Genetic testing for inheritable cardiac channelopathies

Dr Eszter Szepesváry[1]

Clinical Fellow

[1] *Inherited Cardiovascular Diseases Unit, Great Ormond Street Hospital, London, UK*

Dr Juan Pablo Kaski[1,2]

Consultant Paediatric Cardiologist

[1]*Inherited Cardiovascular Diseases Unit, Great Ormond Street Hospital, London, UK*

[2]*UCL Institute of Cardiovascular Science, London, UK*

Address for Correspondence:

Dr Juan Pablo Kaski

Lead Clinician, Inherited Cardiovascular Diseases Unit

Great Ormond Street Hospital

Great Ormond Street

London WC1N 3JH

United Kingdom

Tel: +44 (0)20 7829 8839

E-mail: j.kaski@ucl.ac.uk

Short introduction

Cardiac channelopathies are rare genetic disorders associated with an increased risk of ventricular arrhythmia and sudden death, often in previously asymptomatic and ostensibly healthy young individuals with a structurally normal heart. This article aims: (a) to review the clinical characteristics and genetic basis of common cardiac ion-channel diseases, (b) to highlight some of the genotype-phenotype correlations available to date, and (c) to summarise the current clinical practice of genetic testing for inheritable cardiac channelopathies.

Introduction

Since the completion of the Human Genome Project in 2003, a revolutionary technological development has taken place in genomics, the science that evolved from genetics, molecular biology, and bioinformatics. Rapid advances in genotyping methods, characterised by miniaturisation and automation and high-throughput analysis of DNA, have reduced the cost and time and increased the accuracy of DNA sequencing. Another great impact of next-generation sequencing and array-based technologies has been the ability to investigate biological phenomena in a more complex manner, at the level not only of the genome, but also the epigenome, proteome, and metabolome, in a comprehensive, and unbiased manner (Schwartz AL, 2011). This has reshaped our view of genome physiology, and also deepened our understanding of genetics in familial and potentially lethal cardiovascular diseases, such as cardiac channelopathies. Technological advances in genotyping, on the other hand, have also provided an enormous amount of data and resulted in a discrepancy between data generation and the linkage of data to clinical significance. This has made integration of genomic information into clinical practice challenging, particularly in the case of rare diseases.

Clinical features of cardiac ion channel disease

Cardiac channelopathies are rare genetic disorders associated with an increased risk of ventricular arrhythmia and sudden death, often in previously asymptomatic and ostensibly healthy young individuals with a structurally normal heart. They include long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), as well as other rarer types, such as short QT syndrome (SQTS), early repolarisation syndrome, progressive cardiac conduction disease (PCCD), and multifocal ectopic Purkinje-related premature contractions.
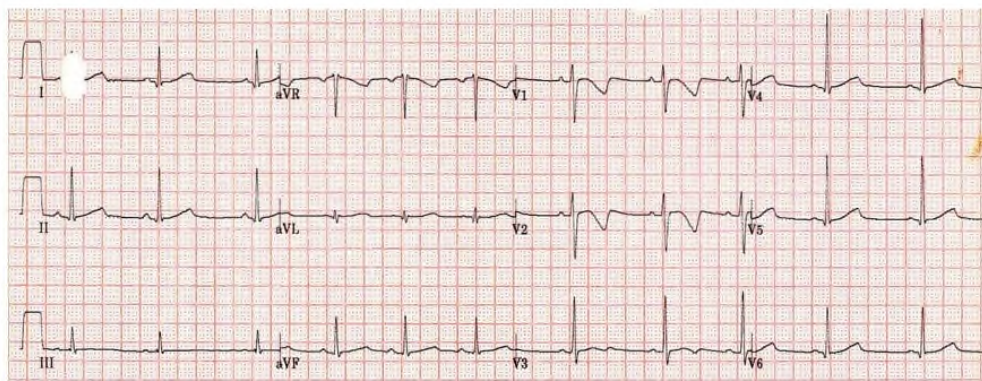
Long QT syndrome

LQTS is characterised by QT prolongation and abnormal T-wave morphology on the surface ECG (Fig.1.), and is associated with syncope and sudden death caused by torsades

de pointes (TdP) and ventricular fibrillation (VF). The estimated prevalence is 1:2000, with a mean age at presentation of 14 years. The diagnosis is made on the basis of a heart rate-corrected QT interval (QTc) ≥ 480ms on repeated ECGs or a LQTS risk score > 3 (Table 1.). The diagnosis can also be made in the presence of unexplained syncope with no secondary causes for QT prolongation and a QTc ≥ 460ms (Priori SG et al, 2015). In 25-40% of patients the QT intervals may be non-diagnostic at rest, which makes diagnosis of LQTS challenging. In these 'concealed' cases additional investigations, including exercise testing, adrenaline challenge and Holter monitoring, may increase diagnostic sensitivity. Additional electrocardiographic features include T wave alternans, prominent U waves and T-U complexes and bradycardia, which may present as either sinus bradycardia, or functional 2:1 AV block when QT interval is very long. Symptoms are often precipitated by adrenergic activation, e.g. physical activity or emotional stress, but may also occur at rest or during sleep. The incidence of syncope is estimated to be 5% per year, whereas the annual rate of sudden death is reported to be between 0.33 and 0.9% in untreated individuals. Some forms of LQTS are associated with extra-cardiac manifestations, such as congenital deafness in Jervell and Lange-Nielsen syndrome, syndactyly in Timothy syndrome (LQT8), or periodic paralysis and dysmorphic features in Andersen-Tawil syndrome (LQT7).
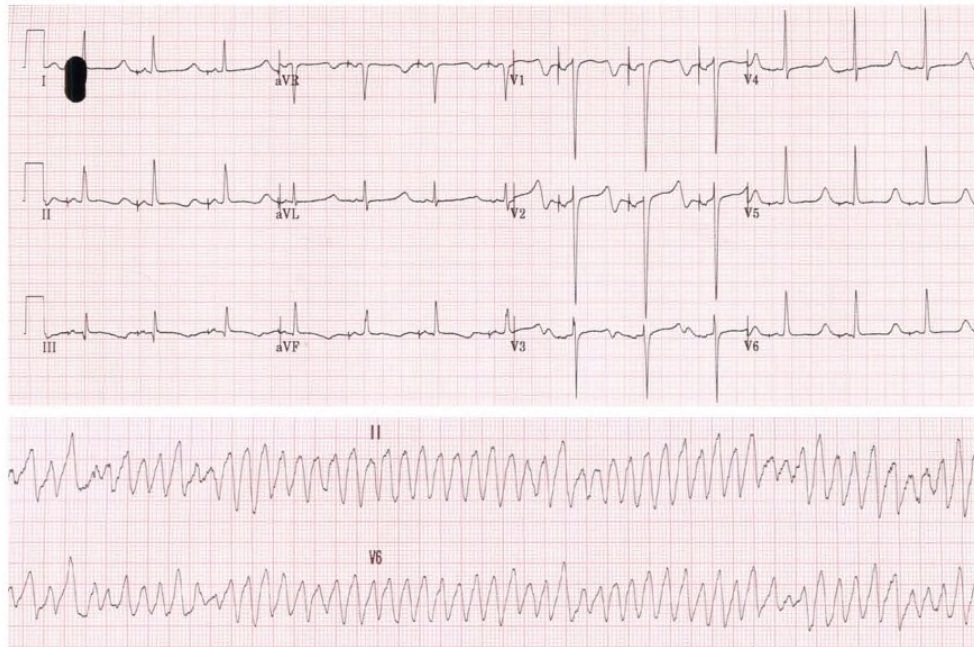
A. LQT1
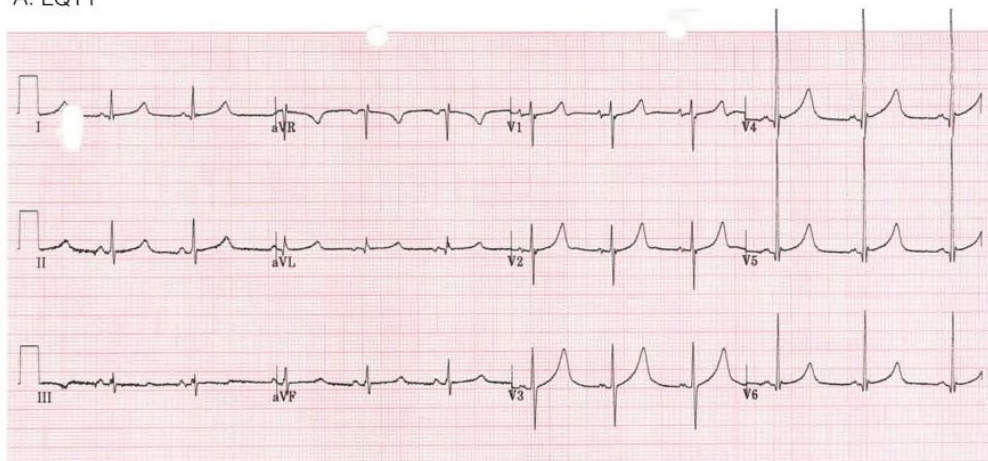
B. LQT2

C. LQT3

Fig. 1. Characteristic ECGs in long QT syndrome.

A)   LQT1 - ECG of a 10 year-old boy with a KCNQ1 mutation and recurrent syncope on exertion, show-ing broad-based T waves.

B)   LQT2 - ECG of a 10 year-old boy with a familial KCNH2 mutation, showing low voltage, notched T waves.

C)   LQT3 - ECGs of a 14 year-old boy with recurrent Torsades des Pointes (TdP) despite medical ther-apy, fitted with an ICD. 12-lead ECG shows atrial pacing with extreme QT prolongation, character-ised by a long isoelectric ST segment and symmetrical T waves (above); rhythm strip demonstrates TdP ventricular tachycardia (below).

Brugada syndrome

BrS is a clinical entity with a characteristic pattern of J point and ST segment elevation in the right precordial leads of a 12-lead ECG, associated with risk of fatal arrhythmic events. Conduction delays at various cardiac levels are also commonly seen. The prevalence ranges from 1:1000 to 1:10,000, with a seemingly higher occurrence in South-East Asian populations (Fowler SJ and Priori SG, 2009). Clinical manifestations are more frequent in adults with a mean age of 41 ± 15 years at presentation and a male predominance. The resting ECG can be completely normal, but fever, excessive alcohol intake and large meals may unmask the typical Brugada ECG pattern. The annual rate of arrhythmic events, including sustained VT, VF and sudden death, is 13.5% in patients with a history of aborted cardiac arrest, 3.2% in patients with syncope and 1% in asymptomatic patients, respectively (Fauchier L et al, 2013). The diagnosis is based on ST-segment elevation with type 1 morphology ≥2mm (Fig. 2.) in one or more, conventionally placed or high right pre-cordial leads, occurring spontaneously or induced by sodium channel blockers (e.g. ajma-line or flecainide).
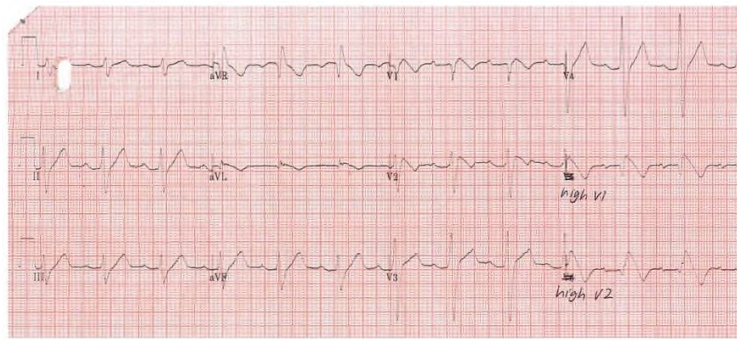
Fig. 2. Characteristic ECG in Brugada syndrome.

Positive Ajmaline challenge test in a 13 year-old boy with a family history of Brugada syndrome, showing cove-shaped ST segment elevation and T wave inversion in the right ventricular precordial leads. ECG tracings from the high right precordial leads (2nd intercostal space) are shown in V5 and V6 position.

Catecholaminergic polymorphic ventricular tachycardia

The main feature of CPVT is bidirectional or polymorphic VT and VF (Fig. 3.) precipitated by a sudden increase in sympathetic tone, such as physical exercise or emotional stress. The prevalence is estimated to be 1:10,000 (Priori SG et al, 2013). The first symptoms usually present within the first decade of life with a mean age of 7-9 years, but later onset has also been reported (Hayashi M et al, 2009).The resting ECG is typically normal with the occasional presence of subtle sinus bradycardia. An exercise stress test is generally diagnostic with the onset of premature bidirectional or polymorphic ventricular ectopics as
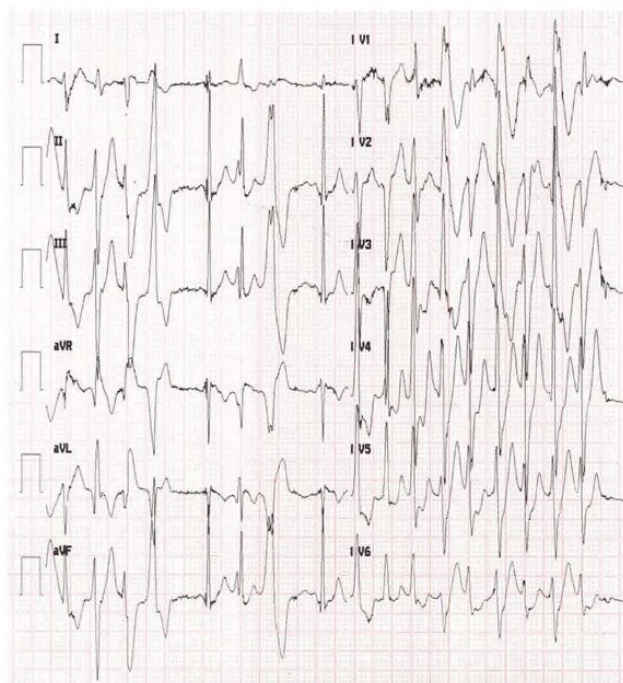
the heart rate approaches 120 beats/min, but in some cases it remains negative. An adrenaline challenge test has been suggested to increase the sensitivity of diagnosis.

Fig. 3. Characteristic ECG in catecholaminergic polymorphic ventricular tachycardia.

Exercise test in an 11 year-old boy with recurrent syncope on exertion showing polymorphic ventricular ectopics and bidirectional ventricular tachycardia.

Other cardiac channelopathies

Short QT syndrome is a recently described channelopathy characterised by reduced length of cardiac repolarisation. QTc interval ≤ 340ms is diagnostic, but SQTS can also be considered if the QTc ≤ 360ms in the presence of a pathogenic mutation or after an episode of otherwise unexplained VT/VF arrest, or when the family history is positive for SQTS or for sudden cardiac death at a young age (Priori SG et al, 2015). In addition to the shortened QT interval, tall and peaked T-waves with almost absent ST-segments appear to be characteristic in some types of SQTS.
Early repolarisation syndrome is another rare condition associated with idiopathic VF. The pattern of early repolarisation described as J point elevation ≥0.1 mV in two adjacent leads with either slurred or notched terminal QRS morphology has been considered as a normal ECG variant. It has been seen especially frequently in athletes and young individuals and at slower heart rates, with an overall prevalence of 5-13% in the general population. However, recent studies of idiopathic VF have suggested an association of the pattern with increased risk of arrhythmic deaths (Haissaguerre M et al, 2008). Early repolarisation syndrome is characterised by the presence of a typical ECG pattern in the context of an otherwise idiopathic VF arrest.

Genetic basis of cardiac channelopathies

Cardiac ion channels (Table 2.) mediate precisely regulated movements of ions conducted through the cell membrane, thereby playing a crucial role in the normal generation and propagation of the action potential of myocardial cells (Fig. 4.). An imbalance of inward and outward currents, mainly affecting repolarisation of myocytes, alters the spatio-temporal pattern of repolarisation within the myocardium and creates a substrate for electrophysiological heterogeneity. This predisposes to the development of ventricular tachyarrhythmias that represent the common clinical endpoint of the different cardiac channelopathies. Abnormal ionic changes are primarily caused by mutations in one or more genes encoding ion channels, cytoskeletal anchoring proteins or components of caveolae. Whilst cardiac channelopathies have been considered to be monogenic disorders, in order

to understand the phenotype of these conditions the function of the whole biological system that effects repolarisation needs to be considered.
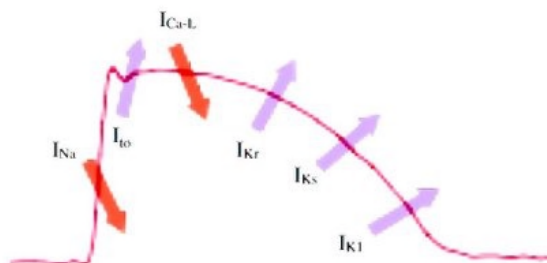

Fig. 4. Major ionic currents of the myocardial action potential.

Phase 0: inward Na+ current (I_{Na}), rapid depolarisation.

Phase 1: transient outward K+ current (I_{to}), early repolarisation, 'notch'.

Phase 2: balance between the inward depolarising Ca^{2+} and the outward delayed rectifier K+ currents (I_{Kr}, I_{Ks}), repolarisation 'plateau'.

Phase 3: inactivation of inward current and increase of outward currents (I_{Kr}, I_{Ks}, I_{K1}).

Phase 4: membrane potential returns to its resting potential.

Genes and genetic heterogeneity.

Since the description of the first cardiac channelopathy causative genes in 1995, a large number of distinct genes with hundreds of mutations have been associated with inheritable channelopathies (Table 3.). Mutations usually cluster in families, or may occur sporadically. They are most commonly inherited as autosomal dominant traits, but autosomal recessive inheritance can also occur.

The genetic basis of long QT syndrome can be identified in 75-80% of cases (Ackerman MJ et al, 2011). Currently, mutations in at least 15 genes have been linked to LQTS, most of which encode voltage-gated potassium, sodium and calcium channels. The majority of mutations cause loss-of-function; however, some result in enhanced activity, as seen in LQT3 or Timothy syndrome. The most common disease-causing genes are KCNQ1, KCNH2 and SCN5A, accounting for 90% of positively genotyped cases. Certain rare mutations in the KCNQ1 gene, and also in KCNE1 gene, cause Jervell and Lange-Nielsen syndrome: a unique, autosomally recessively inherited form of LQTS characterised by extreme QT prolongation, severe to profound congenital deafness and vestibular dysfunction.

In contrast to the relative high yield from genetic testing in LQTS, the genetic cause of Brugada syndrome is only identified in approximately 25% of cases. The genetic background of the condition is very complex and heterogeneous and still not completely understood, with at least 16 genes causally related. Many of these genes play a role in the pathogenesis of other channelopathies, too, thereby creating 'overlap syndromes' or 'mixed phenotypes' that share features of both BrS and other channelopathies (e.g., SQTS or PCCD).

Only two genes, SCN5A and CACN1AC, account for >5% of positively genotyped individuals with BrS (Wilde AA and Behr EE, 2013), with SCN5A mutations accounting for 20-30% of cases (Kapplinger DJ et al, 2010), while the contribution of other genes is less frequent.

Genetic confirmation of CPVT is achievable in about 60-70% of patients. Mutations in the cardiac ryanodine receptor 2 gene (RYR2), inherited as an autosomal dominant trait, are found in 55-65% of affected individuals (Ackerman MJ et al, 2011) whereas pathological variants of calsequestrin gene (CASQ2), autosomally recessively inherited, account for 1-2% of the cases (Ackerman MJ, Marcou CA and Tester DJ, 2013). Mutations in other genes are also implicated in CPVT, but at present it is not clear whether they are part of the same spectrum of disease or represent phenocopies.

There is substantial genetic heterogeneity, with different mutations in the same cardiac ion channel genes resulting in different phenotypes, depending on their functional effect. For example, gain-of-function mutations in SCN5A gene cause LQT3 syndrome, while loss-of-function mutations may be responsible for BrS, familial atrial fibrillation, PCCD and sick sinus syndrome. Similarly, K^+ channel mutations can delay repolarisation (LQTS), lead to Andersen-Tawil syndrome (LQT7), speed up repolarisation (SQTS), or trigger atrial fibrillation. Abnormal changes in intracellular Ca^{2+} handling can cause Timothy syndrome (LQT8), BrS, SQTS and CPVT.

Clinical heterogeneity

The clinical heterogeneity of channelopathies is not only a consequence of the involvement of various genes with multiple mutations in pathogenesis. The manifestation of disease may vary significantly, even in the case of the very same pathological variant of a gene, from silent carrier state to SCD. This is caused by the incomplete penetrance and variable expressivity of these conditions. CPVT is a highly penetrant channelopathy with early manifestation compared to Brugada syndrome, which has a generally low, age and sex-related penetrance with later onset of symptoms, predominantly in males. Although the exact mode of action from a systems biology perspective is poorly understood, several genetic and epigenetic factors are known to influence gene expression. For example, polymorphisms, either within established susceptibility genes for channelopathies or in genes that modulate cardiac ion-channel function through transcriptional or post-translational effects, may modify disease penetrance and expression (Giudicessi JR and Ackerman MJ, 2013). Furthermore, compound or digenic heterozygosity, when two different mutations are found either on the same alleles of a chromosome pair or in two different disease-associated genes, can be associated with earlier and more severe disease expression. In multigenerational pedigrees, 4-8% of LQTS probands were found to harbour a second independent disease-causative mutation.

Other candidate modifiers have been postulated, some of which participate in autonomic responses (Schwartz PJ et al, 2013) and some are determinants of the repolarisation reserve (Varro A and Baczko I, 2011). Individual differences in autonomic tone, and in the

magnitude of catecholaminergic response to stress, and also in the capacity to compensate for functional or inherited impairment of repolarisation currents, are known to influence susceptibility to triggered arrhythmia. Genetic determinants of these factors may well contribute to the expression of a certain ion channel disease.

Repolarisation reserve

The cardiac repolarisation process is governed by interactions of multiple ion channels and their regulators. Any alteration in the function of an individual component, through genetic or acquired mechanisms, can modulate repolarisation and allow changes that elicit susceptibility to ventricular arrhythmia. On the other hand, there is also a degree of redundancy in the system that enables it also to tolerate alterations to a certain degree. This 'buffer-capacity' is known as the repolarisation reserve and represents a functional compensatory mechanism for the loss of a single ionic component (e.g. up-regulation of I_{Ks} when I_{Kr} is reduced). However, if the repolarisation reserve is reduced, a change in a single current may be poorly tolerated. This occurs if a compensatory mechanism is attenuated by a drug or affected by a subclinical mutation per se, but bradycardia, hypokalaemia, gender, and underlying cardiac pathology are also known factors that interact and determine repolarisation reserve capacity (Xiao L et al, 2008). The concept originally suggested a static nature for the relationship between the main ionic current, I_{Kr} determining repolarisation and other ionic components (I_{Ks}, $I_{Na,L}$) that provide reserve against I_{Kr} inhibition. More recent data, however, have suggested a more dynamic interaction (Roden DM, 2008), and involvement of various ionic mechanisms (e.g. inward sarcolemmal sodium-calcium exchanger current (I_{NCX}), as well as hyperpolarization activity current (I_f), which contributes to the pacemaker current in the sinus node) are also observed.

Genotype-phenotype correlations

While determinants of heterogeneity in the channelopathies remain incompletely understood, several important associations between genotype and arrhythmic risk and demographic features and electrocardiographic phenotype have been elucidated. In LQTS in particular, these correlations may carry diagnostic, prognostic and therapeutic implications, underpinning the importance of genotyping.

Patients with LQT1 typically have broad-based T waves with a delayed upstroke on the surface ECG. They may also show paradoxical lengthening of the QT interval in response to sympathetic stimulation; QT prolongation during exercise is even greater with pore region mutations than with non-pore mutations, associated with a greater risk of exercise-triggered cardiac events (Jons C et al, 2009). In childhood, males have also been found to have a higher risk for developing arrhythmia. Arrhythmic events are likely to occur on exercise, particularly during swimming. Patients respond very well to β-blocker therapy with no apparent shortening of the QTc interval at rest, but a decrease in the number of cardiac events (Priori et al, 2003).

LQT2 patients tend to show low-amplitude and notched or bifid T wave morphology on resting ECG. There is a phase-specific QT-T response on exercise with only an initial out-of-proportion QT prolongation and a more prominent appearance of the flat and bifid repolarisation pattern, followed by appropriate shortening of the QTc interval. The arrhythmic trigger is often a sudden auditory or emotional stimulus. Women during the 9-month postpartum period have an especially high risk of arrhythmia. Patients with transmembrane pore region mutations show a longer QT interval and experience more arrhythmic events at a younger age than those with frame-shift or nonsense mutations affecting any other region of the HERG channel. Missense mutations affecting the C-terminus of Kv11.1 are associated with the lowest risk for cardiac events. (Shimizu W et al, 2009)

In LQT3 syndrome long isoelectric ST segments are followed by short symmetrical T waves on the surface ECG. The QT interval shortens appropriately on exercise, and arrhythmic events tend to occur during sleep or at rest. Patients have a higher incidence of lethal cardiac events than those with LQT1 or LQT2. Response to β-blocker therapy is less effective than in LQT1, but targeting the excessive late sodium current, which is a result of the gain-of-function mutation of the sodium channel, with inhibitory agents such as mexiletine, may provide a more gene-specific therapy (Shimizu W, 2008).

Other channelopathies possess less well-established genotype-phenotype correlations. In CPVT, early onset of disease has been associated with RYR2 mutations, and male carriers in particular have been found to have a fourfold increased risk of cardiac events compared to female carriers (Priori SG et al, 2002).

Genetic testing for primary arrhythmia syndromes in clinical practice

Comprehensive or targeted genetic testing is recommended for patients with a strong clinical suspicion of LQTS or CPVT, and represents a class I indication. Given the lower yield of genetic testing in BrS and other channelopathies, testing of patients with high suspicion of the specific condition may be useful, as a class II indication. Following the identification of a disease-causing mutation in a proband, mutation-specific predictive genetic testing is recommended for first degree relatives (Ackerman MJ et al, 2011).

Targeted post-mortem genetic analysis should be considered in all sudden death victims in whom an inheritable channelopathy is suspected (Priori SG et al, 2015). This, so-called molecular autopsy is able to identify a post-mortem diagnosis of heritable cardiac channelopathy in 15-20% of cases. Moreover, comprehensive clinical cardiological screening of first-degree relatives of a SADS victim results in the diagnosis of an ion channel disorder, most commonly LQTS, BrS and CPVT, in up to 50% of cases, including paediatric relatives (Guidici et al, 2014).

Interpretation of results of genetic testing for inheritable cardiac channelopathies

In the era of high-throughput DNA analysis several genetic variants are identified and classifying these as disease-causing or normal variants is crucial, but may be very challenging and requires expertise. Variants found in individuals with ion channel disease are usually non-synonymous single nucleotide substitutions. These may cause a single change in the amino acid sequence of the encoded protein (missense mutation), or result in its truncation by a premature stop codon (nonsense mutation). Generally, it is easier to classify a novel nonsense variant as pathogenic. However, if a novel missense variation segregates with disease status in a family, is clearly absent from a control population, is located in a highly conserved amino acid sequence, and/or changes the physico-chemical property of the protein significantly it may well be considered as potentially disease-causing. *In silico* and *in vitro* tools are also available for helping to predict the functional effect of a variant. If despite all considerations a novel variant remains unclassified the term 'sequence variation of unknown/uncertain significance' (VUS) is used. These have limited value in confirming a clinical diagnosis and cannot be solely used for identifying at-risk relatives. However, their presence as a second variant may modify disease expression.

The pathogenic mutation:VUS ratio is the 'signal-to-noise' ratio of the genetic test and represents its positive predictive value. It is highly disease-dependent, being approximately 20:1 in CPVT and LQTS; that means a relatively low rate of false positivity compared to a less desirable ratio of 10:1 for BrS (Ackerman MJ et al, 2011). Conversely, in cardiac channelopathies a negative test result in a clinically affected individual does not rule out disease, especially in syndromes with a low yield from genetic testing, such as BrS or SQTS.

Ethical aspects of genetic testing in ion channel disease

Predictive testing in clinically unaffected family members can help to elucidate disease status and inheritance risk. Given the clinical heterogeneity of channelopathies, predictive genetic testing as part of the clinical screening helps to identify relatives at risk. In some cases, such as LQTS and CPVT, prophylactic treatment and life-style modification may be recommended. However, predictive testing may also have implications in terms of participation in sports, employment and life insurance (Ingles et al, 2011). Genetic counselling is therefore extremely important pre- and post-testing, as both positive and negative results may carry significant clinical and psychosocial impacts that need to be addressed in detail, and should be carried out in the setting of an expert inherited cardiovascular diseases service. The 'right not to know' and the possibility to decline molecular screening should be included in the communication with the relatives.

Predictive genetic testing in children is a particularly complex issue that should be managed on a case-by-case basis. In some of the inherited cardiovascular diseases, such as some of the later-onset cardiomyopathies, postponing testing to an older age with a better understanding may be advisable. However, for most of the inheritable channelopathies (e.g., LQTS, CPVT) pre-symptomatic testing can be performed earlier in life, given that sudden death may occur at any age, but the risk of an arrhythmic event can be significantly and effectively reduced by initiating prophylactic treatment.

Summary

The diagnostic, prognostic and therapeutic implications of genetic testing in cardiac channelopathies are very much disease-dependent. Given the genetic and clinical heterogeneity of these rare conditions the current yield from genetic testing in confirming clinical diagnosis varies from 20% for BrS and SQTS to 75-80% for LQTS. Its diagnostic impact is reasonably well-established in LQTS and CPVT compared to BrS, but the effect on prognosis and therapy is only valuable in LQTS at present. However, once a disease-causing mutation is identified it does have further value in identifying silent carriers or at-risk relatives within families, with appropriate genetic counselling and considerations of the ethical aspects of predictive testing.

Keypoints

1. Inheritable cardiac channelopathies are rare genetic disorders associated with an increased risk of ventricular arrhythmia and sudden death, often in previously asymptomatic and ostensibly healthy young individuals with a structurally normal heart.

2. The common clinical endpoint of the different cardiac channelopathies is a predisposition to development of ventricular tachyarrhythmias that results from an imbalance in ionic currents of cardiac repolarisation, mainly caused by mutations in genes encoding ion channels and associated structures.

3. Channelopathies are genetically heterogenous conditions with variable expressivity and incomplete penetrance.

4. Genetic testing in cardiac channelopathies may have diagnostic, therapeutic and prognostic values, however these are very much disease-dependent. The highest yield is in long QT syndrome with 75-80% diagnostic confirmation of the disease, and may therapeutic and prognostic implications.

5. Interpretation of genetic test results may be challenging and requires expertise.

6. Predictive genetic testing is offered for clinically unaffected family members in a cascade manner with special consideration of ethical aspects, particularly in children.

Conflict of interest:

None.

References:

Ackerman MJ, Marcou CA, Tester DJ (2013) Personalized medicine: Genetic diagnosis for cardiomyopathies/channelopathies. *Rev Esp Cardiol.* **66**(4):298-307.

Ackerman MJ, Priori SG, Willems S et al. (2011) HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace* **13**(8):1077–109.

Fauchier L, Isorni MA, Clementy N et al. (2013) Prognostic value of programmed ventricular stimulation in Brugada syndrome according to clinical presentation: an updated meta-analysis of worldwide published data. *Int J Cardiol,* **168**(3):3027–9.

Fowler SJ, Priori SG (2009) Clinical spectrum of patients with a Brugada ECG. *Curr Opin Cardiol,* **24**(1):74–81.

Giudicessi JR, Ackerman MJ (2013) Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes. *Transl. Res.* **161**(1):1–14.

Guidici V, Spanaki A, Hendry J et al. (2014) Sudden Arrhythmic Death Syndrome: Diagnostic Yield of Comprehensive Clinical Evaluation of Pediatric First-Degree Relatives. *Pacing Clin Electrophysiol* **37**(12):1681-85.

Haissaguerre M, Derval N, Sacher F et al. (2008) Sudden cardiac arrest associated with early repolarization. *N Engl J Med* **358**(19):2016–23.

Hayashi M, Denjoy I, Extramiana F et al. (2009) Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation* **119**(18):2426–34.

Ingles J, Zodgekar PR, Yeates L et al. (2011) Guidelines for Genetic Testing of Inherited Cardiac Disorders. *Heart Lung Circ* **20**(11):681-7.

Jons C, Moss AJ, Lopez CM et al. (2009) Mutations in conserved amino acids in the KCNQ1 channel and risk of cardiac events in type-1 long-QT syndrome. *J Cardiovasc Electrophysiol.* **20**(8):859-65.

Kapplinger JD, Tester DJ, Alders N et al. (2010) An international compendium of mutation in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm* **7**(1):33–46.

Priori SG, Blomstrom-Lundqvist C, Mazzanti A et al. (2015) ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J,* **36**(41):2793-867.

Priori SG, Wilde AA, Horie M et al. (2013) Executive summary: HRS/ EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* **15**(10):1389–406.

Priori SG, Schwartz PJ, Napolitano C et al. (2003) Risk stratification in the long-QT syndrome. *N Engl J Med* **348**(19):1866–74.

Priori SG, Napolitano C, Memmi M et al. (2002) Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* **106**(1):69-74.

Roden DM (2008) Repolarization reserve - a moving target. *Circulation* **118**(10):981–2.

Schwartz AL (2011) The Future of Children's Health in the Genomic Era. *Rambam Maimonides Med J.* 2(3):1-12

Schwartz PJ, Ackerman MJ, George AL Jr et al (2013) Impact of genetics on the clinical management of channelopathies. *J Am Coll Cardiol.* **62**(3):169-80.

Shimizu W, Moss AJ, Wilde AA et al. (2009) Genotype-phenotype aspects of type 2 long QT syndrome. *J Am Coll Cardiol.* **54**(22):2052-62.

Shimizu W (2008) Clinical impact of genetic studies in lethal inherited cardiac arrhythmias. *Circ J.* **72**(12):1926-36.

Xiao L, Xiao J, Luo X et al. (2008) Feedback remodeling of cardiac potassium current expression: a novel potential mechanism for control of repolarization reserve. *Circulation* **118**(10):983–92.

Wilde AA, Behr EE (2013) Genetic testing for inherited cardiac disease. *Nat. Rev. Cardiol.* **10**(10):571–83.

Varro A, Baczko I (2011) Cardiac ventricular repolarization reserve: a principle for understanding drug-related proarrhythmic risk. *Br J Pharmacol.* 164(1):14–36.

Tables

Table 1. Diagnostic criteria for LQTS

Criteria		Points
ECG (in the absence of condition affecting these features)		
QTc = QT / √ RR	≥ 480ms	3
	460 - 479 ms	2
	450 - 459 ms (men)	1
QTc ≥ 480ms at 4 min into recovery on exercise test		1
Torsades de pointes VT		2
T wave alternans		1
Notched T waves in 3 leads		1
Sinus bradycardia (resting HR < 2nd percentile for age)		0.5
Clinical history		
Syncope	with stress	2
	without stress	1
Congenital deafness		1
Family History		
Definite LQTS		1
Unexplained SCD <30yo in first degree relatives		0.5

Adapted from Scwartz PJ et al. (2012) Long-QT Syndrome From Genetics to Management. *Circ Arrhyth Electrophysiol.* **5**(4):868-877.

Table 2. Main cardiac ion channels and their genes, contributing to currents of cardiac action potential

Current	Description	AP phase	Type of activation	Protein	Gene
Inward					
I_{Na}	Na+ current	phase 0	voltage, depolarisation	Na$_V$1.5	SCN5A
$I_{Ca,L}$	Ca^{2+} current, L-type	phase 2	voltage, depolarisation	Ca$_V$1.2	CACNA1C
$I_{Ca,T}$	Ca^{2+} current, T-type	phase 2	voltage, depolarisation	Ca$_V$3.1/3.2	CACNA1G
Outward					
$I_{to,f}$	transient outward current, fast	phase 1	voltage, depolarisation	KV 4.2/4.3	KCND2/3
$I_{to,s}$	transient outward current, slow	phase 1	voltage, depolarisation	KV 1.4/1.7/3.4	KCNA4 KCNA7 KCNC4
I_{Kur}	delayed rectifier, ultrarapid	phase 1	voltage, depolarisation	KV1.5/3.1	KCNA5 KCNC1
I_{Kr}	delayed rectifier, fast	phase 3	voltage, depolarisation	HERG	KCNH2
I_{Ks}	delayed rectifier, slow	phase 3	voltage, depolarisation	KVLQT1	KCNQ1
I_{K1}	inward rectifier	phase 3,4	voltage, depolarisation	Kir 2.2/2.2	KCNJ2/12
I_{KATP}	ADP-activated K+ current	phase 1,2	[ADP]/[ATP] ↑	Kir 6.2	KCNJ11
I_{KAch}	Muscarinic-gated K+ current	phase 4	Acetylcholine	Kir 3.1/3.4	KCNJ3/5
I_{KP}	background current	all phases	metabolism, stretch	TWK-1/2 TASK-1 TRAAK	KCNK1/6 KCNK3 KCNK4
I_{F}	Pacemaker (funny) current	phase 4	voltage, hyperpolarisation	HCN2/4	HCN2/4

Adapted from Grant AO (2009) Cardiac Ion Channels. *Circ Arrhythmia Electrophysiol.* **2**(2):185-94.

Table 3. Genes associated with cardiac channelopathies

Gene	Locus	Inheritance	Protein	Functional effect	Phenotype	Frequency in disease
Long QT syndrome						
KCNQ1	11p15.5-p15.4	AD	$K_v7.1$	loss-of-function	LQT1	30-35%
		AR			JLN1	<1%
KCNH2	7q36.1	AD	$K_v11.1$	loss-of-function	LQT2	25-30%
SCN5A	3p22.2	AD	$Na_v1.5$	gain-of-function	LQT3	5-10%
ANK2	4q25-q26	AD	Ankyrin B	loss-of-function	LQT4	<1%
KCNE1	21q22.11-q22.12	AD	MinK	loss-of-function	LQT5	<1%
		AR		loss-of-function	JLN2	<1%
KCNE2	21q22.11	AD	MiRP1	loss-of-function	LQT6	<1%
KCNJ2	17q24.3	AD	Kir2.1	loss-of-function	LQT7 (ATS1)	<1%
CACNA1C	12p13.33	AD	$Ca_v1.2$	gain-of-function	LQT8 (TS1)	<1%
CAV3	3p25.3	AD	Caveolin 3	gain-of-function	LQT9	<1%
SCN4B	11q23.3	AD	Na_v β4 subunit	gain-of-function	LQT10	<0.1%
AKAP9	7q21.2	AD	A-kinase anchor protein 9	loss-of-function	LQT11	<0.1%
SNTA1	20q11.21	AD	Syntrophin α1	gain-of-function	LQT12	<0.1%
KCNJ5	11q24.3	AD	Kir 3.4 subunit of I_{KAch} channel	loss-of-function	LQT13	<0.1%
CALM1	14q32.11	AD	Calmodulin 1	loss-of-function	LQT14	<1%
CALM2	2p21	AD	Calmodulin 2	loss-of-function	LQT15	<1%
Brugada syndrome						
SCN5A	3p22.2	AD	$Na_v1.5$	loss-of-function	BrS1	20-30%

Gene	Locus	Inheritance	Protein	Functional effect	Phenotype	Frequency in disease
GPD1-L	3p22.3	NA	Glycerol-3P dh1	loss-of-function	BrS2	<1%
SCN1B	19q13.12	NA	Na_v β1 subunit	loss-of-function	BrS5	<1%
SCN3B	11q24.1	AD	Na_v β3 subunit	loss-of-function	BrS7	<1%
SCN2B	11q23.3	AD	Na_v β2 subunit	loss-of-function	BrS16	<1%
CACNA1C	12p13.33	AD	Ca_v1.2	loss-of-function	BrS3	10%
CACNB2	10p12.33-p12.31	AD	L-type Ca_v β2 subunit	loss-of-function	BrS4	<1%
CACNA2D1	7q21-q22	NA	L-type Ca_v α2/δ1 subunit	loss-of-function	BrS10	<1%
HCN4	15.q24.1	NA	K/Na hyperpolarisation activated cyclic nucleotide-gated channel 4	loss-of-function, ↓ I_f current	BrS8	<1%
KCND3	1p13.2	AD	K_v4.3	gain-of-function	BrS11	<1%
KCNE3	11q13.4	NA	MiRP2	gain-of-function	BrS6	<1%
KCNE5	Xq22.3	NA	K_v accessory subunit 5	gain-of-function	BrS15	<1%
KCNJ8	12p11.23	NA	Kir6.1	gain-of-function	BrS 9	<1%
RANGFR	17p13.1	NA	RAN guanine nucleotide release factor 1	loss-of-function	BrS12	<1%
SLMAP	3p14.3	NA	sarcolemma associated protein	loss-of-function	BrS13	<1%
TRPM4	19q13.33	NA	Transient receptor potential cation channel subfamily M member 4	loss-of-function	BrS14	6%

Catecholaminergic polymorphic ventricular tachycardia						

Gene	Locus	Inheritance	Protein	Functional effect	Phenotype	Frequency in disease
RYR2	1q43	AD	Ryanodin receptor 2	loss-of-function	CPVT1	50-60%
CASQ2	1p13.1	AR	Calsequestrin 2	loss-of-function	CPVT2	1-2%
TRDN	6q22.31	AR	Triadin	loss-of-function	CPVT5	NA
CALM1	14q32.11	AD	Calmodulin 1	loss-of-function	CPVT4	<1%
Short QT syndrome						
KCNH2	7q36.1	AD	$K_v11.1$	gain-of-function	SQT1	NA
KCNQ1	11p15.5	AD	$K_v7.1$	gain-of-function	SQT2	NA
KCNJ2	17q24.3	AD	Kir2.1	gain-of-function	SQT3	NA

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; NA, not ascertained or applicable.