**Cardiac Channelopathies: Diagnosis and Contemporary Management**

GJ Mellor1, ER Behr2

1Cardiology Dept. Royal Papworth Hospital, Cambridge, UK

2Cardiology ClinicalAcademic Group, St. George’s, University of London and St George’s University Hospitals NHS foundation Trust, London UK

**Corresponding Author:**

Dr Greg Mellor

Cardiology Dept.

Royal Papworth Hospital

Papworth Road

Cambridge

CB2 0AY

gregmellor@nhs.net

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**Learning Objectives**

To provide an in-depth overview of the major ion channelopathies: Long QT Syndrome, Brugada Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia with particular focus on:

* Diagnosis
* Risk Stratification
* Treatment options
* Underlying genetics and approach to genetic testing

To provide a brief summary of the less well-established or novel inherited arrhythmia syndromes and unexplained cardiac arrest.

**MCQs**

1. Genetic Testing results provide well-established prognostic information in which condition?
	* 1. Brugada Syndrome
		2. Short QT Syndrome
		3. CPVT
		4. **LQTS**
		5. Early Repolarisation Syndrome

Genotype is associated with risk of arrhythmic events in long QT syndrome with LQT1 (KNCQ1) representing a lower risk than LQT2 (KCNH2) and LQT3 (SCN5A) which has the highest risk. Genetic testing may be used to potentially identify family members at risk in Brugada Syndrome, CPVT and Short QT Syndrome. There is no well-established monogenic cause of Early Repolarisation.

1. Which of the following is not associated with an increased risk of sudden cardiac death in Brugada Syndrome?
	* 1. Spontaneous type 1 Brugada ECG pattern
		2. Previous cardiac arrest
		3. **Sudden cardiac death in first-degree relative**
		4. Previous Arrhythmic Syncope
		5. VT induced with single extra-stimulus at electrophysiology study

A family history of sudden death does not increase the risk of an individual’s personal future risk. The other features are all associated with a higher risk of arrhythmic events although a positive EP study has the smallest impact.

1. Which of the following is the preferred first-line drug in long QT Syndrome?
	* 1. **Nadolol**
		2. Metoprolol
		3. Flecainide
		4. Quinidine
		5. Atenolol

Non-selective beta blockers (nadolol and propranolol) are superior to other types of beta-blocker in LQTS. Flecainide may be used as second line treatment in CPVT, alongside beta-blockers or as monotherapy. Quinidine can be beneficial in Brugada Syndrome, Short QT Syndrome and Short-Coupled VF.

1. Which of the following would be considered diagnostic of CPVT?
	* 1. Left Ventricular Hypertrophy
		2. Sinus bradycardia
		3. First degree heart block
		4. **Bidirectional VT on exercise testing**
		5. Right ventricular enlargement

Bidirectional VT during exercise is diagnostic of CPVT. The other features may be seen in healthy athletic individuals.

1. What is the annual risk of recurrence following an unexplained cardiac arrest?
	* 1. 0%
		2. 2.5%
		3. 5%
		4. **7.5%**
		5. 10%

Data from the CASPER study showed appropriate ICD therapy rates in 23% patients over an average follow-up of 3.15 years.

1. Which of the following is the typical trigger for arrhythmic events in the most common form of Long QT Syndrome?
	* 1. **Exercise**
		2. Sudden Arousal
		3. Sleep
		4. Fever
		5. Alcohol binge

Syncope and cardiac arrest in long QT syndrome type 1 is more commonly seen during exercise. Events in LQT2 and LQT3 are associated with sudden arousal and sleep respectively. Fever and alcohol binges may lead to arrhythmic events in Brugada Syndrome.

**Introduction**

The inherited arrhythmia (IA) syndromes are a group of disorders characterised by an increased risk of sudden cardiac death (SCD), abnormal cardiac electrical function and typically, a structurally normal heart1. They share an underlying genetic aetiologywhere disease-causinggenetic variants may lead to absence or dysfunction of proteins involved in generation and propagation of the cardiac action potential.

They also share clinical features and management challenges. Diagnosis is largely electrocardiogram-based with significant overlap between affected individuals and the general population. Day-to-day symptoms are frequently absent such that assessment of the risk of SCD and its prevention are the primary concerns. Available tools for such risk stratification are imperfect and largely based upon expert consensus without a robust evidence base.

This review will focus on the diagnosis, risk stratification and treatment of the most common and well described IA syndromes, namely Long QT Syndrome (LQTS), Brugada Syndrome (BrS) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Other conditions including Short QT Syndrome (SQTS), Early Repolarisation Syndrome (ERS) and Idiopathic Ventricular Fibrillation (IVF) will also be discussed briefly.

**Diagnosis**

IA syndromes may present in a number of ways: following a resuscitated cardiac arrest or arrhythmic syncope, where an abnormal ECG in the absence of ischaemic and structural heart disease may heighten clinical suspicion; unexplained ECG abnormalities in an asymptomatic patient; or through family screening for a specific diagnosis or following a sudden unexplained death. The 12-lead ECG, supported by extended monitoring or provocation with exercise or drugs, is the cornerstone of diagnosis while clinical features and genetic results may also be considered. Diagnosis of an IA syndrome in an individual should lead to recommendation for all first-degree relatives to be assessed.

***Long QT Syndrome***

Long QT Syndrome (LQTS) affects up to 1:2000 live births2. The hallmark features are prolongation of the QT interval on the ECG, reflecting delayed myocardial repolarisation, and polymorphic ventricular tachycardia (Torsades de Pointes) leading to cardiac syncope or sudden death. Significant overlap exists between QT interval measurements in the general population and in those with LQTS3 such that diagnosis, especially in asymptomatic individuals, may not be straightforward. Manual measurement of the QT interval using the maximum slope technique to define the end of T wave (figure 1) is recommended since automated measurements are frequently inaccurate. It is also necessary to correct for physiological changes in QT duration with changing heart rates. While formulae such as Bazett’s correction (QTc=QT/ √RR) are commonly used, they remain inaccurate at extremes of heart rate.

In addition, failure of the QT to shorten at higher heart rates may also be an important diagnostic clue. A physiological reserve in cardiac repolarisation may compensate for impairment of a specific current at rest. As heart rates increase, ‘impaired repolarisation reserve’ in LQTS may be revealed by paradoxical prolongation of the QTc as heart rate increases. This may be demonstrated with a formal exercise test4, a ‘lying to standing’ ECG5 or during adrenaline infusion6. In addition to QT prolongation, LQTS patients often have abnormal T wave morphologies which can be associated with underlying genotype7 (see below). It may be best to think that one should *examine* the QT rather than simply *measure* it.

Current European guidelines8 state that LQTS is diagnosed when the QT is consistently >480ms (in the absence of QT prolonging medication or metabolic disturbance), >460ms when associated with arrhythmic syncope or with a diagnostic score ≥3.5 (Table 1). Finally, LTQS may be diagnosed when a disease-causing genetic variant is identified, regardless of symptoms or ECG findings.

***Brugada Syndrome***

Data on the prevalence of BrS is less precise but is estimated to affect 1:2000 with higher rates reported in South East Asian populations. There is a strong association with sudden death during sleep, particularly in men in the third or fourth decade9. First described in 199210, the underlying mechanisms in BrS remain incompletely understood. However, it is agreed that abnormalities within the right ventricular outflow tract (RVOT) are responsible both for the characteristic ECG changes and the development of polymorphic VT/VF. Evidence is also emerging of a subtle cardiomyopathic process causing fibrosis of the RVOT epicardium11.

The key diagnostic feature of BrS is the presence of the ‘type 1 Brugada ECG pattern’ in the right ventricular leads of the 12 lead ECG. This consists of partial RBBB, ≥0.2mV J-point elevation (JPE) and coved ST segment elevation followed by T wave inversion10 (Figure 2). Other, similar morphologies have been described as type 2 (>0.2mV JPE with saddle-shaped ST segment) and type 3 (0.1-0.2mV JPE) Brugada patterns but are not diagnostic. While they may raise suspicion in at-risk individuals they are not uncommon in the general population and in particular athletic individuals12. Since the RVOT is often superior to the standard V1 and V2 ECG electrode positions in the fourth intercostal spaces. The use of high right ventricular leads with electrodes in corresponding positions in the second and/or third intercostal space have been shown to increase sensitivity of observing a type 1 Brugada ECG pattern13.

ECG changes in patients with BrS can be dynamic or concealed and therefore, in suspected cases, provocative testing with sodium-channel blocking drugs can be considered (class IIa recommendation8). Ajmaline, commonly used in the UK, is the most sensitive14. Precipitation of a type 1 Brugada ECG pattern in ≥ 1 lead (Including high RV leads) after a dose up to 1mg/kg (max 100mg) constitutes a positive result1. Low rates of SCA in patients diagnosed following a positive sodium channel blocker provocation alone and the possibility of false-positive results have led to concerns over potential inaccuracy. This led to the proposal of a diagnostic scoring system for BrS. Similar to that used in LQTS , the ‘Shanghai Score’ includes variables based on the ECG, symptoms, family background and genetics (Table 2)15. The score recognises that a type 1 ECG pattern may also be seen in the context of fever which is given intermediate weight between a spontaneous and drug-induced ECG.

***CPVT***

CPVT has an estimated prevalence ~1:10,0001 and is characterised by syncope, cardiac arrest or sudden death with physical exertion or emotion in the context of a structurally normal heart and normal resting ECG. It typically presents during childhood and VF may be the first presentation in up to 30% of cases16. The pathognomonic feature is sustained bidirectional or polymorphic VT. However, polymorphic ventricular ectopy may be the only positive finding on exercise testing16. Reports of SCD occurring in children with multiple prior syncopal events where the diagnosis has been missed are not uncommon and therefore a low threshold for exercise testing in children with exertional syncope is recommended17.

***Others***

Other arrhythmia syndromes have been associated with cardiac arrest but are either very rare or have incompletely understood pathogenicity and/or associated genetics.

Short QT syndrome (SQTS) is a very rare cause of SCD associated with a short QT interval and tall peaked T waves on the resting ECG1. There is some debate as to the absolute QT limit that should be considered diagnostic18 with expert consensus suggesting a QTc ≤330ms as diagnostic1.

Idiopathic VF (IVF) is a term used for survivors of cardiac arrest where subsequent evaluation does not reveal a specific cause1. ECG, cardiac MRI, exercise testing and sodium channel blocker provocation should ideally all have been performed. In a recent study of cardiac arrest survivors 7% were ultimately diagnosed with IVF19. The term short-coupled VF (SC-VF) is used in cardiac arrest survivors when VF is seen to be initiated by a single monomorphic premature ventricular contraction (PVC) occurring early (usually <300ms) after the preceding QRS, in the absence of other pathology. This is the likely mechanism of cardiac arrest in IVF patients, thus IVF and SC-VF may be considered similar patient groups. Early Repolarisation Syndrome (ERS) is a further clinical entity overlapping with IVF. In ERS the sole clinical findings in a cardiac arrest survivor is ≥0.1mV J-point elevation in the inferior and/or lateral ECG leads20 which may be augmented at time of cardiac arrest. VF has again been shown to be initiated by a short-coupled PVC.

**Genetics**

Inheritance patterns and disease-associated genes are now well described for the most common IA syndromes. Clinical genetic testing is indicated to allow cascade screening of potentially at-risk family members and may, in some cases, offer prognostic information and/or guide therapy21. Genetic testing to confirm or refute borderline cases is less useful, since understanding of the relationship between phenotype and genotype remains incomplete.

Since first descriptions of each condition, a multitude of genes have been implicated as causative, leading to increasingly larger gene panels employed in clinical testing. However recent reappraisal has questioned evidence for pathogenicity in many so-called ‘minor’ genes.

Currently within the NHS genetic testing is moving toward central commissioning and standardisation. Criteria for testing are laid out in a National Genomic Testing Directory. Testing is performed on disease-specific panels of genes curated through the Genomics England PanelApp, a publicly available knowledgebase.

***LQTS***

LQTS is most commonly inherited in an autosomal dominant fashion. Variable penetrance is typical and most likely due to variations in repolarisation reserve. Genetic testing is positive in around 75% of affected individuals21. Pathogenic variants in three canonical genes account for the majority of gene positive cases. Loss-of-function variants in the genes *KCNQ1* (LQT1) and *KCNH2* (LQT2) encoding the potassium channel alpha subunits of the IKs and IKr outward repolarising currents are most commonly identified. A significant minority (5-10%) is due to gain-of-function variants in *SCN5A* encoding the alpha subunit of the sodium channel Nav1.5 (LQT3). Specific genotype-phenotype correlations22 have been established for T wave morphology, triggers for arrhythmic events, response to exercise testing, and to beta-blockade. LQT1 patients are more likely to experience events triggered by physical exertion, particularly swimming (See figure 3), while an association with sudden arousal or auditory triggers is reported in LQT2. LQT3 patients are more likely to have events during sleep or at rest22. Typically, broad-based T waves are seen in LQT1, notching of the T waves in LQT2 a prolonged isoelectric ST segment and late peaking T wave in LQT3.

Recent reappraisal has shown that the evidence supporting causation in a further 14 so-called ‘minor’ genes is limited23 with only *CACNA1C*24, encoding the alpha subunit of the L-type calcium current, and genes encoding other calcium handling proteins, the calmodulins25 (*CALM1, CALM2* and *CALM3)* and Triadin (*TRDN*), being considered causative. These latter forms are important in severe paediatric disease whilst syndromic forms of LQTS are also described: Anderson-Tawil Syndrome (*KCNJ2*) and Timothy Syndrome (*CACNA1C*). Finally, Jervell and Lange-Neilsen Syndrome refers to homozygous or compound heterozygous variants in KCNQ1 and/or KCNE1 and typically presents in childhood with profound QT prolongation associated with congenital sensorineural deafness26. Genes implicated in LQTS are summarised in table 3.

***Brugada***

Inheritance in BrS has been considered to follow a Mendelian autosomal dominant pattern. However, the yield of genetic testing is currently only around 20%21 with loss-of-function variants in *SCN5A* accounting for the vast majority of gene-positive cases. Similarly to LQTS, evidence supporting causation in more than 20 other previously implicated genes has recently been reappraised and none were considered suitable for diagnostic testing27. Evidence of a more complex inheritance pattern in BrS is mounting. Genome wide association studies (GWAS) have identified that common genetic variants at three loci have a cumulative effect on the likelihood of having BrS28 with a derived polygenic risk score able to predict the type 1 Brugada ECG pattern response to sodium channel blocker29.

***CPVT***

CPVT is caused by excess calcium release within the cardiomyocyte in response to catecholamines. With a yield of genetic testing of up to 65%21, the majority of gene positive cases are due to gain-of-function variants in *RYR2*16 which encodes the ryanodine receptor, integral to intracellular calcium-mediated calcium release. There is an autosomal dominant pattern of inheritance with incomplete penetrance whilst autosomal recessive forms with variants in calsequestrin-2 (*CASQ2*) accounts for ≤5% of cases. Rarely, other genes are implicated including *CALM* and *KCNJ2*.

***Others***

In SQTS pathogenic gain-of-function variants in potassium channel genes *KCNQ1*, *KCNH2* and *KCNJ2* account for up to 20% of index cases21. Studies of genetic testing in unexplained cardiac arrest or IVF have shown a 9-17% yield implicating genes associated with established channelopathies or even cardiomyopathies, likely reflecting concealed forms30. A founder haplotype in the gene *DPP6* has been identified in several large pedigrees with idiopathic VF in the Netherlands31. To date cases have not been reported outside of this region.

***Risk Stratification***

***LQTS***

The risk in asymptomatic LQTS patients is generally low. The 5-year risk of arrhythmic events off treatment was reported as ≤3% for 75% of patients in a large Italian registry32 and only 2% of previously asymptomatic patients treated at the Mayo clinic33 experienced an event over 6.7 years. In common with other IA syndromes, prior syncope is a marker of higher future risk with 25% of previous symptomatic patients experiencing a breakthrough event despite treatment in the above study33. Age, sex and genotype are relevant in addition to absolute QTc duration for further risk stratification. Patients with LQT1 have the most favourable outcome. Event rates are higher for LQT2 and LQT3 and risk increases with increasing QTc duration32. A QTc≥500ms denotes significantly increased risk and ≥600ms very high risk. Pre-pubertal males with LQT1 and post-pubertal females with LQT2 appear to be at higher risk34 with a further increase in risk in women with LQT2 in the first year post-partum. Presentation at a young age and on-going symptoms despite treatment are poor prognostic indicators. Variant specific risk has been explored with *SCN5A*-E1784K associated with more favourable outcomes in LQT335 and variants within the intracellular C-loop portion of KCNQ1 associated with a higher risk of life-threatening events in LQT1 and better response to beta-blockers36.

***Brugada***

The prognosis in BrS is highly variable and risk stratification imperfect37. A spontaneous type-1 ECG pattern and prior symptoms (i.e. previous cardiac arrest or unexplained syncope) portend a worse prognosis38 while it has also been shown that a family history of SCD does not increase an individual’s risk39. Further refinement of risk is however controversial, particularly with reference to programmed electrical stimulation (PES) for induction of VT/VF. A pooled analysis of several studies40 showed limited positive predictive value in asymptomatic patients with a spontaneous type 1 ECG. A negative result was clinically unhelpful, and the aforementioned clinical features were stronger predictors of events. A short ventricular effective refractory period (VERP <200ms) during EP study has also been associated with an increased risk of events41 and various ECG markers of risk have been suggested. However, validation in multiple cohorts is lacking and attempts to incorporate multiple predictors into prognostic scoring systems also require testing in large cohorts with long follow-up periods before routine clinical use.

***CPVT***

Young age at first presentation and prior aborted sudden death are associated with a worse outcome42. All patients with CPVT should be counselled regarding avoiding competitive sport and strenuous exercise and limiting exposure to stressful environments1.

***Others***

Risk stratification in other IA syndromes is limited by the small numbers and/or poor definition of the phenotype. In general, treatment and particularly ICD implantation is not recommended in asymptomatic patients. Exceptions may be made where there have been multiple SCDs within a family with limited options for medical treatment or in exceptional circumstances such as identification of the DPP6 IVF risk haplotype which has a 50% risk of VF by the age of 5031.

**Treatment**

Treatment decisions are based upon the perceived risk of sudden death. In-depth discussion and shared decision making are vital. Treatment begins with counselling to avoid potential arrhythmic triggers. Medical treatments are available with varying efficacy. Invasive treatments including ICD implant, catheter ablation or left cervical sympathectomy are generally reserved for high-risk patients only.

***LQTS***

All patients should avoid known QT prolonging drugs1. Crediblemeds.org provides an updated reference list and smartphone app for patients. Patients should be aware of the need to avoid and correct potential causes of hypokalaemia, such as gastrointestinal disturbance. Historically, patients with LQTS have been recommended to avoid competitive sports and swimming in particular although recent data suggest that event rates in those who continue to compete may be lower than previously feared43. Current guidelines support an individualised approach under expert advice1 where exercise may continue in those without high risk features and who are otherwise well managed.

β-blockers are the first line treatment for all sub-types (including LQT335) and are indicated in guidelines for all patients with prior symptoms, those with a resting QTc>470ms and for genotype-positive individuals regardless of phenotype1. Nadolol is preferred44 at 0.75-1.5mg/kg. Propranolol (2-4mg/kg) may be used where nadolol is unavailable. Side-effects are common, therefore low starting doses with gradual up-titration is recommended. Patients with LQT1 have a better response to β-blockers than LQT2 and LQT322,34. Those who are intolerant of β-blockers or whose symptoms are refractory can be considered for left cardiac sympathetic denervation (LCSD)45. Some low-risk patients may not require β-blockade if counselled appropriately46. ICD implantation has a class I indication following cardiac arrest whilst break-through symptoms on β-blockers is a class IIa indication1. ICD implantation should only be considered in asymptomatic patients in exceptional circumstances. Other interventions such as mexiletine and atrial pacing can be considered on an individual patient basis.

**BrS**

All patients should avoid potentially arrhythmic medications ([www.brugadadrugs.org](http://www.brugadadrugs.org)). Fever should be treated promptly as it may precipitate arrhythmic events47 with young patients and those with SCN5A pathogenic variants at particular risk. Such patients may consider presentation to hospital for ECG monitoring if fever persists although the absolute risk of a life-threatening event remains unclear. Other reported triggers, including binges of alcohol and eating large meals late at night, should be discouraged.

Implantation of an ICD1 is the only proven intervention for prevention of sudden death in BrS. Additional therapy can include oral quinidine48. Recent studies of epicardial substrate-based ablation of the RVOT49 have shown promise in reducing the risk of arrhythmic events. However, due to the invasive nature and risk of procedural complications, ablation should currently be restricted to ICD recipients who have multiple episodes of VT/VF. In the setting of VT/VF storms isoproterenol and/or quinidine may be used to acutely suppress ventricular arrhythmias50.

***CPVT***

Treatment with β-blockers is recommended in all symptomatic cases1 with nadolol showing superior efficacy although event rates remain high in a significant proportion of patients. Adjunctive therapy with flecainide51 has been shown to reduce the burden of ventricular arrhythmias on exercise and may also be considered as monotherapy. Left cardiac sympathetic denervation (LCSD) reduces events in patients who remain symptomatic despite β-blockers52 although long-term follow-up is lacking. ICD implantation may be recommended for those who remain symptomatic despite maximal tolerated pharmacological therapy and where LCSD is not possible1. However, there are significant concerns over the risks of ICD therapy in CPVT: it can be difficult to cardiovert bidirectional VT successfully; inappropriate shocks may lead to VT/VF storms; there can be technical difficulties in implantation in paediatric patients and the need for life-time protection can lead to an increased risk of device-related complications and the potential for multiple re-interventions. Furthermore, even in patients presenting with a cardiac arrest, implantation of an ICD did not reduce mortality compared to medical therapy but led to higher rates of appropriate and inappropriate therapy, and device-related complications in a recent study53.

***Others***

Quinidine may be effective in prolonging the QT interval in SQTS. ICD implantation is recommended for those who have survived a cardiac arrest1. In unexplained cardiac arrest, rates of recurrent cardiac arrest are around 7.5%/year54. Therefore, ICD is recommended for all survivors of an unexplained cardiac arrest. Both quinidine and catheter ablation (where a single site can be identified) have been shown to reduce triggering ectopy in SC-VF.

**Conclusions**

The IA syndromes are a group of conditions which do not cause day-to-day symptoms but carry a risk of SCD in otherwise young and healthy people. The risk to an individual is highly variable and tools for assessment are limited but improving. While ICD implantation remains the default for high risk patients, medical and interventional treatment are improving and counselling regarding ICD-associated risks is essential. As understanding of underlying pathophysiology and genetics improves and clinical tools evolve it is hoped that personalised risk assessment and treatments will become the norm.

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***Tables***

|  |  |
| --- | --- |
| Electrocardiographic findings# | Points |
| A | QTc ≥480 ms | 3 |
|  | QTc 460-479 ms | 2 |
|  | QTc 450-459 (in males) | 1 |
| B | QTc 4th minute of recovery from exercise stress ≥480 ms | 1 |
| C | Torsades de pointes\* | 2 |
| D | T wave alternans | 1 |
| E | Notched T wave in 3 leads | 1 |
| F | Low heart rate for age@ | 0.5 |
| Clinical History |
| A | Syncope with stress\* | 2 |
|  | Syncope without stress\* | 1 |
| B | Congenital deafness | 0.5 |
| Family History |
| A | Family member with definite LQTS$ | 1 |
| B | Unexplained sudden cardiac death below age 30 among immediate family members$ | 0.5 |

**Table 1. Modified Schwartz score for diagnosis of LQTS** ≥3.5 points=high probability of LQTS; 1.5-3 points=intermediate probability of LQTS; ≤ 1 point=low probability of LQTS. *#In the absence of disorders known to affect the electrocardiographic features, \*Mutually exclusive, @Resting heart rate below 2nd percentile for age, $The same family member cannot be counted in A and B.*

|  |  |
| --- | --- |
|  | ***Points*** |
| ***ECG (12-lead/Ambulatory)*** |
|  | *Spontaneous type 1 Brugada ECG pattern\** | *3.5* |
| *Fever-induced type 1 Brugada ECG pattern\** | *3* |
| *Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge\** | *2* |
| ***Clinical History*** |
|  | *Unexplained cardiac arrest or documented VF/PMVT* | *3* |
| *Nocturnal agonal respirations* | *2* |
| *Suspected arrhythmic syncope* | *2* |
| *Syncope of unclear mechanism/unclear aetiology* | *1* |
| *Atrial flutter/fibrillation in patients <30 years**without alternative aetiology* | *0.5* |
| ***Family History*** |
|  | *First- or second-degree relative with definite BrS* | *2* |
| *Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative* | *1* |
| *SADS <45 years in first- or second-degree relative*  | *0.5* |
| ***Genetic Test Result*** |
|  | *Probable pathogenic mutation in BrS susceptibility gene* | *0.5* |

**Table 2. Diagnostic Scoring system for Brugada Syndrome.**Score ≥3.5=Definite/Probable, 2-3=Possible, <2 Unlikely*. Only the highest score in each category should be counted. \*In nominal or high leads. BrS=Brugada Syndrome; SADS=Sudden Arrhythmic Death Syndrome*

|  |  |  |
| --- | --- | --- |
| Gene | Notes |  |
| *KCNQ1* | Canonical LQT1; events triggered by exercise; broad based T waves | Decreased outward I Ks |
| *KCNH2* | Canonical LQT2; events with sudden stimulation; notched T waves | Decreased outward IKr |
| *SCN5A* | Canonical LQT3; events during sleep; late onset T wave | Increased inward INa  |
| *CACNA1C* | Isolated LQTS and Timothy Syndrome | Increased inward ICa |
| *CALM-1,-2,-3* | Assoc. AV block, typically age ≤3 years | Calmodulin; reduced Ca binding |
| *TRDN* | Presentation in childhood | Loss-of-function in Triadin; increased Ca release from SR |
| *KCNJ2* | Anderson-Tawil Syndrome | Reduced outward IK in skeletal and cardiac muscle |

**Table 3. Causative genes in autosomal dominant LQTS.** *KCNQ1, KCNH2* and *SCN5A* variants account for >80% gene-positive cases. Other genes previously implicated in LQTS but with limited/disputed evidence for causation include *AKAP9, ANK2, CAV3, KCNE1, KCNE2, SCN4B, SNTA1.*

***Figure Legends***

**Figure 1. Manual measurement the QT interval**. The QT interval is measured from the beginning of the earliest onset of the QRS to the end of the T wave. The ‘maximum slope intercept method’ (indicated) defines the end of the T wave as the intercept between a tangent drawn through the steepest slope of the descending T wave and the iso-electric line.

**Figure 2. 12 lead ECG of patient with Brugada syndrome**. A type 1 Brugada ECG pattern seen in lead V1. A type 2 Brugada ECG pattern seen in lead V2.

**Figure 3. ILR recording of Torsades de Pointes in LQT1 patient during swimming.** Note late coupled PVCs with abnormal repolarisation prior to TdP initiation.