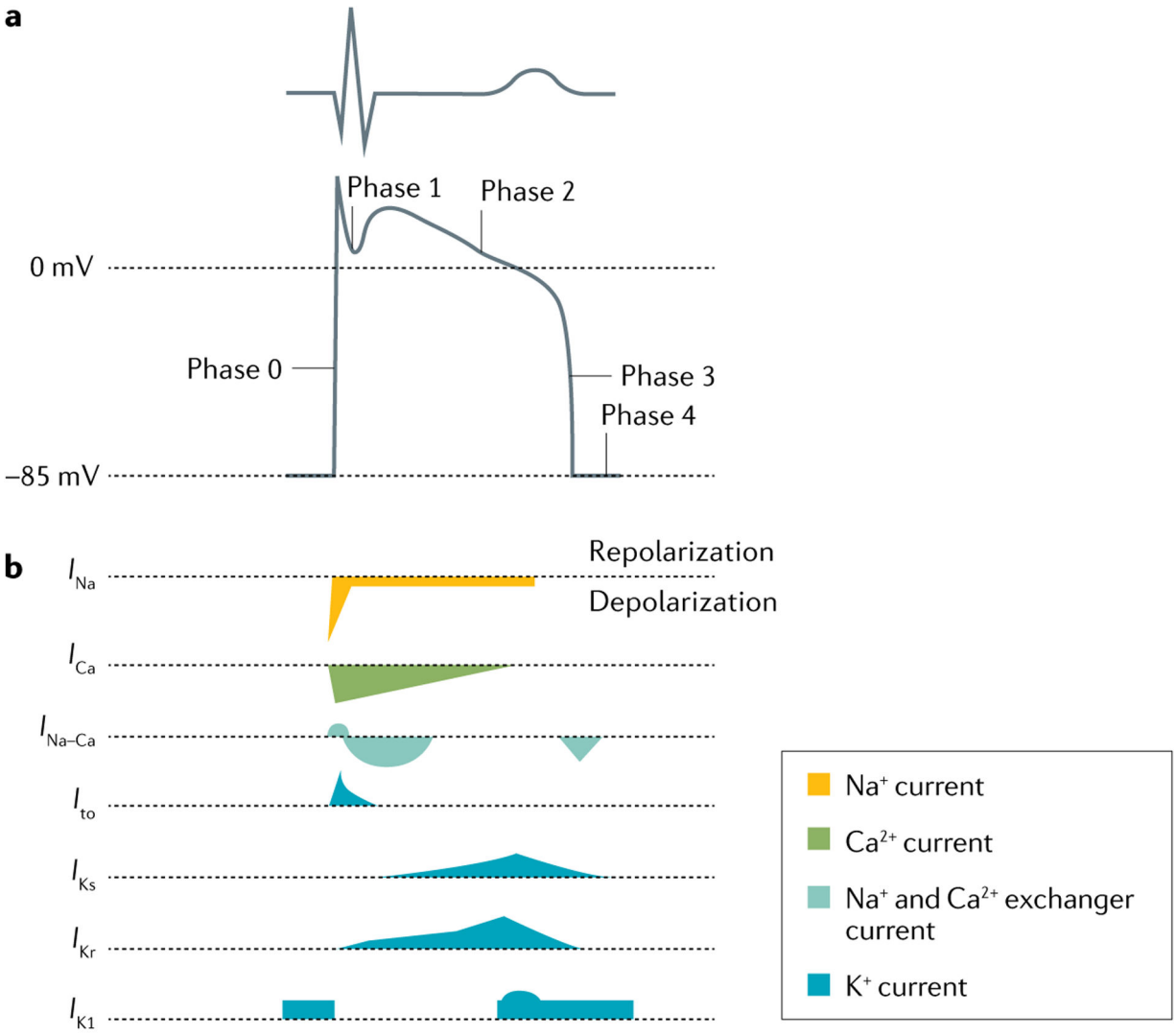

Fig. 3 |. Ventricular action potential and ionic currents.

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.

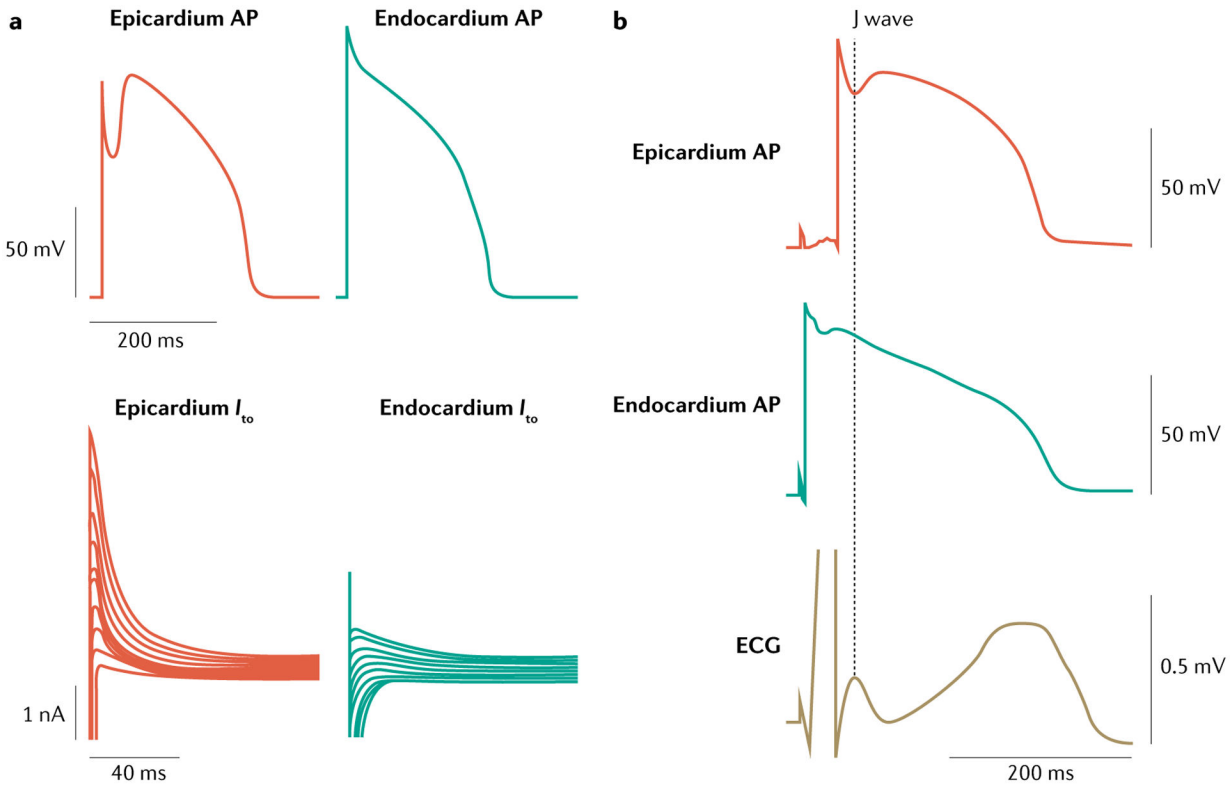

Fig. 4 |. Spatial dispersion of repolarization.

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).

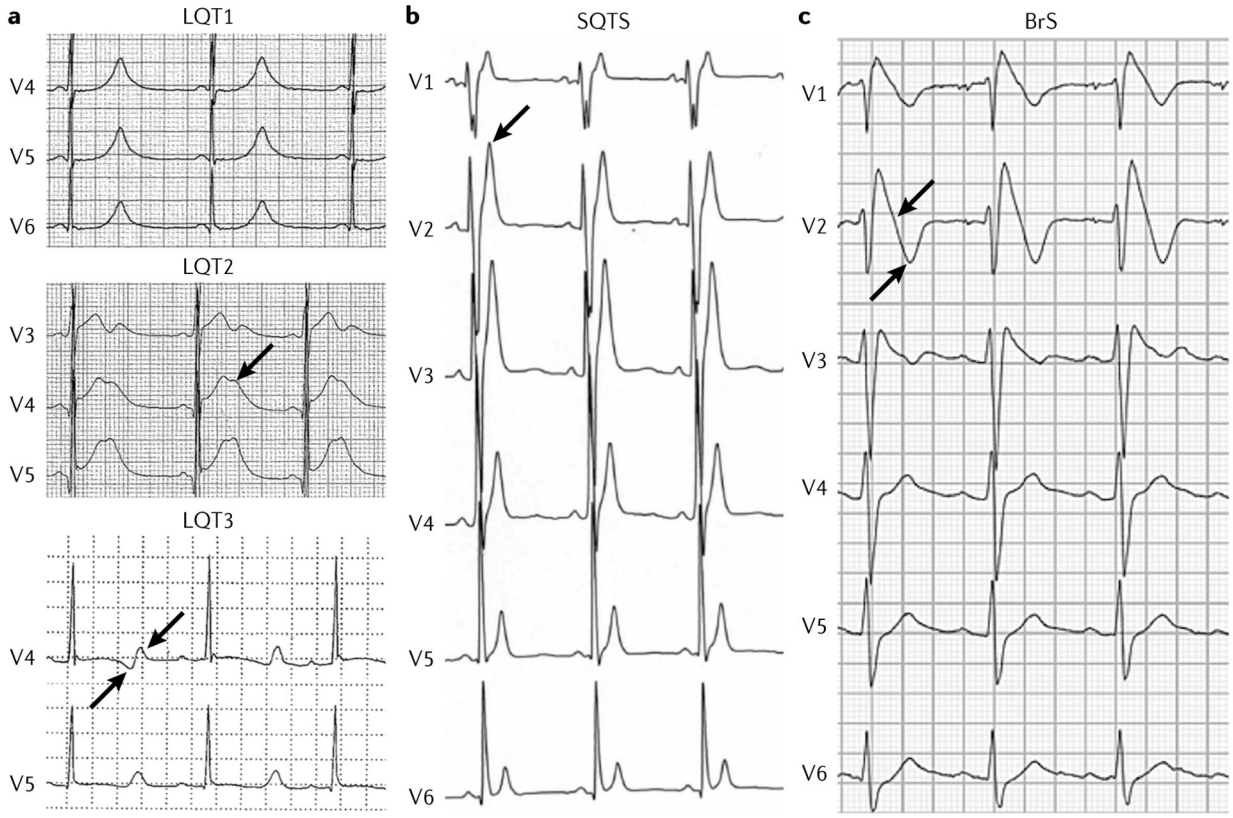

Fig. 5 |. Examples of ECG traces.

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).

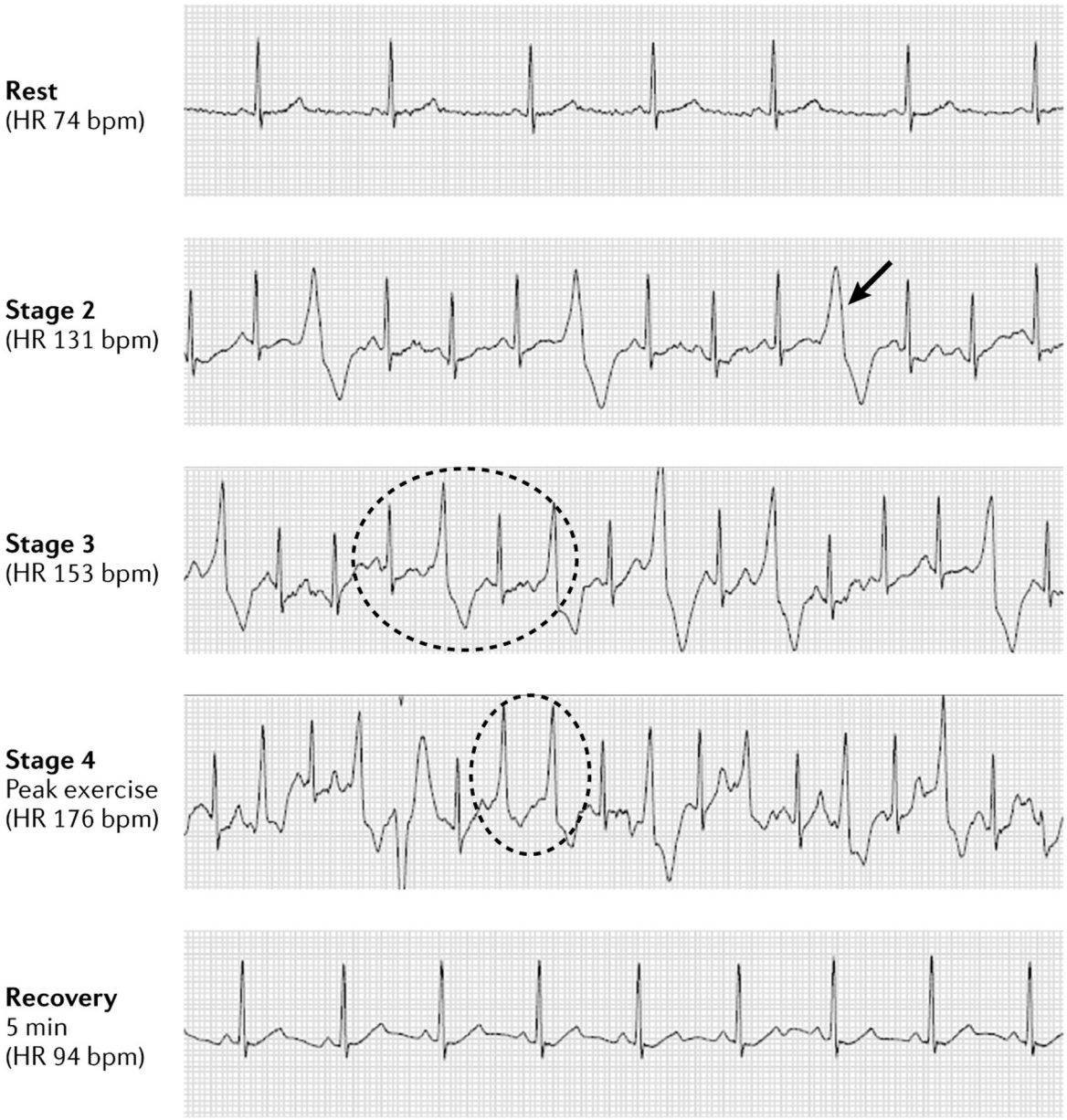

Fig. 6 |. Catecholaminergic polymorphic ventricular tachycardia exercise test.
Exercise stress test in a patient with catecholaminergic polymorphic ventricular tachycardia as confirmed by genetic analysis. Sinus rhythm was normal at rest, with ectopy increasing with exercise. The patient demonstrated 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.

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 $K_V7.1$)	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 $K_V11.1$)	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 $Na_V1.5$)	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 $Ca_V1.2$)	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.