# Inherited arrhythmia syndromes

***Inherited arrhythmia syndromes are an important contributor to sudden death in children and adults. These cardiac 'channelopathies' lead to arrhythmias in a structurally normal myocardium and are often variable in penetrance and expressivity. The clinical features and management options for the four major channelopathies are outlined.***

The inherited arrhythmia syndromes form a group of genetic diseases that confer susceptibility to potentially lethal cardiac arrhythmias, leading to syncope or sudden death. While most arrhythmias occur in a dilated, restrictive or ischaemic heart, these disorders cause arrhythmias in a structurally normal myocardium. The majority are channelopathies, caused by mutations in genes mediating the ion channel currents of the cardiac action potential.

The first presentation of a cardiac channelopathy may be sudden cardiac death, which in people under 35 years of age has an incidence of 1.8 per 100 000 in England and Wales, or 400 cases per year (Papadakis et al, 2009). Inheritance of arrhythmia syndromes is characterized by variable penetrance (not all mutation carriers show a disease phenotype) and expressivity (differing severity of phenotype), complicating diagnosis and management.

This review outlines the key features and genetic basis of the cardiac ion channelopathies (*Table 1*). Genetic disorders causing arrhythmias and structural heart disease (e.g. hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, familial Wolff–Parkinson–White syndrome) are discussed elsewhere (Watkins et al, 2011).

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## Arrhythmia syndromes

### Long QT syndrome

Inherited long QT syndrome, defined by prolonged ventricular repolarization, is the commonest of the genetic arrhythmia disorders, with a prevalence of 1 in 2000 (Schwartz et al, 2009). The first genetic locus was identified in 1991 (Keating et al, 1991) and genetic

**Table 1. Genetic basis of inherited arrhythmia syndromes**

| Disease | | Gene | Function |
|---|---|---|---|
| Long QT syndrome * | LQT1 | KCNQ1 | $I_{Ks}$ potassium channel α subunit |
| | LQT2 | KCNH2 | $I_{Kr}$ potassium channel α subunit |
| | LQT3 | SCN5A | $I_{Na}$ sodium channel α subunit |
| | LQT4 | ANK2 | Anchoring protein |
| | LQT5 | KCNE1 | $I_{Ks}$ potassium channel β subunit |
| | LQT6 | KCNE2 | $I_{Kr}$ potassium channel α subunit |
| | LQT7 | KCNJ2 | $I_{K1}$ potassium channel |
| | LQT8 | CACNA1C | $I_{Ca,L}$ calcium channel α subunit |
| | LQT9 | CAV3 | Caveolae coat protein |
| | LQT10 | SCN4B | $I_{Na}$ sodium channel β4 subunit |
| | LQT11 | AKAP9 | A-kinase-anchoring protein |
| | LQT12 | SNTA1 | Membrane scaffold |
| CPVT † | CPVT1 | RYR2 | Ryanodine receptor |
| | CPVT2 | CASQ2 | Cardiac calsequestrin |
| Brugada ‡ syndrome | | SCN5A | $I_{Na}$ sodium channel α subunit |
| | | GPD1L | Glycerol-3-phosphate dehydrogenase 1 like |
| | | CACNA1C | $I_{Ca,L}$ calcium channel α subunit |
| | | CACNB2B | $I_{Ca,L}$ calcium channel β subunit |
| | | SCN1B | $I_{Na}$ sodium channel β-1 subunit |
| | | KCNE3 | $I_{to}$ voltage-gated potassium channel, Isk-related family |
| | | SCN3B | $I_{Na}$ sodium channel type III β |
| | | HCN4 | $I_f$ hyperpolarization-activated potassium channel 4 |
| Short QT syndrome | | KCNH2 | $I_{Kr}$ potassium channel α subunit |
| | | KCNQ1 | $I_{Ks}$ potassium channel α subunit |
| | | KCNJ2 | $I_{K1}$ potassium channel |
| Idiopathic ventricular fibrillation | | SCN5A | $I_{Na}$ sodium channel α subunit |
| | | SCN3B | $I_{Na}$ sodium channel β subunit Navβ3 |
| | | DPP6 | Dipeptidyl-aminopeptidase-like protein 6 |
| | | KCNJ8 | $I_{K(ATP)}$ ATP-sensitive potassium channel |
| Familial atrial fibrillation | | KCNE2 | $I_{Kr}$ potassium channel α subunit |
| | | KCNJ2 | $I_{K1}$ potassium channel |
| | | KCNQ1 | $I_{Ks}$ potassium channel α subunit |
| Progressive cardiac conduction disease | | SCN5A | $I_{Na}$ sodium channel α subunit |
| | | TRPM4 | Calcium-activated non-selective cation channel |

*LQT1 accounts for 30–35% of cases of long QT syndrome, LQT2 accounts for 25–30% and LQT3 accounts for 5–10%. † CPVT1 accounts for 50% of cases of catecholaminergic polymorphic ventricular tachycardia (CPVT). ‡ Mutations in SCN5a are found in 30% of cases of Brugada syndrome.

classification (*Table 1*) has increasingly replaced the long QT syndrome clinical subtypes of Romano–Ward syndrome (autosomal dominant long QT syndrome), Jervell–Lange–Nielson syndrome (autosomal recessive long QT syndrome, congenital deafness), Andersen–Tawil syndrome (long QT syndrome, periodic paralysis, dysmorphic features) and Timothy syndrome (long QT syndrome, congenital heart defects, neuropsychiatric features).

Most long QT syndrome is caused by loss of function gene mutations in the outward K+ current (e.g. LQT1 is caused by mutations in KCNQ1, the voltage-gated K+ channel) or gain of function mutations in the inward Na+ current (e.g. LQT3 is caused by mutations in SCN5A, the α-subunit of the voltage-gated Na+ channel). Both prolong myocardial repolarization, such that cardiac myocytes may begin to depolarize again before cardiac repolarization is complete. This 'early afterdepolarization' can produce ventricular extrasystoles (seen on electrocardiogram as the R-on-T phenomenon), in turn triggering torsades de pointes (Morita et al, 2008). While torsades de pointes usually self-terminates after 10–12 cycles as a result of refractoriness, leading to presyncope or syncope, in a minority of cases torsades de pointes degenerates into ventricular fibrillation.

In addition to QTc prolongation, patients with long QT syndrome show variable abnormalities of the T wave which may correlate with the underlying genotype (*Figure 1*). LQT1 patients often have a broad and pronounced T wave, or late onset of a normal T wave. LQT2 patients often have low amplitude or bifid T waves and patients with LQT3 have particularly delayed T waves, which are peaked and/or bifid, or symmetrical with a steep downslope. One cannot reliably make a genetic diagnosis on the basis of T wave morphology and should bear in mind normal variants, i.e. bifid T waves are normal in children and can persist up to approximately 14 years of age.

The effect on the QT interval and the risk of sudden cardiac death varies considerably in long QT syndrome, even within a family carrying the same mutation. Moreover, identical gene mutations can manifest as an entirely different clinical or electrical disorder: mutations causing LQT3 in SCN5A also present phenotypically as Brugada syndrome (Bezzina et al, 1999).

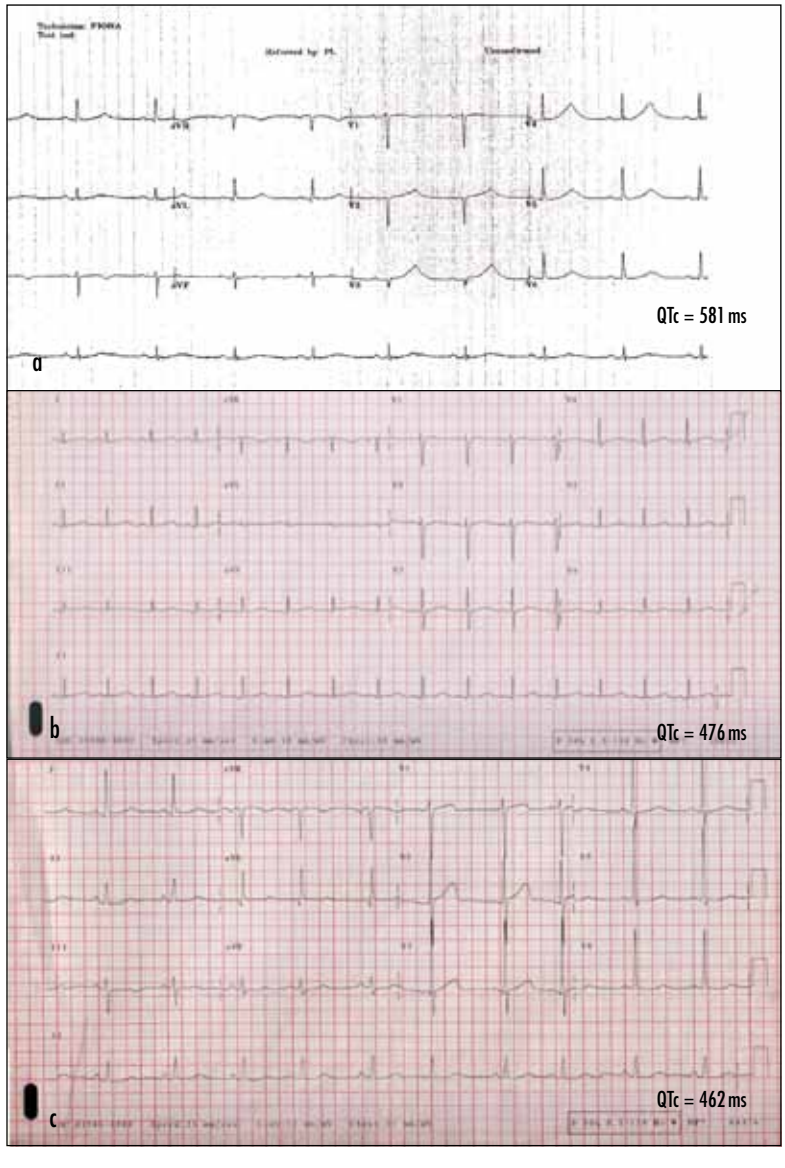
## Brugada syndrome

Brugada syndrome is characterized by right bundle–branch block and right praecordial ST segment or T wave abnormalities associated with sudden cardiac death as a result of ventricular arrhythmias (Brugada and Brugada, 1992). The prevalence of Brugada syndrome is highest in south-east Asia, presenting in adulthood with arrhythmias occurring at rest and while asleep, giving rise to the Thai name *lai tai* (death during sleep).

There is a strong male predominance (M:F 8:1) and autosomal dominant inheritance (Priori et al, 2000). Up to 30% of patients carry mutations in SCN5A, the alpha subunit of the cardiac voltage-gated Na+ channel (Miura et al, 2008), leading to reduced $I_{Na}$. Mutations in other ion channel ($I_{to}$) and membrane transporter proteins have also been identified (*Table 1*).

Diagnosis of Brugada syndrome requires one of the described electrocardiogram variants (*Figure 2*). Type I has 'coved' ST elevation in the right praecordial leads, with types 2 and 3 showing variable 'saddle-back' ST elevation. Type 2 and 3 electrocardiograms are not diagnostic of Brugada syndrome unless conversion to a type 1 pattern occurs after sodium channel blockade. The Brugada appearance may be dynamic because of variability in autonomic tone, such that the electrocardiogram changes are not apparent at rest.

***Figure 1. Example electrocardiograms of patients with long QT syndrome. a. Example of LQT1 electrocardiogram illustrating broad tented T waves in the anterior chest leads. b. LQT2 electrocardiogram illustrating bifid T waves in lead V3. Note marked QT prolongation of 476 ms in this male patient. c. Example of LQT3 mutation carrier – note the flat isoelectric segment in lead V6 and small symmetrical T wave.***



### Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia is an inherited arrhythmia leading to ventricular tachycardia at times of emotional or physical (catecholaminergic) stress, with high risk of sudden cardiac death. Inheritance may be dominant or recessive and usually manifests in childhood, with a mean age of onset of symptoms of 7–9 years (Ylanan et al, 2010).

In catecholaminergic polymorphic ventricular tachycardia the resting electrocardiogram is usually normal and the diagnosis is suggested by exercise or catecholamine stress testing which induces significant, reproducible ventricular ectopy progressing to bigeminy and bidirectional ventricular tachycardia. Approximately 50% of catecholaminergic polymorphic ventricular tachycardia occurs as a result of mutations in the cardiac ryanodine receptor (RYR2), leading to spontaneous or excessive calcium release from the sarcoplasmic reticulum, delayed afterdepolarizations and arrhythmias (Priori et al, 2001). Mutations have also been identified in other calcium handling proteins, e.g. calsequestrin and ankyrin B.

### Short QT syndrome

Short QT syndrome is a rare condition of shortened QT interval associated with syncope, atrial fibrillation and risk of sudden death (Gaita et al, 2003; Brugada et al, 2004). It is caused by gene mutations causing gain of function effects in potassium channels (KCNH2, KCNQ1, KCNJ2), shortening cardiac repolarization. Short QT syndrome presents early and is a cause of sudden cardiac death in neonates. Diagnostic criteria suggest that the QT interval may be as short as <330 ms, but ranges up to 370 ms (Gollob et al, 2011).

***Figure 2. Type 1 electrocardiogram in Brugada syndrome.***

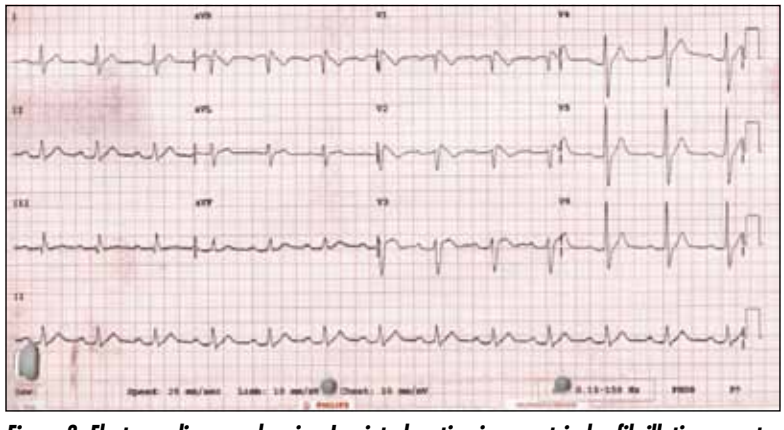
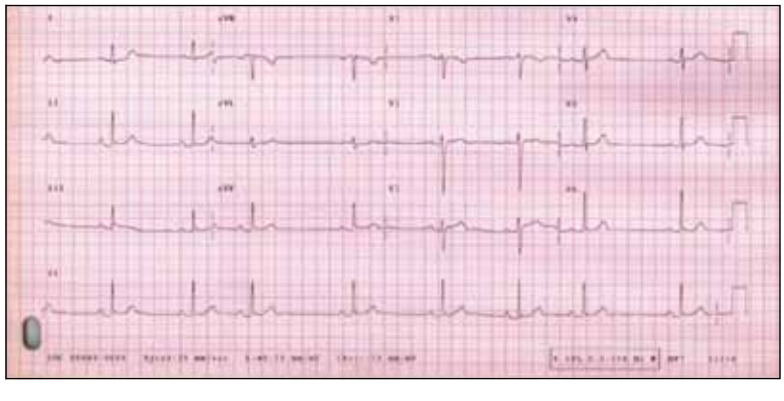


***Figure 3. Electrocardiogram showing J-point elevation in a ventricular fibrillation arrest survivor.***



### Idiopathic ventricular fibrillation

Idiopathic ventricular fibrillation is likely to represent a heterogeneous group of poorly characterized channelopathies predisposing to sudden cardiac death through spontaneous ventricular fibrillation. There may be baseline electrocardiogram features of early repolarization, demonstrated by elevation of the J-point (*Figure 3*) (Haïssaguerre et al, 2008). Several idiopathic ventricular fibrillation loci have been defined, e.g. SCN5A, DPP6, KCNJ8 and SCN3B, and more are likely to emerge (Alders et al, 2009; Haïssaguerre et al, 2009; Valdivia et al, 2010).

## Clinical evaluation and investigation

The presentation of cardiac channelopathies tends to occur at either end of the clinical spectrum: with ventricular arrhythmia or sudden death, or in asymptomatic family members through screening. In general, malignant phenotypes present earlier, often in childhood or young adulthood. A first presentation of inherited long QT syndrome is unusual beyond 40 years of age.

Identifying patients with inherited heart disease can be challenging. Palpitations and syncope, which may be the presenting symptoms of ventricular tachycardia, are common in young adults, and usually benign. Careful evaluation of the history may reveal red flags for an underlying arrhythmia: exertional or recurrent syncope, palpitations followed by collapse, or a family history of sudden or unexplained death.

There are a number of examples of patients with long QT syndrome suffering delayed or misdiagnosis after presentation (MacCormick et al, 2009). Presentation may be atypical and long QT syndrome should be considered in patients or family members with a history of an unexplained seizure caused by cerebral hypoxia as a result of arrhythmia. Similarly, of 17 patients with Brugada syndrome who survived cardiac arrest, 14 patients (82%) had a preceding history of syncope (Priori et al, 2000).

In families with a channelopathy, the history may reveal a specific trigger of arrhythmias, which in long QT syndrome correlates with genotype. Exercise, classically swimming and diving, is a trigger to ventricular arrhythmia in LQT1 (Schwartz et al, 2001). In LQT2, sudden auditory stimuli, for example an alarm clock or telephone, precipitates arrhythmia. Patients with LQT3 and Brugada syndrome are most at risk of arrhythmia during sleep and catecholaminergic polymorphic ventricular tachycardia classically presents in children following exercise or emotional stress.

All patients presenting to the emergency department or secondary care following a collapse should have a 12-lead electrocardiogram. When evaluating the QT interval, the longest QT of all electrocardiogram leads should be measured, corrected for heart rate (*Figure 4*). The Bazett formula is most widely accepted (QTc = QT / √RR), although this tends to overestimate the QT interval during tachycardia and underestimate during bradycardia.

Upper limits for the QT interval are defined as QTc <440 ms for men and women <460 ms (Roden, 2008), but strict application of these criteria misses a proportion of long QT syndrome patients (identified by a genetic mutation) whose QT interval lies within the 'normal' range. Outside the setting of a known long QT syndrome family, where family members can be screened for a defined mutation, the identification of these individuals at increased risk of arrhythmia is extremely difficult. Similarly, 2.5% of normal people will lie outside the defined range for a 'normal' QT interval.

Once electrocardiogram changes are identified, or a ventricular arrhythmia is recorded on Holter or REVEAL monitoring, a genetic aetiology is a diagnosis of exclusion. For example, in the presence of a long QT interval, drug causes (e.g. sotalol, amiodarone, macrolides, fluoxetine, haloperidol, methadone) should be excluded, as well as hypokalaemia, hypocalcaemia, hypomagnesaemia and hypothyroidism, which also prolong the QTc. Patients with drug-induced long QT syndrome may also have LQT mutations, but only show a phenotype after provocation with ion channel-blocking drugs (often $I_{Kr}$ antagonists).

Exclusion of underlying structural heart disease is a prerequisite for diagnosis of cardiac ion channel disease, and magnetic resonance imaging is the imaging gold standard to identify subtle myocardial abnormalities such as the fibrosis of arrhythmogenic right ventricular cardiomyopathy, sarcoidosis and amyloidosis, all of which may present with ventricular arrhythmias (Lubitza et al, 2008).

Pharmacological challenge is routinely used in sudden cardiac death screening clinics. Sodium channel blockade with ajmaline or flecainide can reveal a concealed Brugada appearance, or induce conversion of a type 2 or 3 Brugada pattern to type 1, and should be performed where there is clinical suspicion of the diagnosis. Exercise or adrenaline challenge is used in suspected cases of catecholaminergic polymorphic ventricular tachycardia, where polymorphic ventricular ectopy or ventricular tachycardia may be seen at increasing heart rates. Adrenaline challenge is also of value in diagnosis of LQT1 – a paradoxical increase in QT (≥30 ms) is seen with low dose adrenaline and has high sensitivity and specificity for the diagnosis (Vyas et al, 2006).

The role of the electrophysiology study in inherited arrhythmias is evolving. In long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, it provides minimal diagnostic or prognostic information (Stephenson and Berul, 2007). In Brugada syndrome there are conflicting results, with some evidence to suggest that inducible ventricular tachycardia or ventricular fibrillation at electrophysiology study is a predictor of future sudden cardiac death or arrhythmia, particularly in patients with symptoms (Brugada et al, 2001). In contrast, however, Priori et al (2002) and the FINGER Brugada syndrome registry showed a low predictive value of electrophysiology testing for the risk stratification of Brugada patients for sudden cardiac death (Priori et al, 2002; Probst et al, 2010). Recent data suggest that patients with ventricular refractory periods of <200 ms at electrophysiology study are more likely to develop significant ventricular arrhythmias (Priori et al, 2012).

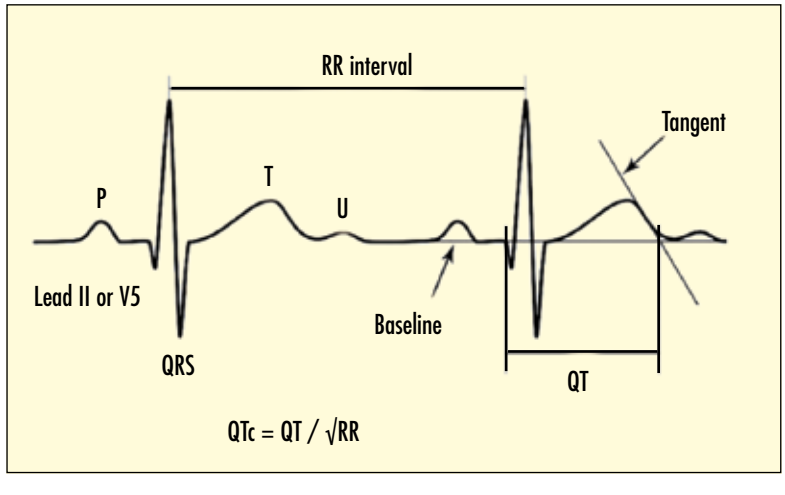
Catheter ablation of triggering ventricular foci has been reported in small case series of patients with Brugada syndrome and idiopathic ventricular fibrillation, with success in reducing arrhythmia burden (Stephenson and Berul, 2007). Modification of the right ventricular outflow tract epicardium in refractory Brugada patients has been shown to restore the coved ST segment to normal with a reduction in ventricular fibrillation episodes (Nademanee et al, 2011).

## Diagnostic criteria and genetic testing

After a new diagnosis of a cardiac channelopathy, family screening should initially be offered to first degree relatives, with further cascade screening if new cases are identified (Svendsen and Geelen, 2010). Evaluation of family members begins with a detailed review of the index case: the clinical history and investigations, genetic testing results and, where applicable, post-mortem report and a cardiac pathologist's review of available histology in a deceased relative suspected of sudden arrhythmic death.

The variability of penetrance and expressivity in cardiac channelopathies leads to difficulty in evaluating borderline cases, often asymptomatic family members, where the significance of subtle or mild electrocardiogram abnormalities is unclear. This uncertainty has prompted

***Figure 4. Measurement of the QT interval. Reproduced from Postema et al (2008). All measurements should be in seconds to ensure accurate calculation.***



development of diagnostic scoring systems for many of the inherited cardiac arrhythmia syndromes. For long QT syndrome, the Schwartz criteria (Schwartz et al, 1993) (*Table 2*) incorporate the nature of the presentation (e.g. aborted sudden cardiac death), the presence of a family history and electrocardiogram changes. A score of ≥4 suggests a high probability of long QT syndrome, a score of 2–3 intermediate probability and a score ≤1 low probability.

The Schwartz criteria pre-date genetic testing and take no account of a known long QT syndrome mutation in the family. The criteria are poorly sensitive for concealed forms of long QT syndrome, only identifying 38% of carriers of a familial long QT syndrome mutation (Priori et al, 1999). Genetic testing in clear-cut long QT syndrome identifies mutations in 75% of patients, adds prognostic and therapeutic information (see below), and allows family members with subclinical features to be identified. However, in index patients with normal or borderline QT intervals, those without other clinical features or a family history, genetic testing has a significantly lower yield and is not yet part of routine work-up.

Diagnosis of Brugada syndrome is currently based on clinical and electrocardiogram criteria: the presence of a type 1 electrocardiogram with one of documented ventricular fibrillation or polymorphic ventricular tachycardia, a family history of sudden cardiac death <45 years old, coved electrocardiograms in family members, syncope or nocturnal agonal respiration (Antzelevitch et al, 2005). The role of genetic testing is less clear than in long QT syndrome. Genetic testing has low sensitivity in Brugada syndrome: mutations in SCN5A are identified in only 30% with the syndrome. Furthermore, identification of a genetic mutation does not influence management or prognosis and only helps with identification of family members who cannot easily undergo clinical or electrocardiogram evaluation, e.g. for geographical reasons.

**Table 2. Schwartz criteria for diagnosis of long QT syndrome**

| Clinical evaluation | | | Score |
|---|---|---|---|
| Electrocardiogram | QTc (Bazett's formula) | ≥480 ms | 3 |
| | | 460–479 ms | 2 |
| | | 450–459 ms (in males) | 1 |
| | Torsades de pointes | | 2 |
| | T wave alternans | | 1 |
| | Notched T wave in three leads | | 1 |
| | Bradycardia (resting rate < second percentile for age) | | 0.5 |
| Clinical history | Syncope with stress (or) without stress | | 2 (or) 1 |
| | Congenital deafness | | 0.5 |
| Family history | Family members with definite long QT syndrome (score ≥4) | | 1 |
| | Unexplained sudden cardiac death aged <30 years in immediate family | | 0.5 |

From Schwartz et al (2001)

## Risk stratification and management

Patient management is based on risk stratification for sudden cardiac death. Generally, patients at lower risk of malignant arrhythmias can be managed conservatively or pharmacologically, while those at high risk require implantable cardioverter defibrillator insertion for primary or secondary prevention (Zipes, 2006). In addition to this spectrum of risk, patient age, psychological factors and preference are important factors guiding choice of therapy.

Risk factors for sudden cardiac death have been derived from cohort follow up. In LQT1 and 2, the duration of QT prolongation is the most important risk factor for cardiac events: syncope or sudden cardiac death in those with a QTc interval in the lowest quartile (<446 ms) was under 20%, but exceeded 70% in those with a QTc in the highest quartile (>498 ms) (Moss, 1993; Priori et al, 2003, 2004). Additional risk factors are a personal history of aborted sudden cardiac death or syncope, but not sudden cardiac death of a sibling (Kaufman et al, 2008). Males have an increased risk of events during pre-adolescence and females during adolescence and subsequently. Patients with LQT2 and LQT3 are at higher risk than those with LQT1 (Zareba et al, 2003).

In Brugada syndrome, those at highest risk are men with a spontaneous type 1 electrocardiogram and a history of syncope, where the risk of ventricular fibrillation varies from 1.9–8.8% per year, depending on the series. Neither family history of sudden cardiac death or a confirmed SCN5A mutation are predictive of sudden cardiac death.

There is little randomized controlled trial level evidence supporting management of patients with inherited arrhythmia syndromes. Patients with long QT syndrome are counselled to avoid involvement in competitive sports and avoidance of drugs which further prolong the QT interval (www.qtdrugs.org) as well as genetic-specific triggers, including unsupervised swimming for LQT1, and sudden auditory stimuli during sleep for LQT2. Brugada patients should avoid drugs which can induce the Brugada pattern, i.e. class Ia and Ic antiarrhythmics, as well as beta-blockers, tricyclic antidepressants, nicorandil, lithium, cocaine and propofol (www.brugadadrugs.org).

Beta-blockade is the mainstay of pharmacological management in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia. Patients with LQT1 derive the most benefit from beta-blockade and there is a degree of protection in LQT2 and 3, although symptomatic bradycardia can in turn lead to a need for permanent pacing (Priori et al, 2004). Sodium channel blockers (e.g. mexilitine, flecainide) may be of use in LQT3, where there is prolongation of the Na+ current, but their use is not yet established. Beta-blockade is also indicated for patients with clinically diagnosed catecholaminergic polymorphic ventricular tachycardia and

asymptomatic gene-positive catecholaminergic polymorphic ventricular tachycardia, as a result of the relatively high penetrance of the disease. The efficacy of beta-blocker therapy can be assessed by repeat exercise testing. There is a trend to prescribe implantable cardioverter defibrillators to ensure full protection against sudden cardiac death in this population, but this can be associated with a high inappropriate shock rate for exercise-induced bigeminy as opposed to ventricular tachycardia or ventricular fibrillation.

In Brugada syndrome, quinidine, which blocks $I_{to}$, normalizes the cardiac action potential and reduces the inducibility of ventricular fibrillation, and may have a role in children (Belhassen et al, 2004). The use of quinidine in asymptomatic adults with resting type 1 electrocardiograms is currently being evaluated in an international registry study. Isoprenaline and cilostazol can be used to control a ventricular tachycardia storm in patients with Brugada syndrome by increasing $I_{Ca}$. Quinidine and disopyramide have also been used to prolong repolarization and prevent ventricular fibrillation in patients with KCNH2 mutations in short QT syndrome.

Aborted sudden cardiac death or recurrent ventricular arrhythmia despite medical therapy are general indications for insertion of an implantable cardioverter defibrillator. The Heart Rhythm UK guidelines for implantable cardioverter defibrillator insertion are summarized in *Table 3*. The morbidity associated with implantable cardioverter defibrillator insertion is particularly relevant in young patients, as a number of box and/or lead changes may be required over their lifetime. There may be a psychological morbidity from inappropriate shocks (Daubert et al, 2007). As such, while secondary prevention with implantable cardioverter defibrillator therapy (following aborted sudden cardiac death) is clearly justified, there is uncertainty about which asymptomatic patients are at sufficient risk to warrant primary prevention by implantable cardioverter defibrillator implantation. Left cardiac sympathetic denervation is an option for intractable arrhythmia in patients failing beta-blocker therapy and reduces ventricular arrhythmia in LQT1, LQT2 and catecholaminergic polymorphic ventricular tachycardia (Schwartz et al, 2004). The evolution in implantable cardioverter defibrillator technology to fully subcutaneous systems may influence device prescription in the channelopathy population in the future, e.g. in Brugada syndrome where prophylactic pacing is less of an issue a fully subcutaneous implantable cardioverter defibrillator without intracardiac leads offers advantages, *vs* in long QT syndrome where atrial pacing at 80/min prevents arrhythmic events.

## Conclusions

Inherited arrhythmia syndromes remain an important cause of sudden cardiac death in the young. Careful attention to red flag symptoms, consideration of family history and close scrutiny of a 12-lead electrocardiogram remain crucial to identifying new cases. The ongoing recruitment of larger, genotyped cohorts will allow interrogation of genotype–phenotype correlations and lead to improved risk stratification. Evolving implantable cardioverter defibrillator technology and genetically directed pharmacotherapy are emerging as low morbidity, effective treatments for the prevention of sudden cardiac death. **BJHM**

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**Table 3. Indications for implantable cardioverter defibrillator insertion (Heart Rhythm UK guidelines)**

| | Previous ventricular fibrillation or cardiac arrest | Symptomatic | Asymptomatic |
|---|---|---|---|
| Long QT syndrome | Implantable cardioverter defibrillator insertion recommended in addition to beta-blockade | Implantable cardioverter defibrillator insertion recommended in patients with continuing syncope despite beta-blockade or left cardiac sympathetic denervation | Consider in asymptomatic patients at higher risk of sudden cardiac death, e.g. markedly prolonged QTc |
| Brugada syndrome | Implantable cardioverter defibrillator insertion recommended | Implantable cardioverter defibrillator insertion recommended in patients with syncope | Evidence on management of asymptomatic patients with type 1 electrocardiogram is conflicting. Not recommended for asymptomatic patients who require drug provocation to evoke a type 1 electrocardiogram |
| Catecholaminergic polymorphic ventricular tachycardia | Implantable cardioverter defibrillator insertion recommended in addition to beta-blockade or left cardiac sympathetic denervation | Implantable cardioverter defibrillator insertion recommended in patients with sustained ventricular tachycardia (or exercise-induced sustained ventricular tachycardia) or syncope despite beta-blockade or left cardiac sympathetic denervation | |

Adapted from Garratt et al (2010)

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## KEY POINTS

- A family history of premature sudden cardiac death, deafness, epilepsy or pacemaker implantation should always be sought in a syncopal patient.
- The most common inherited channelopathies are long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. Patients with long QT syndrome or Brugada syndrome should avoid drugs which exacerbate the phenotype.
- Most symptomatic patients with long QT syndrome respond to beta blockade.
- Ventricular fibrillation arrest is a class I implantable cardioverter defibrillator indication for patients with long QT syndrome or Brugada syndrome.
- Implantable cardioverter defibrillators are indicated in long QT syndrome for syncope despite beta blockade +/- sympathectomy.