

# Ion Channel Diseases: an Update for 2016

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## Opinion statement

Ion channelopathies are a frequent cause of sudden cardiac death (SCD) in patients with structurally normal hearts. These are generally Mendelian inherited electrical disorders with variable penetrance and expressivity. The ability to predict the development of life threatening arrhythmias in these patients is challenging. This chapter will present an update on the genetics, the role of genetic testing, and management of the inherited cardiac channelopathies with a focus on the relatively more common syndromes associated with an increased risk of SCD.

## Introduction

Sudden cardiac death (SCD) due to ventricular arrhythmias is a daunting public health problem with 200,000–450,000 events in the USA annually [1–4]. Most patients who experience SCD or sudden cardiac arrest (SCA) are ultimately discovered to have coronary heart disease [5]. However, the majority is apparently low-risk having no clinically apparent heart disease, compromising preventive strategies [6]. A measurable portion of young victims of SCD have heritable heart diseases which fall into two categories those that are autopsy “positive” and autopsy “negative.” In the former, gross examination of the heart reveals a possible cause of SCD whereas in the latter the heart is anatomically and histologically normal. The former group include the inherited

cardiomyopathies and the latter the channelopathic primary electrical diseases. The identification of the genes associated with cardiomyopathies [7, 8] and channelopathies [9–11] was a landmark event that provided insights into disease mechanisms, facilitated improvement in SCD risk prediction and the management of patients with heritable cardiovascular disease. This review will focus on the inherited channelopathies.

The inherited channelopathies have been considered to be Mendelian inherited traits with a mutation in a disease-causing gene producing the phenotypic manifestation of disease. However, it is increasingly evident that even the most straightforward disease-causing channelopathies are complex systems biology problems with

variable penetrance (proportion of mutation carriers that exhibit disease) and expressivity (range of phenotypic expression for a given genotype) and disease expression being significantly influenced by environmental factors such as exercise [long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT)], fever [Brugada syndrome (BrS)], and medications (BrS, LQTS). Without exception, these channelopathies are genetically heterogeneous with mutations in multiple genes producing the disease phenotype and extensive allelic heterogeneity characterized by many different disease-causing mutations in the same gene. These mutations are often considered “private” with each affected family carrying a unique mutant variant, with some notable exceptions of founder mutations in Finnish and South African populations causing LQTS [12, 13]. In some circumstances, different mutations in the same gene may produce a variety of disease phenotypes. This is exemplified by mutations in *SCN5A*, the cardiac sodium channel gene which have been associated with LQTS type 3, BrS, cardiac conduction system disease (CCD), sudden infant death syndrome (SIDS), heritable forms of atrial fibrillation (AF), sick sinus syndrome (SSS), and dilated cardiomyopathy (DCM) [14]. *SCN5A* is a fascinating, veritable genetic landfill.

In the post-genomic era, it is evident that some of the rarer heritable arrhythmias are not the result of single mutations in ion channel gene and instead exhibit more complex genetics. The genetic architecture of the heritable heart disease is a continuum of complexity with conditions like LQTS, CPVT, and hypertrophic cardiomyopathy (HCM) exhibiting Mendelian behavior with respect to disease susceptibility, while other conditions, such as BrS, early repolarization syndrome (ERS), and DCM many not be monogenic requiring the contribution of multiple rare and common genomic variants to produce disease (Fig. 1) [15••].

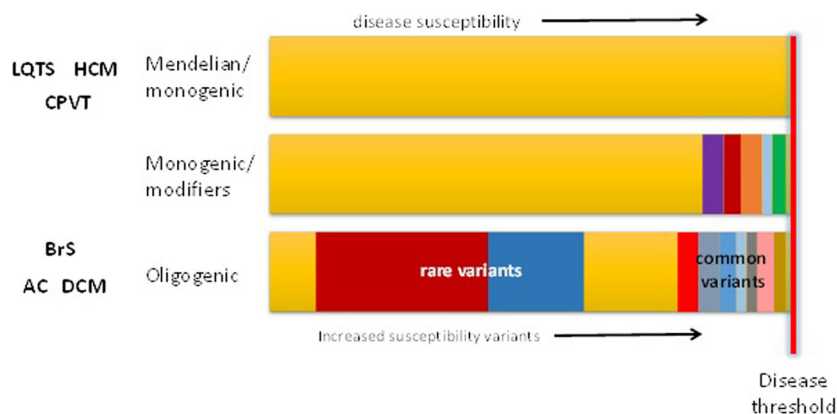
Heritable arrhythmia syndromes are difficult diagnostic problems—and in the case of heritable ventricular arrhythmias, the stakes are high, where commonly

the presentation is SCD. There is no single definitive diagnostic test for most of these syndromes. It is important to remember that the evaluation of autopsy negative SCA or death in a family member, where there is a suspicion of heritable arrhythmias, is an evaluation of families and not individuals. Clearly, a detailed and accurate family history is a key part of the evaluation. The clues in the personal history suggesting the presence of a heritable arrhythmia include symptoms related to serious ventricular arrhythmias such as syncope, palpitations, nocturnal agonal respirations, or a history of SCA. If the patient has experienced a significant event, the circumstances surrounding that event and particularly the absence of reversible causes are important. In addition to a family history of SCD or SCA other important findings are still births, SIDS, and unexplained motor vehicle accidents. The physical examination in inherited arrhythmias is important primarily to rule out other causes of cardiac events. Significant bradycardia is present in some inherited channelopathies. In rare syndromic forms of LQTS, musculoskeletal and craniofacial abnormalities are seen.

The single most informative screening test is the electrocardiogram (ECG). The resting rate and intervals are important and may be diagnostic in LQTS. The right precordial leads are keys in BrS and arrhythmogenic cardiomyopathy (AC). Exercise and ambulatory electrocardiography and the ECG in response to pharmacological challenge can be informative. Assessment of left ventricular function is an essential part of the evaluation typically with transthoracic echocardiography, but in some cases, the assessment of tissue characteristics with contrast enhanced MRI and T1 mapping may provide useful additional information. Therapy remains a challenge but for the highest risk patients implantable cardioverter defibrillators (ICDs) are often the treatment of choice.

## Genetic testing/medical genetics/genetic counselors/holistic care

A cornerstone of the evaluation and treatment of patients and families suspected of having inherited arrhythmias is genetic testing. Disease-based gene panels are typically used for genetic testing but should be used for screening or



**Fig. 1.** Genetic architecture of heritable cardiovascular disease. The syndromes represented by the *top bar* behave more like single gene traits (LQTS, CPVT, hypertrophic cardiomyopathy, HCM). Other heritable cardiovascular diseases exhibit more complex genetics with both rare and chronic genetic variants contributing to phenotypic expression. Modified after Bezzina et al. [15••]. AC arrhythmogenic cardiomyopathy, DCM dilated cardiomyopathy, BrS Brugada syndrome.

for definitive diagnosis in index cases. Rare variants of uncertain significance (VUS) are often discovered on genetic testing. The next generation of clinical genetic testing employs exome and whole-genome sequencing, and clinicians can anticipate an increasing number of incidental findings. Therefore, clinicians should be familiar with the basic attributes and limitations of clinical sequencing [16]. A structured inherited cardiovascular disease clinic may improve the likelihood of making a diagnosis in suspected cases of inherited arrhythmias and SCD [17, 18]. The initial evaluation of patients and family members requires not only review of medical records but also pedigree development, collection, and collation of medical testing such as imaging studies, pathological specimens, autopsy reports, and results of previously performed genetic testing. These tasks may be greatly expedited by a genetic counselor [19]. Genetic testing may have profound implications for patients and families. It is essential that the specific test performed and indications are thoroughly reviewed before testing. In the discussion of the test results, one needs to be prepared to discuss the implications of the test for the patient and other family members, the meaning of VUS, mosaicism, and issues related to paternity and consanguinity. The genetic counselor is an indispensable part of the care team in delivering this aspect of care [16, 19].

The genetic test is only part of the management of a patient with an inherited arrhythmia. The treatment of patients with inherited arrhythmias may vary from medication and lifestyle modification to device implantation to left cardiac sympathetic denervation (LCSD). In general, patients will require adjustment to both the underlying disease and therapy which could be assisted by access to psychologists with an interest in patients with heart disease. A properly resourced, structured clinic provides the platform for optimized, multidisciplinary evaluation and management of patients and families with suspected inherited heart disease. The collective efforts of the clinic staff and access to a variety of experts in related disciplines will result in improved quality of care [17, 20], patient satisfaction [21], and improvement in appropriate use of diagnostic testing [22, 23] and therapeutic intervention. We have found that

such a clinic staffed with the relevant expertise is an invaluable resource to patients and families not only at the time of the initial evaluation but also in an ongoing fashion as medical, genetic, and social questions relevant to the inherited heart disease arise. This clinic will serve as an ideal environment for specialized training for physicians, counselors, nurses, and other providers interested in the care of patients with inherited arrhythmias [24].

## Arrhythmic syndromes

### Long QT syndrome

#### Definition/presentation/clinical manifestations

The LQTS is the prototypic and most common heritable arrhythmia syndrome; consequently, it is the one which has been studied most extensively. There are several criteria for diagnosing LQTS, the most definitive criteria include either the presence of a definitive pathogenic mutation in one of the LQTS genes or a heart rate corrected QT (QTc)  $\geq 500$  ms using Bazett's formula on repeated resting ECGs and in the absence of a secondary cause for QT prolongation. The secondary causes of QT prolongation include drugs, acquired heart diseases (ventricular hypertrophy or failure), QRS prolongation, electrolyte abnormalities, and in some instances, diet. LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms on repeated resting ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation [25••]. There are several LQTS risk scores that can be used in equivocal cases that include ECG features including the QTc, the presence of T wave morphologic abnormalities, low heart rate, age clinical, and family history criteria [26].

The canonical presentation of patients with LQTS is unmistakable with QT interval prolongation, macroscopic T wave alternans, and a characteristic polymorphic VT called torsades de pointes [27]. The arrhythmic presentation may cause syncope or palpitations. Often, the episodes of TdP are self-limited and recurrent; however, if left uncorrected can result in SCA. Unfortunately, SCD may be the first manifestation of LQTS, thus mandating aggressive evaluation and treatment. The majority of presentations are diagnostic and therapeutic dilemmas usually identified by QT prolongation on the ECG. Increasingly, family members of probands who have been suspected of having LQTS present for evaluation. Interestingly, there is a correlation between the triggers of arrhythmic events and the genotype in LQTS. Arrhythmic events occurring during physical or emotional stress are often seen in patients with LQT1, at rest or precipitated by sudden noises in LQT2 patients and at rest or during sleep in LQT3 patients [28]. These are general correlations with common exceptions.

The ECG is the key to making the diagnosis with prolongation of the QTc as the hallmark. However, the resting 12-lead ECG changes are varied and depending upon the subtype of LQTS. Ten to 40 % of patients who harbor a disease-causing mutation will have a normal QTc or "concealed" LQTS [29]. The characteristic features of the most common causes of LQTS are illustrated in Fig. 2. LQTS1 exhibits a broad-based T wave with the duration of the T wave accounting for much of the QT prolongation. Patients with LQTS2 commonly exhibit variability in the T wave morphology with flat, at times notched T waves. LQTS3 is characterized by a long isoelectric ST segment often with the



**Fig. 2.** Representative single lead ECG recordings from patients with LQTS types 1–3 and Brugada syndrome.

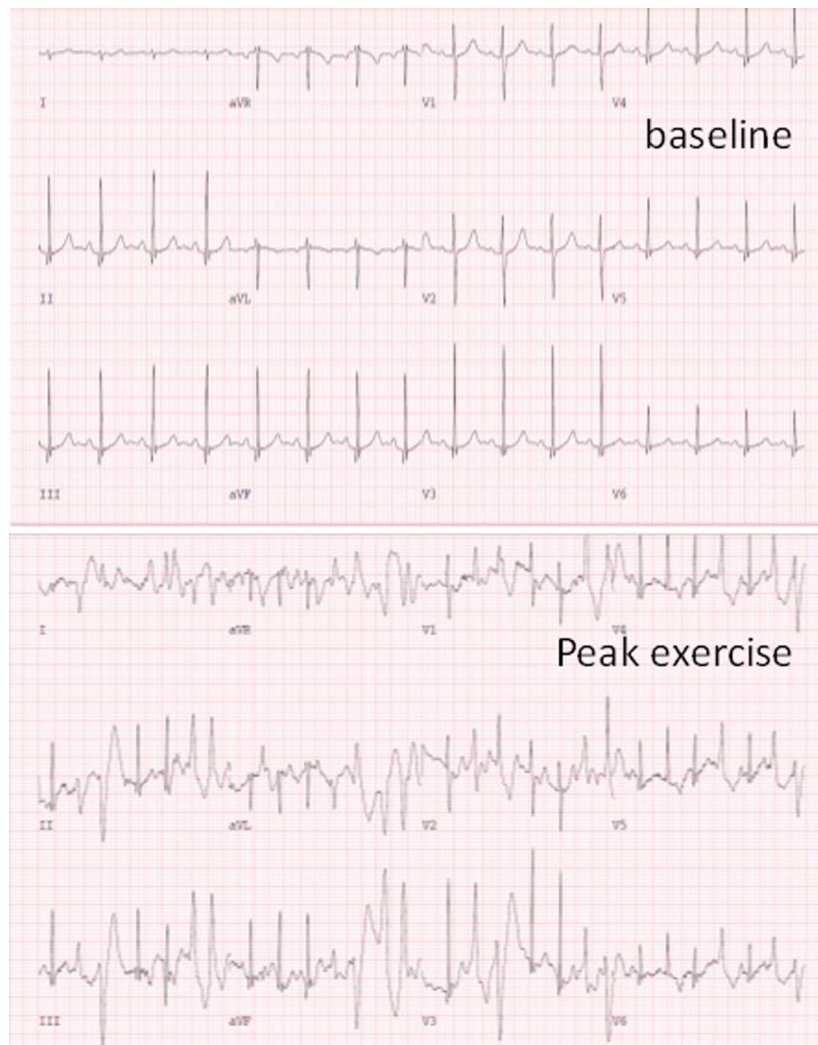
diminutive T wave [30]. Of note, there is substantial variation within each subgroup and even among family members carrying the same genotype. The effect of exercise and changes in heart differ among the three common LQTS variants. In LQTS1, QT shortening with exercise is sluggish or nonexistent and the QTc increases with heart rate. Patients with LQTS2 tend to exhibit normal QT shortening with exercise, but more pronounced morphological changes in the T wave may appear. In LQTS3, QT shortening with exercise and increase rate may be exaggerated with a shorter QTc at higher heart rates [31] (Fig. 3).

## Epidemiology

LQTS is worldwide prevalence in prevalence although there may be a lower incidence in Africa and African-Americans. The incidence estimates are variable. Data from ECG and molecular screening of Italian infants suggest an incidence of 1:2000 live births. Mutations are discovered in 43 and 29 % of infants with a QTc  $\geq 470$  and  $\geq 460$  ms, respectively [32]. These reflect manifest LQTS and are likely to be a lower limit estimate, not accounting for individuals with borderline QT intervals and those with concealed forms of the syndrome. The prevalence estimates for congenital LQTS in adults are more difficult to come by and confounded by the presence of acquired heart diseases, medications, and a number of other environmental factors.

## Genetics/genetic testing

The inherited arrhythmic syndromes are heterogeneous and LQTS is no exception. As of 2015, there are 15 genes that have been linked to LQTS [15••]. This heterogeneity reflects the fact that there are a number of ways to prolong the cardiac ventricular action potential (and therefore QT) by way of a single-gene



**Fig. 3.** Resting and peak exercise ECGs in a patient with CPVT and an RyR2 mutation.

defect. The allelic variability is extensive, in some cases hundreds of distinct mutations in a single disease gene can produce the LQTS phenotype. In general, disease-causing mutations occur in genes encoding ion channel proteins, their regulators and membrane adaptor proteins. LQTS1, 2, and 3 are caused by mutations in the potassium (K) channel  $\alpha$  subunit genes *KCNQ1*, *KCNH2*, and the sodium (Na) channel  $\alpha$  subunit, *SCN5A*, respectively. These channels are essential in controlling the duration of the ventricular action potential and repolarization of cardiac muscle. K and Na channels have opposite effects on membrane voltage and one might anticipate that mutations in these channels might differentially affect function; K channel mutations that produce LQTS are loss-of-function mutations whereas Na channel mutations that produce the same phenotype are gain-of-function. LQTS1-3 account for >90 % of all genotyped cases of LQTS and about in 15–20 % of individuals who have a prolonged resting QTc no gene mutations are found [29]. The remainder of genes harboring LQTS mutation are rare. Notably, mutations in auxiliary or  $\beta$ -

subunits of ion channels (*KCNE1* combines with *KCNQ1* to produce the K current  $I_{Ks}$ ) and (*KCNE2* combines with *KCHN2* to produce  $I_{Kr}$ ) result in clinical phenotypes similar to patients with mutations in their associated  $\alpha$ -subunits. A recessive form of LQTS, the Jervell and Lange-Nielsen (JLN) syndrome which involves the same (homozygous) or different (compound heterozygous) *KCNQ1* mutations from both parents is more virulent and associated with deafness. In some cases, deafness may be inherited as a recessive trait but arrhythmia susceptibility in these families may be dominant, so it is important to carefully evaluate hearing members of these families.

Some of the LQTS mutations underlie arrhythmic syndromes where abnormal ventricular repolarization and potentially lethal ventricular arrhythmias are one feature of a complex trait. One example is Andersen-Tawil syndrome (LQTS7) which has been associated with polymorphic ventricular tachycardia (PMVT), myotonia and syndromic, dysmorphic facies and mutations in the inward rectifier K channel gene *KCNJ2* that encodes the inward rectifier K ( $I_{K1}$ ) channel. Timothy syndrome is an even more malignant complex multisystem disorder associated with QT prolongation and a high risk of SCD that is due to mutations in the L-type calcium channel, *CACNA1C*. Most recently, mutations in the genes encoding calmodulin (*CALM1, 2, 3*) have been associated with highly lethal arrhythmias in the setting of LQTS and CPVT. These so-called calmodulinopathies are rare and often fatal early in life [33, 34].

The variable penetrance and expressivity of LQTS is likely the result of common variants in the LQTS genes themselves or unrelated genes (Fig. 1). The near Mendelian behavior of LQTS and the frequency of finding a disease-causing mutation and the prognostic and therapeutic implications of the genotype make genetic testing particularly useful in this situation.

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## Risk stratification

The management of LQTS is dictated by the risk of SCA. A number of clinical features are associated with increased risk. Syncope in childhood and SCA at any age portends an increased risk of recurrent events [35]. In childhood event, rates tend to be similar and LQTS1 boys are at higher risk than girls for cardiac events. In adulthood women with LQTS1 and 2 are at greater risk than men [36]. Overall event rates in LQTS3 may be lower but the proportion of SCA/SCDs are higher and are equally frequent in men and women [31]. Older age is not necessarily associated with lower risk particularly with the development of more common acquired heart diseases such as CAD and hypertensive heart disease. Women especially LQTS2 remain at risk at age 40 years.

The length of the QT is an important prognostic determinant. A longer QTc (especially  $\geq 500$  ms) is associated with increased cardiac event rates as is macroscopic T wave alternans. Patients who are being treated and compliant with therapy and who experience syncope and SCA are at high risk of recurrent events and mortality. There are certain genetic features associated with a higher risk of cardiac events. The rare syndromic variant Timothy syndrome and homozygous mutations associated with Jervell and Lange-Nielsen have particularly high rates of malignant arrhythmias [37]. In the case of LQTS1 and 2, specific types of mutations may be associated with a worse prognosis. In both circumstances mutations in transmembrane domains of the protein and in particular in the ion selective pore region are associated with higher event rates. Those that exhibit a

dominant negative mechanism, that is they can reduce or eliminate the function of normal channel proteins, produce higher event rates [38, 39]. There are subgroups of patients that exhibit low risk of major adverse events. The low-risk groups include silent mutation carriers with normal QTc intervals [40] and patients with LQTS1 or 2, QTc  $\leq$ 500 ms and no cardiac events before age 20 [41].

## Management

The risk for life-threatening arrhythmias is the primary driver of the management of patients with LQTS. The HRS/EHRA/APHRS expert consensus statement summarizes the approach and classes of treatment. Class I treatments are recommended, Class IIa recommendations "can be useful," Class IIb recommendations "may be considered," and Class III recommendation are contraindications where treatment fails to provide any additional benefit and may be harmful. It should be noted that all of the recommendations for this and all other heritable arrhythmias in this review are based on data from small, nonrandomized studies and registries, as such the level of evidence is C, that of expert opinion [25••].

Class I recommendations indicated for all patients include lifestyle modifications such as avoidance of drugs that prolong QT interval and prompt treatment of intercurrent illnesses particularly those likely to be associated with altered fluid and electrolyte balance. We recommend aggressive treatment of fever in LQTS3 patients. In general, competitive sports should be avoided by all LQTS patients. We recommend avoidance of all activities where even a momentary loss of consciousness may be dangerous, such as swimming in open water, rock climbing, and skydiving. For patients with LQTS1, avoidance of strenuous exercise, especially swimming without supervision is recommended while exposure to abrupt loud noises (alarm clock, phone ringing, etc.) is a common trigger in LQT2 and should be avoided whenever possible. In limited circumstances for genotype confirmed, low-risk patients with borderline QTc prolongation ( $\leq$ 460 ms), no history of cardiac symptoms, no family history of SCD, and no other contraindications to sports participation after full evaluation, competitive sports may be allowed. We require consent of the patient, parents, coaches, and training staff, the use of appropriate LQTS therapy, and the availability of automated external defibrillators (AEDs) and personnel trained in basic life support at all practices and competitive events [42]. A recent task force has suggested that under specific circumstances with an AED readily available competitive sports may be permitted in patients with channelopathies [43•].

Treatment with beta-blockers is a Class I recommendation for all LQTS patients with symptoms, documented arrhythmia or those without symptoms and a QTc  $\geq$ 470 ms. At present, long-acting, nonselective beta-blockers such as nadolol or sustained-release propranolol are preferred except in patients with bronchospasm where cardioselective beta-blockers should be used. There is some evidence that particularly in symptomatic LQTS1 and LQTS2 patients nonselective beta-blockers may be superior to metoprolol [44]. Beta-blockers can be used (Class IIa) in asymptomatic patients QTc  $\leq$ 470 ms and may be useful in combination with a Na channel blocker such as mexiletine, flecainide, or ranolazine in patients with LQTS3, especially those with a QTc  $>$ 500 ms [45–47].

In high-risk patients, particularly those who present with SCA and those with syncope or documented arrhythmias on treatment, ICD therapy is a Class I



recommendation [48, 49]. Primary prevention ICD placement should be considered in very high-risk patients such as symptomatic patients with a QTc >500 ms or two or more gene mutations including those with the JNL variant. ICD therapy, even the subcutaneous ICD (S-ICD) is invasive with significant and lifelong considerations for patients. Complications such as inappropriate shocks, lead failure, and infection are not infrequent, and especially in younger patients, multiple device replacements will be required. Careful assessment of the risks and benefits must be considered before device implantation [50–52]. Notably, the presence of one sudden death in a family is not an indication for ICD placement in an otherwise low-risk patient [53].

Left cardiac sympathetic denervation (LCSD) is an effective treatment for reducing the probability of cardiac events in high-risk LQTS and CVPT patients. LCSD is recommended in high-risk patients who are intolerant of or refractory to beta-blockers alone, who cannot or do not wish to undergo ICD placement or for those with recurrent ventricular tachyarrhythmias requiring treatment. In experienced centers, the procedure can be done in a minimally invasive fashion under thoracoscopic guidance [54–58, 59•]. This procedure is particularly useful in very high-risk infants and children in whom ICD therapy may be relatively contraindicated because of size considerations. Finally and importantly, ICD placement is not indicated in asymptomatic patients.

## Brugada syndrome (BrS)

### Definition/presentation/clinical manifestations

Far less is known about most of the other heritable arrhythmia syndromes. BrS is particularly relevant in this regard, even its transmissibility as a Mendelian trait has been questioned (Fig. 1) [15••]. The most recent guidelines define BrS electrocardiographically. The diagnosis is made by the presence of a type 1 ECG (Fig. 2) comprised of ST segment elevation of  $\geq 2$  mm and a coved ST segment in  $\geq 1$  RV lead (V1, V2 recorded in the second to fourth intercostal space) spontaneously *or* after provocation with a Class I AAD. Patients may exhibit a type 2 or 3 ECG which is comprised of  $\geq 2$  mm (type 2) or  $< 2$  mm ST elevation with a saddleback deformity  $\geq 1$  RV lead (V1, V2 recorded in the second to fourth intercostal space), but they must exhibit a type 1 change with provocation in order to make the diagnosis [25••]. The frequency of a type 1 BrS pattern has been estimated in several large ECG studies from Japan, and the pattern is detected in  $< 1$  % of ECGs [60–62].

Provocative testing to induce a type 1 ECG is performed under continuous ECG monitoring with the ability to quickly defibrillate the patient if needed. The ECG is recorded with the RV leads (V1 and V2) in the conventional position or 1–2 interspaces higher. In the USA, procainamide is infused at 10/mg/kg over 20 min; alternatively, flecainide can be administered orally ( $\sim 400$  mg) followed by ECG monitoring. Outside the USA, other options for drug provocation include intravenous flecainide (2 mg/kg over 10 min), ajmaline 1 mg/kg over 5–10 min, or pilsicainide 1 mg/kg over 10 min. The test is terminated with the development of a type 1 pattern, an increase in ST elevation in type 2 greater than 2 mm or an increase QRS duration of  $> 120$  % from baseline. Caution should be exercised because many BrS patients will have baseline conduction defects that may worsen with provocation [63].

BrS exhibits a male predominance with a typical onset in the fourth to fifth decade of life. Unfortunately, too often, the presentation is SCD or SCA. Patients may present with syncope, near syncope, nocturnal agonal respirations (NAR), palpitations, or chest discomfort. The symptom onset is most often at rest, during sleep with high vagal tone or may be precipitated by fever, but rarely with exercise. Other than fever, reported precipitants of the BrS ECG pattern include vagotonic agents,  $\beta$ -blockers,  $\alpha$ -agonists, tricyclic antidepressants (TCA), alcohol, cocaine, and hypokalemia [63]. BrS is often associated with other electrocardiographic abnormalities including sinoatrial nodal dysfunction, intraatrial conduction delay (prolonged P wave), atrioventricular block, supraventricular arrhythmias, ventricular conduction delay with widening, and fragmentation of the QRS and modest prolongation of the QT interval [63–65].

There are a number of clinical mimics of BrS making the diagnosis difficult even for expert cardiologists [66]. The differential diagnosis of the ECG changes of BrS include drugs including sodium and calcium channel blockers, nitrates, potassium channel opener (e.g., nicorandil, pinacidil) and selective serotonin reuptake inhibitors (SSRI), atypical RBBB, left ventricular hypertrophy, early repolarization, acute pericarditis, ischemia or RV infarction, pulmonary embolism, hypothermia, hyperkalemia, hypercalcemia, thiamine deficiency, autonomic neuropathy, Duchenne muscular dystrophy, arrhythmogenic cardiomyopathy (AC or ARVD/C), pectus excavatum, or any cause of compression of the right ventricle.

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## Epidemiology

BrS exhibits a worldwide prevalence of about 1/10,000 and is lower in parts of Northern Europe (1:100,000) and higher in Asia and Southeast Asia, affecting 5–10/10,000. In some parts of Asia, it is the most common cause of SCD in men under 50 years of age and previously was suggested to be related to Asian-specific sequence in the *SCN5A* promoter [67]. BrS is common enough to have engender folkloric names in Asia such as Lai Tai (Thailand), Bangungot (Philippines), and Pokkuri (Japan). The syndrome exhibit a marked male predominance (8–10:1)—possibly related to density of repolarizing potassium currents [68] or testosterone levels [69].

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## Genetics/genetic testing

Mutations in 12 genes have been associated with BrS. With the exception of *SCN5A* [70] (>80 different mutations) where between 15 and 20 % of the mutations in cases have been described, the remainder of the 11 loci account for only 5 % of mutations. Therefore, in about 80 % of cases of BrS, no mutations have been identified. This creates problems in genetic testing and has raised questions regarding whether BrS is a single gene trait. The primary role for genetic testing in BrS is genetic definition in the proband and cascade testing in family members of affected individuals. Rare mutations have been described in a number of Na (*SCN1B*, *SCN3B*, *SCN10A*), Ca (*CACNA1C*, *CACNB2B*, *CACNA2D1*), K (*KCNE3*, *KCNJ8*, *KCND3*), and nonselective (*TRPM4*) channel subunits and regulators of channel activity (*GPD1L*, *MOG1*) [15••]. The mechanisms of action of these mutations is not fully understood in many cases, but the net effect is a reduction in depolarizing currents, creating a regional imbalance of currents causing shortening of the action potential [71]. There are

other hypothesized mechanisms that posit a requirement for a decrease in conduction velocity in the right ventricle in the setting of a susceptibility mutation accounting for the late onset of symptoms in most patients [72].

There are a number of recently recognized features of BrS that cast doubt on whether this is a Mendelian inherited disorder, as, in a number of cases, more complex genetics is likely at play (Fig. 1). Many cases of BrS are sporadic [73], and there is low penetrance in families with *SCN5A* mutations [74]. Interestingly, in a recent genome-wide association study (GWAS) of BrS patients compared to a general population control group three common variants at loci close to *SCN5A/SCN10A* on chromosome 3 and *HEY2* on chromosome 6 were found to significantly increase disease susceptibility [75]. In most cases, it appears the genetics of BrS may not be straightforwardly due to mutations in a single gene.

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## Risk stratification

Defining the risk of potentially lethal cardiac arrhythmias in BrS is exceptionally challenging, thus complicating management. A type 1 ECG defines the presence of the syndrome but it not sufficiently to define risk, although a spontaneous type 1 ECG is believed to be associated with an increased risk of cardiac events. In this regards, patient registries have been helpful in defining risk factors for BrS. The FINGER registry included 1029 consecutive patients with a spontaneous or provoked type 1 ECG, their median age 45 years, mostly men that presented with SCA (6 %), syncope (30 %), or no symptoms (64 %). The overall event rate in patient in this registry was 1.1 %/year. The predictors of events included symptoms at presentation and a spontaneous type 1 ECG. Features that were not predictors of events were inducibility of ventricular arrhythmias at electrophysiological study, gender, family history of SCD, and the presence of an *SCN5A* mutation [76]. PRELUDE is another smaller registry of 308 consecutive patients who presented without sustained VT or VF. The mean age was similar at 47 years, mostly men, 56 % had a spontaneous type 1 ECG and 20 % an *SCN5A* mutation. The event rate was comparable to the FINGER registry at 1.5 %/year. The predictors of events included syncope at presentation, a spontaneous type 1 ECG, fractionation of the QRS in the right precordial leads and a ventricular effective refractory period (VERP) <200 ms. As in FINGER inducibility, gender and the presence of an *SCN5A* mutation did not predict events [64]. Other studies have also documented that ventricular conduction abnormalities are associated with increased event rates in BrS [77].

Atrial fibrillation may be observed in over 50 % of patient with BrS and has been associated with higher incidence of syncopal episodes and VF in BrS patients [78, 79]. The presence of atrial fibrillation may mandate a more aggressive approach to patients with BrS.

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## Management

The only effective treatment for BrS is placement of an ICD but the decision to implant a device in this patient group is not straightforward except in survivors of SCA and spontaneous sustained VT with or without syncope. Other Class I therapeutic recommendations include lifestyle modification for all BrS patients with avoidance of drugs that may induce or aggravate ST segment elevation in right precordial leads

(listed on Brugada.org), avoidance of excessive alcohol intake and aggressive treatment of fever with antipyretic drugs.

ICD implantation can be useful (Class IIa) in patients with a diagnosis of BrS who have a history of syncope judged to be likely caused by ventricular arrhythmias and may be considered (Class IIb) in those who develop VF during programmed electrical stimulation (inducible patients) or have a spontaneous type 1 ECG but no symptoms. An ICD is not indicated (Class III) in asymptomatic patients with a provoked type 1 ECG.

Pharmacological therapy in BrS should generally be adjunctive. Quinidine may be useful in BrS patients with ICDs that require treatment for recurrent ventricular arrhythmias and may be used in high-risk patients who refuse or cannot undergo implantation of a defibrillator or who have a history of SVT that requires treatment [80, 81]. Isoproterenol infusion may also be useful in suppressing electrical storms in BrS patients [82, 83].

Catheter ablation is another adjunctive therapy in that may have a role in the management of some patients with BrS. VF may be triggered by ventricular ectopy, and radiofrequency ablation of these triggering ventricular ectopic beats has been used in BrS patients with electrical storm. Few anecdotal cases in high-risk BrS implanted with an ICD have shown no short-term recurrence of VF, syncope, or SCD [84]. An ablation approach to the RV substrate in BrS to prevent the development of VF has been developed by Nademanee and colleagues but has not been tested in large numbers of patients [85].

## Catecholaminergic polymorphic ventricular tachycardia (CPVT)

### Definition/presentation/clinical manifestations

A syndrome of multifocal PVCs and syncope without structural heart disease has been described for over a half a century. Reports of bidirectional VT and VF as well as stress-associated VT have been reported by several groups [86]. Arguably, the most complete description is that of Coumel and colleagues [87]. Since these earlier reports the syndrome of CPVT has been clinically and genetically characterized. The diagnosis of CPVT is made in the presence of exercise- or catecholamine-induced bidirectional VT and/or polymorphic PVCs in an individual under the age of 40 years. Of note, CPVT may be present in those older than 40 years; however, other forms of heart disease, notably coronary artery disease, must be ruled out in these patients. Family members of patients with CPVT who themselves have a normal heart and exercise-induced polymorphic PVCs and/or bidirectional/polymorphic VT are considered to have the disease. In individuals that have undergone genetic testing for CPVT, the presence of a definitively pathogenic mutation (proband or family member) is diagnostic [25••].

The typical onset of CPVT is in first or second decade of life with symptoms such as syncope or SCA or polymorphic ventricular arrhythmias precipitated by physical or emotional stress. There is a family history of exercise-related syncope or SCD in ~30 % of patients. CPVT often exhibit a lower than normal resting HR. In the setting of exertion or emotional stress, CPVT patients exhibit ventricular premature complexes of more than two morphologies, polymorphic VT or VF. During exercise, the density and complexity of ventricular ectopy increases with higher levels of exertion and exercise-induced atrial arrhythmias

(e.g., AF) may also be observed [88, 89]. Catecholamine infusion may induce arrhythmias. Notably, programmed stimulation of the ventricle has no diagnostic or prognostic value. If left untreated, CPVT is highly lethal with a 30 % mortality before the age of 40 years [89, 90].

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## Epidemiology

The prevalence estimate for CPVT is 1:10,000, but the diagnosis requires a normal resting ECG and cardiac imaging so it makes a systemic study of epidemiology of CPVT difficult (Fig. 3). The epidemiology is further complicated by different modes of inheritance and mutations in genes that can produce phenocopies of CPVT. Approximately one third of cases of “atypical LQTS” with exercise-induced syncope and a normal QT interval are discovered to have CPVT [91]. Interestingly, as many as one in seven individuals who experience SCD in the absence of structural heart disease harbored a mutation in *RyR2* associated with CPVT [92].

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## Genetics/genetic testing

CPVT exhibits genetic heterogeneity in the mode of transmission and possible disease-causing genes. As noted previously, some of the mutations found in patients with exercise or stress-induced arrhythmias may be phenocopies of CPVT. Two major forms of CPVT with differences in inheritance and disease-causing genes have been described. The autosomal dominant form due to mutations in the cardiac ryanodine receptor (*RyR2*) gene [93, 94]. A less common autosomal recessive variant is produced by mutations in cardiac calsequestrin (*CASQ2*) [95]. Mutations in *RyR2* and *CASQ2* have been found in over 60 % of patients with clinical CPVT [29]. Other genes that have been linked to CPVT include *TRDN* (triadin) [96, 97] and *CALM1* (calmodulin) [33, 98].

Mutations in other genes seen in patients with stress-induced polymorphic ventricular arrhythmias include the *KCNJ2* gene encoding  $I_{K1}$  which has been linked to a syndromic form of LQTS, Andersen-Tawil syndrome, and the *ANK2* gene also known to cause a type of LQTS. It is not clear whether these represent distinct forms of CPVT or are phenocopies. Most importantly, it is unclear if treatment of these forms should be treated in the same way that *RyR2*-based CPVT is treated.

Mutations in *RyR2* are by far the most prevalent cause of CPVT. The ryanodine receptor is a massive tetrameric intracellular  $Ca^{2+}$  channel named for the alkaloid that it avidly binds. The receptor is a central component of excitation contraction coupling in that is highly regulated by kinases (protein kinase A, calcium calmodulin kinase) and other regulatory binding proteins such as FKBP12.6. Disease causing changes in *RyR2* are mostly missense mutations that are not randomly distributed but instead are concentrated in specific regions of the receptor including the FKBP binding region,  $Ca^{2+}$  binding region and the transmembrane domain that forms the  $Ca^{2+}$  selective pore [99]. Genotype-phenotype correlation studies are limited, but there is some suggestion that mutations in the C-terminal transmembrane domain may be higher, although this awaits confirmation [100].

The severity and young age of the presentation in CPVT along with the relatively high yield makes genetic testing an important component of the evaluation of patients who are suspected to have CPVT. Once a mutation is

found, cascade screening should be offered to family members of the proband and presymptomatic treatment of mutation carriers should be considered [25••, 29].

### Risk stratification

There are not many good indicators of risk in CPVT; however, as with other heritable ventricular arrhythmias, SCA or syncope is associated with a high rate of recurrence. The absence of beta-blocker treatment is associated with recurrences. As in LQTS, the preference is for treatment with long-acting (e.g., nadolol) beta-blockers at high doses. Even then, recurrence rates on therapy can be as high as 3–11 % annually [90]. The presence of persistent complex ventricular ectopy on exercise testing despite treatment is associated with worse outcomes.

### Management

The management of CPVT is similar to the other inherited arrhythmias. The recommendations for all patients include lifestyle modification avoiding competitive sports, strenuous exercise, and stressful environments (physical and emotional). All patients and family members that harbor a disease-causing mutation, irrespective of symptoms, should be treated with beta-blockers. Beta-blocker treatment should be with a long-acting beta-blocker (e.g., nadolol) typically at relatively high dose with scrupulous attention to compliance. Survivors of cardiac arrest, those with recurrent syncope or polymorphic or bidirectional ventricular tachycardia despite medical should have an ICD placed. Adrenergic blockade is first-line therapy and should be used if possible in patients with ICDs. In CPVT, an ICD shock could be proarrhythmic and the concern is precipitation of electrical storm. Accordingly, ICDs should be programmed with long delays and high rate cutoffs to avoid shocks [25••]. In experienced centers, LCSD may be considered in patients intolerant to beta blocker or for those with persistent symptoms or arrhythmias despite treatment [101]. Catheter ablation of both triggers and bidirectional tachycardia has been reported in small numbers of cases of CPVT [84, 102].

Patients with recurrent syncope or polymorphic ventricular on treatment with beta-blockers may benefit from the addition of flecainide to their regimen [103, 104]. Verapamil has been used in CPVT although the experience is small and long-term follow up is limited [105]. Dantrolene is ryanodine receptor blocker used in malignant hyperthermia that has shown benefit in experimental models [106], induced pluripotent stem cells (iPSCs) [107], and in a limited number of patients with CPVT [108].

## Rare primary electrical disorders—short QT syndrome, early repolarization syndrome, idiopathic ventricular fibrillation

There are a number of exceedingly rare primary electrical disorders associated with SCD in patients with structurally normal hearts. Treatment of these syndromes has not been well characterized because of the limited number of patients. Identification of those at high risk for one of these disorders, for example arrhythmic syncope or SCA typically mandates the placement of an ICD [25••].

Short QT syndrome highlights the importance of a normal duration of ventricular repolarization, as both long or excessively short QT intervals can be produce lethal arrhythmias [109–111]. The range of the normal QT interval has been debated, but a consensus has emerged around a  $QTc \leq 330$  ms which is more than 2 standard deviations from the mean  $QTc$ . A diagnostic score for short QT syndrome [112] has been developed but is not universally accepted. Most patients at high risk have ICDs implanted and pharmacological therapy is aimed at prolonging the QT interval, for example with quinidine. However, specific drugs may vary in their effectiveness in prolonging the QT in different genetic forms of SQTS and data are too preliminary to recommend drug treatment alone in high-risk patients [113–115]. Mutations in the potassium channel genes *KCHN2* ( $I_{Kr}$ ), *KCNQ1* ( $I_{Ks}$ ), and *KCNJ2* ( $I_{K1}$ ) have been reported in short as well as long QT syndrome, and the genetic changes in SQTS produce a gain-of-function resulting in shorter AP durations.

ST segment or J-point elevation also referred to as early repolarization (ER) is a common ECG finding, particularly in the young, physically active and African-Americans [116, 117] and has been considered a benign variant, previously referred to as a “juvenile” pattern. More recently, ER particularly in the inferior and lateral ECG leads has been associated with ventricular fibrillation (ER syndrome, ERS) [118]. Prominent J-point or ST elevation ( $>0.2$  mV) in this distribution, although observed in a small fraction of the population, has been associated with an increased risk of arrhythmic death and mortality in population studies [119–121].

A less pronounced form of ER in the inferior and lateral leads may be seen in up to 13 % of the population [119–121] and in a higher proportion of patients with idiopathic VF [118, 122, 123]. Interpretation of ER represents a diagnostic dilemma although guidance regarding characterization of the ECG patterns has recently been published in a consensus document [124]. ERS is diagnosed when a patient with ER on the ECG experiences VF, PMVT, or SCA. Patients with autopsy negative SCD and ER on a prior ECG and no evidence for other J-point elevation syndromes such as BrS are also considered to have ERS. With this definition, treatment of ERS survivors is with ICD placement. Management of family members is a dilemma, as this trait does not appear to be inherited in a Mendelian fashion. Therefore, the recommendation is that asymptomatic family members of probands with ERS that have the ER ECG pattern are not considered to have ERS and should not undergo primary prevention ICD placement in the absence of other risk features [25••].

SCD in the absence of a pathological finding and no other heritable cause has alternatively called sudden arrhythmic death syndrome (SADS), sudden unexplained death syndrome (SUDS). SUDS and sudden unexplained nocturnal death (SUNDS) has been described in young Asian men and is due to BrS in most cases. In the case SCA when evaluation of the patient does not reveal a molecular etiology, this may be referred to as idiopathic VF (IVF). The role of genetic testing in IVF when there is no evidence for a specific heritable syndrome has been debated [22, 125].

In the evaluation of a SADS victim, the priority is the evaluation of the family for the presence of cardiovascular disease, and, in some cases, a molecular autopsy of the decedent may direct the evaluation. In the absence of guidance, it is reasonable to fully evaluate first-degree relatives. We typically have used resting, exercise and ambulatory ECG recordings and assessment of

heart size and function, mostly with transthoracic echocardiography, although cardiac magnetic resonance imaging (CMR) or multidimensional cardiac CT scanning may be useful in some situations. IVF survivors should have an ICD placed. In the setting of recurrent ventricular arrhythmias in patients with J-point syndromes such as BrS and ERS, acute treatment with amiodarone, beta-blockers, or procainamide is typically not effective and quinidine, isoproterenol and cilostazol may be better options.

## Conclusions

Heritable arrhythmic syndromes, often the result of mutations in cardiac ion channel genes, are important causes of SCD and SCA particularly in the young. Genetic testing has helped to better define and understand these syndromes. The management critically involves estimating risk of SCD or a sustained arrhythmia. In those at highest risk, ICD placement is indicated.

## Compliance with Ethical Standards

### Conflict of Interest

Gordon F. Tomaselli and Andreas S. Barth each declare no potential conflicts of interest.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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