Genetics of inherited primary arrhythmia disorders

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Abstract: A sudden unexplained death is felt to be due to a primary arrhythmic disorder when no structural heart disease is found on autopsy, and there is no preceding documentation of heart disease. In these cases, death is presumed to be secondary to a lethal and potentially heritable abnormality of cardiac ion channel function. These channelopathies include congenital long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, and short QT syndrome. In certain cases, genetic testing may have an important role in supporting a diagnosis of a primary arrhythmia disorder, and can also provide prognostic information, but by far the greatest strength of genetic testing lies in the screening of family members, who may be at risk. The purpose of this review is to describe the basic genetic and molecular pathophysiology of the primary inherited arrhythmia disorders, and to outline a rational approach to genetic testing, management, and family screening.

Keywords: long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, short QT syndrome, genetics

Introduction

In the general population, the incidence of sudden death ranges from 1/100,000 in adolescents to 1/1,000 in individuals aged 45–75 years.¹ In young adults, there is some variability in the reported incidence of sudden death, with estimates ranging from 1/22,000 to 1/128,000 in nonathletes, and ranging from 1/250,000 in Italian athletes to 1/164,000 in US athletes.² A sudden unexplained death is felt to be due to a primary arrhythmic disorder when no structural heart disease is found on autopsy and there is no preceding documentation of heart disease. In these cases, death is presumed to be secondary to a lethal and potentially heritable abnormality of cardiac ion channel function caused either by an aberration in the genes encoding these proteins, or genes encoding “accessory” proteins essential to ion channel function. These “channelopathies” include congenital long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), and short QT syndrome (SQTS). It is believed that these disorders are responsible for 10%–15% of cases of sudden unexplained death in young adults and children.³ The management of a survivor of cardiac arrest typically culminates in implantation of an implantable cardioverter-defibrillator (ICD), as the risk of recurrent potentially lethal arrhythmias remains significant.⁴ An important component of the management of these individuals is a rigorous attempt at characterizing their arrhythmic substrate both for targeted management of arrhythmia risk and to direct genetic testing. In certain cases, genetic testing may have an important role in supporting a diagnosis of a primary arrhythmia...
disorder, and can also provide prognostic information, but by far the greatest strength of genetic testing lies in the screening of family members, who may be at risk. Post-mortem genetic evaluation, or “molecular autopsy” is becoming increasingly important in the evaluation of sudden unexplained death, particularly for identification of pathogenic mutations in genes underlying normal ion channel function, and also in cardiomyopathy genes in the setting of subclinical cardiomyopathy. This approach may have a significant impact on screening of family members at risk, but is not yet a routine component of post-mortem testing.5,6

A significant proportion of familial arrhythmia syndromes remain gene-elusive, even in the setting of an established phenotype with a clear pattern of familial inheritance. Historically, there are two main approaches to the identification of the culprit gene in these cases. The first is linkage analysis, which is used to identify the location of a disease gene within the chromosomes based on its relative location to established genetic markers.7 The second approach is candidate gene screening, which is based on the understanding of the ion channels and proteins involved in the generation of the cardiac action potential, and a focused analysis of the genes most likely to generate the observed arrhythmic phenotype. Genome wide association studies (GWAS), in which individuals are genotyped for the majority of common single nucleotide polymorphisms and the frequency of particular alleles in cases are compared with controls, have had some utility in the inherited arrhythmias.8 GWAS have been important, in certain cases, for identifying additional determinants of cardiac repolarization that would have been otherwise challenging to elucidate. Whole exome sequencing is emerging as an important tool for identifying culprit genes in inherited arrhythmia disorders, and has been useful in identifying candidate genes in arrhythmogenesis.9,10

The purpose of this review is to describe the basic genetic and molecular pathophysiology of the primary inherited arrhythmia disorders, and to outline a rational approach to genetic testing, management, and family screening.

**Long QT syndrome**

The hallmark of LQTS is the finding of QT prolongation on surface electrocardiography (ECG), in association with a risk of ventricular arrhythmias, syncope, or sudden death (Figures 1 and 2).11 Long QT syndrome was first described in 1957 by Jervell and Lange-Nielsen, when an association was made between congenital deafness, syncope, and QT interval prolongation on ECG in one family with an autosomal recessive form of the disease.12 Subsequently, the more common form of autosomal dominant LQTS was described by Romano and Ward.13,14 LQTS was the first inherited arrhythmia disorder in the absence of structural heart disease to be described. Population prevalence is thought to be in the range of 1/2,000.15 The QT interval reflects the total duration of cardiac depolarization and repolarization. QT prolongation typically is the result of prolongation of the plateau and
The dominant repolarizing currents are $I_{Ks}$ and $I_{Kr}$. Repolarization occurs with the time-dependent inactivation of $I_{Cal}$ and activation/reactivation of the inward rectifying currents, which include $I_{Kr}$ and $I_{Ks}$. As a result of this, K is extruded from the cell, and the resting membrane potential is restored. The relative contribution of each of the ion currents to the action potential duration is influenced by adrenergic tone. Catecholamines activate adrenergic receptors, triggering increases in intracellular cAMP and activation of a complex cascade of protein phosphorylation. Increased cAMP directly results in an increased rate of depolarization in sinoatrial cells. Phosphorylation of calcium handling proteins, such as L-type calcium channels and ryanodine receptors, results in increased intracellular calcium and myocardial contractility. At rest, $I_{Kr}$ likely has minimal activity. The activity of $I_{Ks}$ is enhanced with adrenergic stimulation, which allows for shortening of the action potential duration with exercise. Impairment of $I_{Ks}$ can prevent appropriate shortening of the action potential duration during exercise. This is the likely explanation for the observation that exercise is a common trigger for sudden death in LQTS due to defects in the gene encoding $I_{Ks}$. The effect of autonomic tone on $I_{Ks}$ is less clear. In LQTS, prolongation of the action potential creates an electrophysiologic milieu that allows L-type calcium channels to recover from inactivation and to reactivate. This has the potential to trigger early afterdepolarizations that can lead to a form of ventricular arrhythmia known as torsades des points.

**Genetics of LQTS**

From the earliest descriptions of LQTS by Jervell, Lange-Nielsen, Romano, and Ward, it was apparent that LQTS, with its familial preponderance, was a genetic condition. In 1991, linkage analysis from a multigenerational family with many affected individuals demonstrated that the genetic defect mapped to the small arm of chromosome 11. Despite the unifying features of LQTS, namely syncope, torsades des points, and QT prolongation on ECG, there was significant heterogeneity in clinical presentation, arrhythmia triggers, and specific ECG findings of T wave morphology among unrelated individuals. Ultimately, linkage analysis in other cohorts demonstrated that not all kindreds with LQTS shared this locus. The genetic heterogeneity of LQTS was ultimately proven in 1994 when linkage analysis identified loci on chromosomes 7 and 3. This led to classification of LQTS into subtypes based on genetic loci. The first subtype was mapped to chromosome 11 and was classified as LQTS type 1 (LQT1). LQTS types 2 and 3 were characterized next, and linked to loci on chromosomes 7 and 3, respectively. There are currently a total of 15 subtypes of LQTS, each with a unique genetic basis for an ion channelopathy that results in slowing of myocardial repolarization (Table 1). In general, across all genetic subtypes, the clinical penetrance of LQTS is in the range of 40%, with a broad range of 25%–100%. The gene at the LQTS1 locus on chromosome 11 is the $KCNQ1$ gene. This gene encodes the alpha-subunit of the voltage-gated potassium channel, which is responsible for the slow component of the delayed rectifier current ($I_{Kr}$). Mutations in this gene that impair channel function reduce $I_{Kr}$, causing prolongation of the repolarization phase of the action potential. Transmembrane mutations are related to longer QTc, more frequent cardiac events, and greater QTc prolongation with exercise. Cytoplasmic loop mutations that affect sites of adrenergically mediated phosphorylation are specifically associated with QT prolongation during exercise, while the QTc may be normal at rest. The gene at the LQTS2 locus on chromosome 7 is $KCNH2$, which encodes the alpha-subunit of the voltage-gated potassium channel and mediates the rapidly activating component of the delayed rectifying potassium current in the heart ($I_{Kr}$). Loss-of-function mutations result in a reduced $I_{Kr}$ and delayed cardiac repolarization manifesting as a prolonged QT interval on ECG. Mutations in the pore region of this channel are more likely to be associated with cardiac events and sudden death. The gene at the LQTS3 locus on chromosome 3 is $SCN5A$, which encodes the voltage-gated sodium channel, Nav1.5. $SCN5A$ gain-of-function mutations responsible for LQT3 result in an increased late inward Nav 1.5 current that slows cardiac repolarization, causing a prolonged QT interval. Mutations affecting $KCNQ1$, $KCNH2$, and $SCN5A$ are responsible for over 90% of genetically defined cases of LQTS. Less common forms of LQTS have also been described, with heterogeneous molecular etiologies expressed as QT prolongation and risk of lethal ventricular arrhythmias. The genes involved typically encode an ion channel or an
Table 1 Long QT syndrome by genetic subtype

<table>
<thead>
<tr>
<th>LQTS subtype</th>
<th>Culprit gene</th>
<th>Protein</th>
<th>Functional effect of mutation</th>
<th>Frequency of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>Alpha-subunit of I\textsubscript{Kr}</td>
<td>Loss-of-function, reduced I\textsubscript{Kr}</td>
<td>30–35</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNQ2</td>
<td>Alpha-subunit of I\textsubscript{Kr}</td>
<td>Loss-of-function, reduced I\textsubscript{Kr}</td>
<td>25–30</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>Alpha-subunit of I\textsubscript{Na}</td>
<td>Gain-of-function, increased late I\textsubscript{Na}, inward current</td>
<td>5–10</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANK2</td>
<td>Ankyrin-B; links membrane proteins with underlying cytoskeleton</td>
<td>Loss-of-function, disrupts multiple ion channels</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE</td>
<td>Beta-subunit of I\textsubscript{Kr}</td>
<td>Loss-of-function, reduced I\textsubscript{Kr}</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE</td>
<td>Beta-subunit of I\textsubscript{Kr}</td>
<td>Loss-of-function, reduced I\textsubscript{Kr}</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT7</td>
<td>KCNJ</td>
<td>Alpha-subunit of I\textsubscript{Kr}</td>
<td>Loss-of-function, reduced I\textsubscript{Kr}</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1</td>
<td>Alpha-subunit of I\textsubscript{CaL}</td>
<td>Gain-of-function, increased I\textsubscript{CaL}, inward current</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>Caveolin-3; a scaffolding protein in caveolae</td>
<td>Increased late I\textsubscript{Na}, inward current</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>Beta 4-subunit of I\textsubscript{Na}</td>
<td>Gain-of-function, increased late I\textsubscript{Na}, inward current</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT11</td>
<td>AKAP9</td>
<td>A kinase-anchor protein-9; sympathetic I\textsubscript{Kr} activation</td>
<td>Loss-of-function, reduced I\textsubscript{Kr}</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT12</td>
<td>SNTA1</td>
<td>Alpah-syntrophin; regulation of I\textsubscript{Na}</td>
<td>Increased late I\textsubscript{Na}, inward current</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT13</td>
<td>KCNJ</td>
<td>Kir 3.4</td>
<td>Loss-of-function, reduced I\textsubscript{Na}, inward current</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT14</td>
<td>CALM1</td>
<td>Calmodulin-1</td>
<td>Altered calcium signaling</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT15</td>
<td>CALM2</td>
<td>Calmodulin-2</td>
<td>Altered calcium signaling</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Abbreviation: LQTS, long QT syndrome.

accessory protein that is critical to ion channel expression, function, or localization in the cell membrane. LQT3 arises as a result of a mutation in KCNJ5, which encodes the inwardly rectifying potassium channel, and results in reduced membrane expression of the protein. Other structural proteins have been implicated in LQTS. Ankyrin-B (ANK2) was identified in the course of linkage analysis of a large family with LQTS.42 LQT4 is characterized by a mutation within ANK2, the protein product of which is a structural protein (ankyrin-B) responsible for coordinated assembly of the sodium/calcium exchanger, the sodium/potassium ATPase pump, and the inositol triphosphate receptor.47 Screening of candidate genes in LQTS cohorts with no mutation in any of the more common LQTS genes has identified the remainder. These include CAV3, A kinase-anchor protein-9 (AKAP9), and SNTA1, which appear to modify ion channel function.33,46,48 In the case of LQT11, a mutation within AKAP9, which encodes an A kinase-anchoring protein responsible for facilitating phosphorylation of KCNQ1 by protein kinase A, impairs I\textsubscript{Kr} augmentation, leading to a clinical phenotype similar to that for LQT1 and LQT5.48 LQT8, or Timothy’s syndrome, occurs secondary to gain-of-function mutations within CACNA1c, which encodes an L-type calcium channel responsible for a depolarizing calcium current (I\textsubscript{CaL}).49 This current contributes to prolongation of the plateau phase within the cardiac action potential, effectively prolonging repolarization and accounting for the resultant long QT interval. Abnormalities of calcium signaling have recently been implicated in LQTS. Recently, with the use of whole exome sequencing, specific mutations in CALM1 and CALM2 have been identified. These result in dysfunctional calmodulin, which may prolong repolarization by more than one mechanism.27 Impaired Ca\textsuperscript{2+}-dependent inactivation of L-type calcium channels or dysregulation of voltage-gated sodium channels may lead to an increased depolarizing current during the plateau phase of the cardiac action potential.

The phenotypic expression of LQTS can also be influenced by modifier genes that may be common genetic variants in the general population but can have an important impact on QT interval and possibly the clinical outcome. Some of these modifiers are single nucleotide polymorphisms in genes encoding signaling proteins, as in NOS1AP.58–60 Others are variants within the LQT genes themselves that may have an impact on the QT interval in addition to an identified pathogenic mutation in any of the other, or same, LQT gene(s). Examples of these variants have been reported in KCNE1,61 KCNH2,62 and SCN5A.63

GWAS have provided further insight into the genetic determinants of cardiac repolarization. It was by this method that the first nucleotide polymorphisms in genes encoding signaling proteins as in NOS1AP were revealed.58–60
Subsequently, GWAS was useful in identifying other genetic loci, which, collectively, confer significant inherited variability in the QT interval. In addition, certain single nucleotide polymorphisms that are present in 1%–3% of the population may lead to acquired LQTS and events in the setting of low potassium, calcium, magnesium, and certain QT prolonging drugs.

There are distinct phenotypes that reflect the genetic heterogeneity of LQTS, although the final common characteristic is prolonged repolarization and risk of arrhythmia. There are unique ECG characteristics that typify the most common LQT subtypes. In LQT1, the T wave is characteristically broad-based, while the T wave in LQT2 is typically bifid and of low amplitude. In contrast, in LQT3, prolongation of the ST segment accounts for QT prolongation and is typically followed by a relatively small-amplitude T wave. In addition, certain forms of LQTS are accompanied by extracardiac manifestations, including periodic paralysis in Andersen–Tawil syndrome (LQT7), and syndactyly, immune deficiency, and autism in Timothy’s syndrome (LQT8).

The Jervell and Lange-Nielsen syndrome, with sensorineural deafness in association with QT prolongation and arrhythmia, arises secondary to homozygous or compound heterozygous mutations in either KCNQ1 or KCNE1, the genes encoding the alpha-subunits and beta-subunits of I_Ks, respectively. The cardiac manifestations are most often inherited in an autosomal dominant fashion, while the sensorineural deafness requires mutations in both allele copies, accounting for the original characterization of the syndrome as autosomal recessive.

The influence of genotype, sex, and age on the LQT phenotype have been well described by the International LQT Registry research group. The most common LQT subtypes have distinct arrhythmia triggers. Episodes of torsades des points in LQT1 typically occur at elevated heart rates, such as with exercise, while events during sleep are less common. This can be understood in the context of the normal function of I_Ks. This current becomes critical for shortening of the action potential at high heart rates, and its activity is increased under conditions of increased adrenergic tone, providing a link between exercise-induced arrhythmia and loss-of-function mutations in KCNQ1. I_Ks is responsible for repolarization reserve at lower heart rates, and serves to shorten the QT interval at resting heart rates and in the early phases of heart rate elevation in response to emotional or physical stress, prior to I_K activation. Patients with LQT2 appear to be susceptible to events during both sleep and exercise, while having a particular vulnerability to abrupt auditory stimuli, such as alarm clocks. Conversely, arrhythmic events in the context of LQT3 occur rarely during exercise and most frequently during sleep.

There is significant variability in the event rates in LQTS, even within the same genetic subgroup. Because of the implications for clinical management, efforts have been made to identify clinical and genetic variables that may contribute to the risk stratification of patients. Clinically, the QTc has been shown to be an independent predictor for clinical events when >500 msec. The onset of arrhythmic events in childhood is an important predictor of risk, with individuals having their first event in infancy being at very high risk of future events. A risk stratification model has been proposed for predicting a first cardiac event, and divides LQTS patients into low-risk, intermediate-risk, and high-risk groups on the basis of symptom history, QTc, and age.

Sex has also been shown to correlate with event rates in an age-dependent manner. Affected males have an increased event rate during childhood; however, in adolescence and early adulthood, the trend reverses. In fact, analysis of affected individuals 40 years of age or older from the International LQTS Registry reveals that affected females continue to be at an increased risk of arrhythmic death relative to their male counterparts. Analysis of sex in relation to genetic subtype has revealed that females with LQT2 and males with LQT3 are at particularly high risk for sudden death or first cardiac arrest. In genotype-positive individuals, a family history of sudden death in a first-degree relative has not been shown to be associated with a greater risk of death in LQTS.

The prognosis of LQTS is also related to the underlying genetic abnormality. Observations from the International LQTS Registry suggested that the frequency of clinical events prior to initiation of beta-blocker therapy from birth to 40 years of age was significantly higher in LQT2 (46%) and LQT3 (42%) patients relative to those with LQT1 (30%). There is also evidence that events in LQT3 are more likely to be lethal. In one study of patients prescribed beta-blocker therapy over an average of 5 years, cardiac event rates also differed according to subtype. Events such as syncope or cardiac arrest were reported to occur in 10% of LQT1 patients, but at higher rates in LQT2 (23%) and LQT3 (32%) patients. Although LQT1 and to a certain extent LQT2 patients appear to respond to beta-blockers, this therapy is of less obvious efficacy in LQT3. Mutations that result in amino acid changes in specific regions of the ion channel also confer an increased arrhythmia risk. For example, in LQT1, mutations in the cytoplasmic loops of the KCNQ1 protein or mutations with dominant-negative effects.
ion current effects are associated with a worse prognosis, especially when compared with mutations affecting the C-terminal regions of the protein. Similarly, in LQT2, mutations in the pore region of the \textit{KCNH2} protein result in a greater risk of arrhythmia, especially in males.

Accuracy in the diagnosis of LQTS is further confounded by the observation that LQTS patients may have QTc values within normal limits even if they are genotype-positive, or may show QT prolongation only under specific circumstances, resulting in the potential for significant overlap in QTc between healthy controls and LQTS patients. Scoring systems have been proposed, but lack sensitivity when compared with analysis of QTc alone. In an effort to improve diagnostic accuracy, strategies have been developed to determine QTc values at rest and also to characterize the dynamic changes that occur on a daily basis and with physiological stress. The first step involves serial ECG testing or acquisition of previously acquired ECGs in order to take account of the considerable temporal variability of the QTc in LQTS. Given the autosomal dominant inheritance pattern of the condition, examination of the ECGs of family members may be helpful if the phenotype is present in a first-degree relative. Exercise stress testing has been used extensively in the past to identify parameters of repolarization that may be indicative of LQTS. When stress testing is inconclusive, intravenous administration of epinephrine followed by analysis of the QT response in relation to heart rate may be useful in differentiating LQTS patients from healthy controls. Collectively, these relatively simple techniques may help guide the clinician in reaching a diagnostic conclusion.

Genetic testing in LQTS

The diagnosis of LQTS is made on clinical grounds, but incorporation of genetic testing in the evaluation of LQTS can be a powerful supportive tool, particularly as the results may assist in risk stratification, guide therapy, and facilitate family screening. Genetic testing for LQTS should not preclude careful clinical evaluation. Interpretation of clinical genetic testing results is not always straightforward. In particular, the clinical significance of novel genetic variants is frequently unclear. An analysis of culprit mutations in LQTS types 1–3 has revealed important features that provide a framework to differentiate between pathogenic and benign variants. For example, although non-missense mutations account for less than 5% of mutations, their likelihood of being pathogenic, regardless of their location within the ion channel, is greater than 99%. \textit{KCNQ1} and \textit{KCNH2} missense mutations within the transmembrane, linker, or pore regions also have a high likelihood of being pathogenic, and in the case of \textit{KCNH2} may also be predictive of cardiac events. In contrast, the significance of missense mutations in the interdomain linkers of \textit{SCN5A} is less clear.

Management of LQTS

Beta-blocker therapy is the first-line treatment for LQTS. However, when genotype-specific management of LQTS is considered, not all beta-blockers are equivalent. The four beta-blockers studied have equal efficacy in preventing first cardiac events in LQT1, but in LQT2, nadolol is the only beta-blocker that offers a significant risk reduction. Propranolol has been shown, at high concentrations, to also block \textit{I_{Kr}}, which may explain its inferior protective capacity in LQT2. An adjunctive therapy to be considered in LQT2 is long-term oral potassium supplementation. There are limited data regarding the use of beta-blockers in the less common LQTS subtypes. In LQTS3, beta-blockers appear to have much less of a protective effect, but do have some efficacy in reducing event rates and should be considered first-line therapy. There is some evidence that propranolol may have a specific advantage in this subtype, an effect likely mediated by its weak sodium channel properties. Adjunctive therapies such as mexiletine or ranolazine can be considered in very select cases of LQTS3.

Lifestyle advice is of particular importance in the management of LQTS. Individuals with any LQTS subtype must avoid QT-prolonging drugs. In LQT1, high-intensity exercise is restricted, especially swimming. In LQT2, the high rate of nonexercise triggers warrants avoidance of arousal sources such as loud telephones or alarms. Patients with very long QTc intervals (>500 msec) may shorten their QT interval with potassium supplements and/or spironolactone. In the postpartum period, compliance with beta-blockers and caution regarding sudden auditory arousal are essential.

In LQTS, ICD implantation is reserved for patients with recurrent events despite treatment, in whom a contraindication to medical therapy exists or in whom the calculated risk of sudden cardiac death (SCD) is very high. Left sympathetic denervation also reduces the risk of SCD in high-risk LQTS. It is useful for patients in whom recurrent events occur despite use of medication or after implantation of an ICD.

Short QT syndrome

SQTS is characterized by an abbreviated QT interval and a risk of both atrial and ventricular arrhythmias (Figure 3). Because
it is a rare condition, there are limited data on its prevalence and demographics. A review of 61 reported cases found a male preponderance (75%). The median age of symptom onset was 21 years. SCD was reported in 33% and atrial fibrillation in 18%. The initial description of SQTS included a QTc < 300 msec. The distribution of QT intervals in the general population, however, follows a bell-shaped distribution. The lower limit of normal for the QT interval is approximately 350 msec for males and 360 msec for females. A diagnostic scoring system has been proposed, which incorporates several features of the condition to aid in identifying SQTS and subsequent decision-making (Table 2). PQ segment depression is frequently seen in SQTS, and may be an additional unique ECG feature characteristic of this condition. The current guideline consensus is that the case definition should be a corrected QT interval < 330 msec. However, this represents an extreme of QT shortening and may lead to missing the diagnosis in more moderate cases. In the proposed diagnostic scorecard reported by Gollob et al, a corrected QT interval of < 370 msec may still satisfy a diagnosis of SQTS. The mechanism of arrhythmogenesis in SQTS likely involves increased dispersion of repolarization within the myocardium. Analogous to LQTS, gain-of-function repolarizing currents cause variable degrees of shortening of the action potential.

<table>
<thead>
<tr>
<th>Table 2 Short QT syndrome diagnostic scorecard</th>
</tr>
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<tbody>
<tr>
<td>Diagnostic parameters</td>
</tr>
<tr>
<td>QTc</td>
</tr>
<tr>
<td>&lt; 370</td>
</tr>
<tr>
<td>&lt; 350</td>
</tr>
<tr>
<td>&lt; 330</td>
</tr>
<tr>
<td>J point–T peak interval</td>
</tr>
<tr>
<td>&lt; 120 msec</td>
</tr>
<tr>
<td>Clinical history*</td>
</tr>
<tr>
<td>History of sudden cardiac arrest</td>
</tr>
<tr>
<td>Documented polymorphic VT or VF</td>
</tr>
<tr>
<td>Unexplained syncope</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Family history*</td>
</tr>
<tr>
<td>First-degree or second-degree relative with high probability of SQTS</td>
</tr>
<tr>
<td>First-degree or second-degree relative with unexplained cardiac arrest</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
</tr>
<tr>
<td>Genotype*</td>
</tr>
<tr>
<td>Genotype-positive</td>
</tr>
<tr>
<td>Variant of unknown significance in a culprit gene</td>
</tr>
</tbody>
</table>

**Notes:** Short QT syndrome is characterized by an abbreviated QT interval and a risk of both atrial and ventricular arrhythmias (see Figure 3). Because it is a rare condition, there are limited data on its prevalence and demographics. The J point–T peak interval must be measured in the precordial lead with the greatest amplitude T wave. Clinical history: events must occur in the absence of an identifiable etiology, including structural heart disease. Points can only be received for one of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history: points can only be received once in this section. High-probability SQTS, ≥ 4 points; intermediate-probability SQTS, 3 points; low-probability SQTS, ≥ 2 points. A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points.

**Abbreviations:** SQTS, short QT syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Genetics of SQTS**

Genetic subtypes of SQTS have been identified (Table 3). In SQT1, a gain-of-function mutation in KCNH2 impairs the voltage-dependent inactivation of $I_{Kr}$. This gain-of-function mutation causes increased current flow through the channel and shortens the action potential duration and QT interval. The first mutation described was N588K. This remains the most prevalent genetic subtype of SQTS. Other mutations in this gene have subsequently been identified. Gain-of-function mutations in KCNJ1 are the underlying genetic defect in SQT2. Similarly, these defects increase the repolarizing current, shortening the QT interval. SQT3 is caused by a gain-of-function mutation in KCNJ2, which encodes the alpha-subunit of the inward rectifier potassium current (IK1).

A reduction in depolarizing currents can also shorten the QT interval. Loss-of-function mutations in the L-type calcium channel (CACNA1C, alpha-subunit, and CACNB2b, alpha-subunit) are associated with a shortening of the QT interval and precordial ST elevation reminiscent of BrS. BrS is the dominant phenotype in these patients, and we believe they should be classified as such, thus leaving...

Figure 3 Electrocardiogram characteristic of short QT syndrome. 
Note: The short QT interval is marked by the red arrow.
Functional effect

Not known

Alpha-subunit

CALM1

Rare

1

Alpha-subunit

133

110,123

Gain-of-function

Loss-of-function

Calsequestrin-2

RyR2

CASQ2

Rare

RyR2

Not known

Triadin

KCNQ1

KCNH2

Loss-of-function

Figure 4

Cardiac ryanodine receptor

Table 4 Catecholaminergic polymorphic ventricular tachycardia by genetic subtype

CPVT subtype

Culprit gene

Protein

Functional effect of mutation

Frequency of cases (%)

CPVT1

RyR2

Cardiac ryanodine receptor

Gain-of-function

60

CPVT2

CASQ2

Calsequestrin-2

Loss-of-function

1–2

CPVT3

Locus at 7p22–p14 (homozygous)

Not known

Not known

Rare

CPVT4

CALM1

Calmodulin

Loss-of-function

Rare

CPVT5

TRDN

Triadin

Loss-of-function

Rare

Abbreviation: CPVT, catecholaminergic polymorphic ventricular tachycardia.
pattern, requiring either homozygous CASQ2 mutations, or compound heterozygosity.\textsuperscript{134,135} In CPVT, overall penetrance is 78%.\textsuperscript{136} Genome-wide scanning has revealed another locus at chromosome 7p22–p14 (homozygous) in a family with CPVT and an autosomal recessive pattern of inheritance.\textsuperscript{137}

The mechanism of arrhythmia in CPVT is related to instability in the RyR2 Ca(2+) release channel complex of the sarcoplasmic reticulum, which results in spontaneous Ca(2+) release through abnormal RyR2 channels leading to delayed after depolarization, triggered activity, and ventricular arrhythmias (Figure 3).\textsuperscript{138} Alterations in other calcium handling genes have been identified in CPVT (Table 4). Genome-wide linkage analysis has implicated calmodulin 1 (CALM1) in CPVT.\textsuperscript{139} Candidate gene screening has identified mutations in triadin (TRDN) as a cause of CPVT.\textsuperscript{140} Finally, SCN5A has been implicated in exercise-induced polymorphic ventricular arrhythmias, with the recent identification of a novel missense mutation in a highly conserved region of the gene in a large family with a CPVT phenotype.\textsuperscript{141}

Genetic testing for CPVT

Genetic testing is recommended in the evaluation of an individual with documented exercise-induced bidirectional VT or polymorphic VT, and when these arrhythmias occur in the context of emotional stress.\textsuperscript{142} Consideration may also be given to genetic testing in the evaluation of cardiac arrest in the setting of exertion or emotional stress. In sporadic cases, or when examination of the family pedigree suggests autosomal dominant inheritance, sequencing of RyR2 is recommended. CASQ2 sequencing should be considered in sporadic cases when there is a family history of consanguinity or when an autosomal recessive pattern of inheritance is suspected in a large pedigree. CASQ2 mutations are identified in only 1%–2% of all patients with CPVT.\textsuperscript{132} After identification of a pathogenic mutation, genetic testing can be extended to first-degree relatives.

Management of CPVT

The cornerstone of management of CPVT is restriction of moderate-intensity to high-intensity exercise and administration of high-dose beta-adrenergic blockade.\textsuperscript{135} Although verapamil has been given previously for breakthrough arrhythmia on beta-blockers,\textsuperscript{128,143} flecainide may be more effective.\textsuperscript{144} The antiarrhythmic activity of flecainide may have more than one mechanism, as it may confer direct RyR2 channel block\textsuperscript{145} or have a direct effect on voltage-gated sodium channels to raise the threshold for delayed after depolarization-induced triggered activity.\textsuperscript{146} Left cardiac sympathetic denervation may provide excellent long-term rhythm control and can be protective in cases of noncompliance, which are not uncommon in the chronic administration of beta-blockers in younger individuals.\textsuperscript{147} When arrhythmia persists despite medical therapy, an ICD is recommended. However, avoidance of ICD shocks with adequate medication is paramount in CPVT because the adrenergic outflow following a shock may provoke further arrhythmia, and there is a significant risk of arrhythmic death despite ICD implantation.\textsuperscript{148–150}

Gene therapy for this condition is not available for human use, but a recent study in a murine model of CPVT has demonstrated successful gene therapy, with achievement of
sustained infection using a viral vector carrying the wild-type *CASQ2* gene.\(^{151}\)

**Brugada syndrome**

In 1992, Pedro and Josep Brugada described a small cohort of patients with ECG findings of J point and ST segment elevation and a history of cardiac arrest due to ventricular fibrillation.\(^{152}\) BrS shows a marked male predominance (male-to-female, 8:1) and significant population variance according to ethnicity. In European and North American populations, the prevalence varies from 0.012\% to 0.26\%, whereas in Japanese populations the prevalence varies from 0.7\% and 1.0\%.\(^{143,153}\) Cardiac events typically occur at rest or during sleep at night.

The characteristic ECG pattern of BrS (Figure 5) consists of a \(\geq 0.2\) mV coved ST segment elevation followed by a negative T wave in more than one right precordial ECG lead.\(^{154}\) This is called the type 1 Brugada ECG pattern. A type 1 ECG pattern may be exposed by provocative testing with sodium channel-blocking agents or during febrile illness. The mechanism of ST segment changes in the setting of fever is likely secondary to further compromise of \(I_{Na}\) due to accelerated inactivation of the channel with higher body temperature,\(^{159}\) or reduced channel conductance. Sensitivity for ECG detection of this pattern can be increased by placing the right precordial ECG leads in the second or third intercostal spaces.\(^{156,157}\) Other ECG findings may be suggestive of a Brugada pattern, specifically the type 2 and 3 Brugada ECG patterns. These are characterized by a “saddleback” pattern of the ST segment with and without ST elevation, respectively. These patterns are not diagnostic for BrS, but should prompt further evaluation with provocative testing or serial ECG acquisition.\(^{154}\) A blunter, broader R wave in V1 or V2 predicts conversion of both types to a type 1 pattern with sodium channel-blocking drugs.\(^{158}\)

The pathophysiology underlying the Brugada ECG and risk of arrhythmia is incompletely understood, but three main theories have been proposed. Briefly, these may be summarized as: the “depolarization” hypothesis, whereby slow conduction into the right ventricular outflow tract predisposes to electrical re-entry;\(^{159}\) the “repolarization” hypothesis, in which an exaggerated phase 1 notch in the epicardium of the right ventricular outflow tract provokes a transmural dispersion of repolarization favoring phase 2 re-entry;\(^{153}\) and the “developmental” hypothesis, in which abnormal expression of cardiac neural crest cells in the right ventricular outflow tract leads to abnormal connexin expression (*Cx43*) and combined depolarization–repolarization abnormalities favoring arrhythmia.\(^{160}\)

**Genetics of BrS**

Several genes have been implicated in BrS, but in most clinical cases (~65\%) no gene mutation is identified. In 1998, screening of the *SCN5A* gene in a small number of families and individuals with idiopathic ventricular fibrillation and an ECG characteristic for BrS revealed missense, frameshift, and splice donor mutations. In the 11\%–28\% of individuals with positive genetic testing, the most frequent genetic alterations identified were loss-of-function mutations in *SCN5A*.\(^{161,162}\) In this subtype of BrS, clinical findings that correlate with the finding of a pathogenic mutation are longer PR interval on the resting ECG and an exaggerated increase in QRS duration with sodium channel-blocking agents.\(^{163}\) Although *SCN5A* mutations are strongly associated with BrS, genetic background appears to play an important role in expression of the ECG phenotype.\(^{164}\)

Mutations have been identified in several other genes. Mutations in *GPD1L* (BrS2) were identified initially by linkage analysis in a large kindred,\(^{165}\) and then in victims of sudden infant death syndrome.\(^{166}\) In all cases, cellular models demonstrated that the mutations were associated with a significant reduction in sodium current. Candidate gene screening later revealed loss-of-function mutations in *CACNA1C* (BrS3) and *CACNB2* (BrS4) in patients with BrS associated with short QT intervals (three of seven probands with a QTc <360 msec).\(^{121}\) In a later screening study, two
mutations in \textit{CACNA2D1} were found in four BrS probands who were gene-negative for \textit{SCN5A} mutations.  

Candidate gene screening has revealed numerous other genetic causes of BrS. These include mutations in \textit{SCN1B} which result in reduced sodium current (BrS5), \textit{KCNE3} mutations which lead to increased \(I_{\text{to}}\) (BrS6), \textit{SCN3B} mutations which result in reduced sodium current (BrS7), \textit{HCN4} mutations which result in reduced repolarizing \(I_f\) current (BrS8), and lead to action potential prolongation during bradycardia. More recently, \textit{SCN10A}, which encodes Nav1.8, has been identified as a BrS susceptibility gene, with identified mutations causing a significant reduction in normal sodium channel current. The estimated clinical penetrance based on analysis of individuals carrying pathogenic sodium channel mutations is 16%. Table 5 contains a detailed listing of these genes.

### Genetic testing in BrS

Targeted genetic screening of \textit{SCN5A} can be useful in patients with a type 1 Brugada ECG pattern, and if a pathogenic mutation is identified, mutation-specific testing is recommended in first-degree relatives. The diagnosis of BrS is based only on clinical history and ECG findings. The finding of a genetic mutation is an indicator of potential for development of the clinical phenotype. Such patients should be monitored carefully for the spontaneous appearance of a type 1 Brugada ECG or onset of clinical symptoms (syncope, in particular). Advice for the treatment of fever and avoidance of certain medications should be given to mutation carriers whether or not they display the ECG phenotype.

### Management of BrS

There is no effective medical treatment for BrS. The only method proven to prevent sudden death is ICD implantation. However, not all patients are at a level of risk that justifies this intervention. A history of cardiac arrest or unexplained syncope predicts a high rate of recurrent events and is an indication for ICD implantation. The management of asymptomatic patients with a type 1 Brugada ECG is more challenging, as there are conflicting data regarding the importance of a family history of sudden death, inducibility of ventricular arrhythmias on an electrophysiological study, and presence of a spontaneous Brugada type 1 pattern on ECG. An important finding common to many risk stratification studies is that one risk factor in isolation is probably not a strong enough indication for ICD implantation, and that a comprehensive approach with evaluation of multiple risk factors is likely to result in more accurate risk assessment. Novel markers of risk that require more rigorous study include the finding of QRS fragmentation and a ventricular refractory period of < 200 msec on an electrophysiological study.

All patients with a Brugada ECG should be taught to aggressively treat any episodes of fever, to seek ECG monitoring in the event of refractory fever, and to avoid drugs known to exacerbate the condition (http://www.brugadadrugs.org). In addition, all individuals with this condition should carry their ECG when seeking emergency medical care to prevent a false diagnosis of acute myocardial infarction and inappropriate care.

In the setting of refractory arrhythmias, isoproterenol, which increases the L-type calcium current, can be useful as an acute antiarrhythmic. Quinidine, a class Ia antiarrhythmic that blocks \(I_{\text{to}}\) and \(I_{\text{Kr}}\), can also be used in the ambulatory setting for arrhythmia control and to reduce ICD shocks. Neither drug has been tested against ICD implantation, so medical therapy cannot at this time be recommended as an alternative to ICD implantation in high-risk individuals.

### Early repolarization syndrome

Early repolarization is defined as > 1 mm of J-point elevation in any two contiguous ECG leads, with the exception of the right precordial (V1–V3) leads. The right precordial leads are excluded from the diagnostic definition to avoid
inclusion of individuals with Brugada type 1 pattern on ECG. There is, however, some clinical and pathophysiologic overlap between early repolarization (ER) syndrome (ERS) and BrS, and it has even been suggested that the two entities are part of a spectrum of “J-wave syndromes”. Early repolarization can also be manifest as slurring (a smooth transition from the QRS segment to the ST segment) or notching (a positive J deflection inscribed on the S wave).

Early repolarization was historically considered a normal physiologic variant, with a prevalence of 1%–13% in the general population along with a higher incidence in children, males, athletes, and African-Americans. However, it has more recently been associated with arrhythmic events, particularly idiopathic ventricular fibrillation and ventricular fibrillation complicating myocardial infarction. When ER is seen in the context of prior cardiac arrest, the rate of recurrence of ventricular fibrillation is much higher than that seen in survivors of idiopathic ventricular fibrillation who do not have ECG evidence of ER. Conversely, when ER is noted incidentally in an asymptomatic individual, the risk of adverse events is very low. Features that may be associated with increased risk include J point amplitude (>0.2 mV) and J-point elevation in the inferior lead or both the inferior and lateral leads. Additional ECG findings, such as a horizontal or downward sloping ST segment, may also be associated with arrhythmic mortality.

The diagnosis of ERS is made when the ECG features of ER are noted in an individual with a history of idiopathic ventricular fibrillation or polymorphic ventricular tachycardia (Table 6). Other conditions known to cause J-point elevation, such as ischemia, hypokalemia, hypercalcemia, and hypothermia, need to be excluded. J-point elevation is felt to reflect the transmural differences in the early phases of the action potential. The relative prominence of $I_{Na}$ in the epicardium accentuates the notching of the action potential, and data from perfused myocardial wedge preparations have suggested that this is the origin of the inscribed J point. Augmentation of the gradient created by $I_{Na}$ may occur secondary to a relative increase in outward currents ($I_{Na}$, IKATP) or a reduction in the opposing inward currents ($I_{Ca}$, $I_{K}_{st}$).

### Genetics of ERS
ERS is a clinical diagnosis, and the contributory role of genetic testing has not been established. Candidate gene studies have identified rare variants associated with ERS. These include KCNJ8, ABC9, SCN5A, CACNA1C, CACNB2B, and CACNA2D1. Recently, a rare variant was found in the KCND2 gene encoding for the Kv4.2 channel in a patient with J waves in the right precordial leads. However, all of these variants were detected in single patients and only in a minority of the ERS cases studied.

### Management of ERS
A proposed approach to the clinical assessment and management of ER is detailed below. There is an emphasis on identification of clinical predictors of risk rather than on

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### Table 6 Recommendations for the diagnosis and management of ERS syndrome

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<tr>
<th>Expert consensus recommendations on early repolarization diagnosis</th>
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<tr>
<td>1. ER syndrome is diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymporphic VT</td>
<td></td>
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<tr>
<td>2. ER syndrome can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG</td>
<td></td>
</tr>
<tr>
<td>3. ER pattern can be diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG</td>
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<tr>
<th>Expert consensus recommendations on early repolarization therapeutic interventions</th>
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| Class I | 1. ICD implantation is recommended in patients with a diagnosis of ER syndrome who have survived a cardiac arrest  
2. Isoproterenol infusion can be useful in suppression of electrical storms in patients with a diagnosis of ER syndrome  
3. Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ER syndrome  
4. ICD implantation may be considered in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST-segment elevation >1 mm in two or more inferior or lateral leads  
5. ICD implantation may be considered in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J wave amplitude, horizontal/descending ST segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation |  |
| Class IIa | 6. ICD implantation is not recommended for asymptomatic patients with an isolated ER ECG pattern |  |
| Class IIb | 7. ICD implantation is recommended in patients with a diagnosis of ER syndrome who have survived a cardiac arrest  
8. Isoproterenol infusion can be useful in suppression of electrical storms in patients with a diagnosis of ER syndrome  
9. Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ER syndrome  
10. ICD implantation may be considered in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST-segment elevation >1 mm in two or more inferior or lateral leads  
11. ICD implantation may be considered in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J wave amplitude, horizontal/descending ST segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation |  |


**Abbreviations:** ECG, electrocardiogram; ER, early repolarization; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

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ECG features alone to guide management decisions. ICD implantation should be recommended in any individual with a history of resuscitated cardiac arrest. Consideration can be given to ICD implantation in an individual with ER and a history of non-neurocardiogenic syncope or a strong family history of SCD. Arrhythmias occurring in the setting of ER can be managed with quinidine, which has been shown to be effective in normalizing the ECG. Isoproterenol can be used in the acute management of ventricular arrhythmias. Other commonly used antiarrhythmic medications, such as amiodarone, mexiletine, verapamil, beta-blockers, and class Ic antiarrhythmics have little role in the management of arrhythmias in ERS.

Conclusion
Genetic testing has a very important role in the evaluation of individuals with inherited arrhythmia disorders, particularly in screening of potentially affected family members. This is a complex and evolving field, and genetic counseling should be initiated early in the patient encounter, prior to genetic testing, to prepare the patient and their family for possible outcomes. As our understanding of the genetics underlying these primary arrhythmia disorders grows, the interpretation of test results may change, and an ongoing relationship with a genetic counselor over time is essential.

In certain conditions, such as LQTS, genotyping can also provide valuable prognostic information, and can guide therapy. In most cases, however, the greatest role of genetic evaluation lies in streamlining the process of family screening when a pathogenic mutation is found in an affected individual. The evaluation of a victim of sudden unexplained death, post-mortem genetic analysis has been recommended as part of standard practice in parts of Canada and the European Union. This is an important first step in identifying living family members who may be at risk. Guidelines for the appropriate handling of post-mortem tissue and blood samples for future clinical and research gene testing is critical as our understanding of the molecular basis of these diseases evolves. In the short-term, while a frustrating proportion of these cases remain gene-elusive, we must rely on careful proband phenotyping and clinical screening of family members.

The current knowledge gap in our understanding of molecular cardiology has encouraged alternative approaches to genetic testing, as well as investigation of gene–gene interactions and environmental contributions to phenotype expression. GWAS and whole exome sequencing have expanded the potential for genetic diagnostics, and have been contributed to furthering our understanding of molecular electrophysiology. This is a time of exponential growth and discovery in the field of cardiac genetics. The gains made in the last decade are paving the way for the next era of cardiac genetics, ie, genotype-specific therapies, novel drug development, and potentially curative gene therapy.

Disclosure
The authors report no conflicts of interest in this work.

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