Genetic testing for inheritable cardiac channelopathies

Cardiac channelopathies are linked to an increased risk of ventricular arrhythmia and sudden death. This article reviews the clinical characteristics and genetic basis of common cardiac ion-channel diseases, highlights some genotype–phenotype correlations, and summarizes genetic testing for inheritable cardiac channelopathies.

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, characterized by miniaturization 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, 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, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia, as well as other rarer types, such as short QT syndrome, early repolarization syndrome, progressive cardiac conduction disease and multifocal ectopic Purkinje-related premature contractions.

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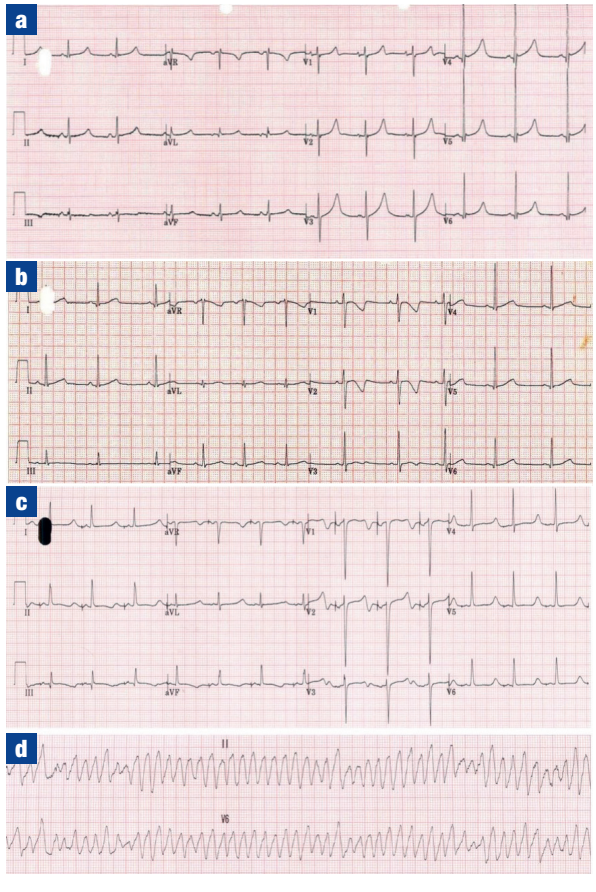
Long QT syndrome

Long QT syndrome (*Figure 1*) is characterized by QT prolongation and abnormal T-wave morphology on the

Figure 1. Characteristic electrocardiograms in long QT syndrome. **a.** Long QT1 – electrocardiogram of a 10-year-old boy with a KCNQ1 mutation and recurrent syncope on exertion, showing broad-based T waves. **b.** Long QT2 – electrocardiogram of a 10-year-old boy with a familial KCNH2 mutation, showing low voltage, notched T waves. **c.** Long QT3 – electrocardiogram of a 14-year-old boy with recurrent torsades des pointes despite medical therapy, fitted with an implantable cardioverter defibrillator. 12-lead electrocardiogram shows atrial pacing with extreme QT prolongation, characterized by a long isoelectric ST segment and symmetrical T waves. **d.** Rhythm strip from the same patient as **(c)** demonstrates torsades des pointes ventricular tachycardia.



surface electrocardiogram, and is associated with syncope and sudden death caused by torsades de pointes and ventricular fibrillation. The estimated prevalence is 1:2000 (Schwartz et al, 2009), with a mean age at presentation of 14 years. The diagnosis is made on the basis of a heart rate-corrected QT interval (QTc) ≥480 ms on repeated electrocardiograms or a long QT syndrome 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 ≥460 ms (Priori et al, 2015). In 25–40% of patients the QT intervals may be non-diagnostic at rest, which makes diagnosis of long QT syndrome 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, T-U complexes and bradycardia, which may present as either sinus bradycardia or functional 2:1 atrioventricular 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 (Moss et al, 1991). Some forms of long QT syndrome 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).

Brugada syndrome

Brugada syndrome is a clinical entity with a characteristic pattern of J point and ST segment elevation in the right precordial leads of a 12-lead electrocardiogram, 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 and Priori, 2009). Clinical manifestations are more frequent in adults with a mean age of 41 ± 15 years at presentation and a male predominance (Priori et al, 2002b). The resting electrocardiogram can be completely normal, but fever, excessive alcohol intake and large meals may unmask the typical Brugada electrocardiogram pattern. The annual rate of arrhythmic events, including sustained ventricular tachycardia, ventricular fibrillation 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 et al, 2013). The diagnosis is based on ST segment elevation with type 1 morphology ≥2 mm (*Figure 2*) in one or more, conventionally placed or high right precordial leads, occurring spontaneously or induced by sodium-channel blockers (e.g. ajmaline or flecainide).

Table 1. Diagnostic criteria for long QT syndrome

	Criteria		Points
Electrocardiogram (in the absence of condition affecting these features)	QTc = QT / √RR	≥ 480 ms	3
		460–479 ms	2
		450–459 ms (men)	1
	QTc ≥480 ms at 4 min into recovery on exercise test		1
	Torsades des pointes		2
	T wave alternans		1
	Notched T waves in three leads		1
	Sinus bradycardia (resting heart rate < second percentile for age)		0.5
Clinical history	Syncope	With stress	2
		Without stress	1
	Congenital deafness		1
Family history	Definite long QT syndrome		1
	Unexplained sudden cardiac death <30 years of age in first degree relatives		0.5

Adapted from Schwartz et al (2012)

Catecholaminergic polymorphic ventricular tachycardia

The main feature of catecholaminergic polymorphic ventricular tachycardia is bidirectional or polymorphic ventricular tachycardia and ventricular fibrillation (*Figure 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 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 et al, 2009). The resting electrocardiogram is typically normal with the occasional presence of subtle sinus bradycardia. An exercise stress

Figure 2. Characteristic electrocardiogram 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. Electrocardiogram tracings from the high right precordial leads (second intercostal space) are shown in V5 and V6 position.

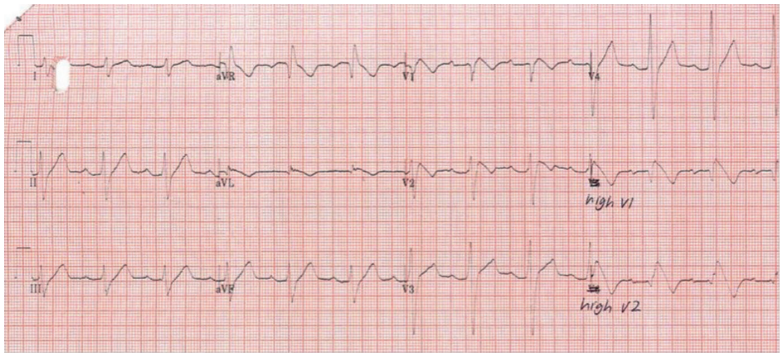
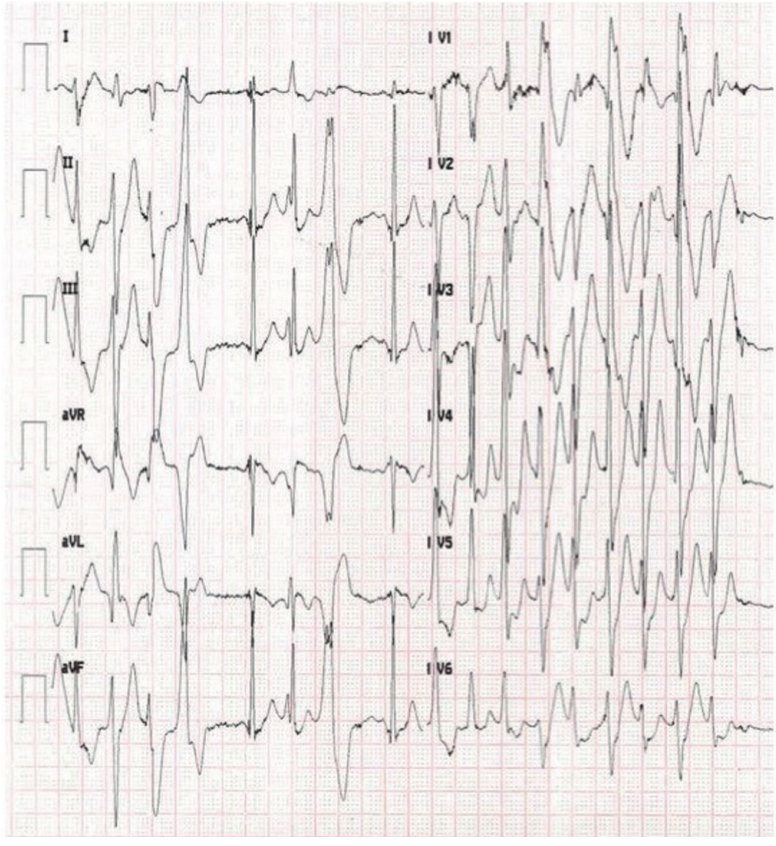


Figure 3. Characteristic electrocardiogram in catecholaminergic polymorphic ventricular tachycardia. Exercise test in an 11-year-old boy with recurrent syncope on exertion showing polymorphic ventricular ectopics and bidirectional ventricular tachycardia.



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.

Other cardiac channelopathies

Short QT syndrome is a recently described channelopathy characterized by reduced length of cardiac repolarization. QTc interval ≤340 ms is diagnostic, but short QT syndrome can also be considered if the QTc ≤360 ms in the presence of a pathogenic mutation or after an episode of otherwise unexplained ventricular tachycardia/ventricular fibrillation arrest, or when the family history is positive for short QT syndrome or for sudden cardiac death at a young age (Priori 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 short QT syndrome.

Early repolarization syndrome is another rare condition associated with idiopathic ventricular fibrillation. The pattern of early repolarization 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 electrocardiogram variant (Klatsky et al, 2003). 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, studies of idiopathic ventricular fibrillation have suggested an association of the pattern with increased risk of arrhythmic deaths (Haïssaguerre et al, 2008). Early repolarization syndrome is characterized by the presence of a typical electrocardiogram pattern in the context of an otherwise idiopathic ventricular fibrillation 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 (*Figure 4*). An imbalance of inward and outward currents, mainly affecting repolarization of myocytes, alters the spatio-temporal pattern of repolarization within the myocardium and creates a substrate for electrophysiological heterogeneity. This predisposes to the development of ventricular tachyarrhythmias that represent the common clinical end point 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, so cardiac channelopathies have been considered to be monogenic disorders. However, the process of cardiac repolarization and its regulation is very complex, and in order to understand the phenotypic features of a certain ion channel disease, the whole biological system that is instrumental in repolarization needs to be considered.

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 has 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 et al, 2011). Currently, mutations in at least 15 genes have been linked to long QT syndrome, 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 the KCNE1 gene, cause Jervell and Lange-Nielsen syndrome: a unique, autosomally recessively inherited form of long QT syndrome characterized by extreme QT prolongation, severe to profound congenital deafness and vestibular dysfunction (Schwartz et al, 2006).

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, depolarization	$Na_v1.5$	SCN5A
	$I_{Ca,L}$	Ca2+ current, L-type	Phase 2	Voltage, depolarization	$Ca_v1.2$	CACNA1C
	$I_{Ca,T}$	Ca2+ current, T-type	Phase 2	Voltage, depolarization	$Ca_v3.1/3.2$	CACNA1G
Outward	$I_{to,f}$	Transient outward current, fast	Phase 1	Voltage, depolarization	KV 4.2/4.3	KCND2/3
	$I_{to,s}$	Transient outward current, slow	Phase 1	Voltage, depolarization	KV 1.4/1.7/3.4	KCNA4 KCNA7 KCNC4
	I_{Kur}	Delayed rectifier, ultrarapid	Phase 1	Voltage, depolarization	KV1.5/3.1	KCNA5 KCNC1
	I_{Kr}	Delayed rectifier, fast	Phase 3	Voltage, depolarization	HERG	KCNH2
	I_{Ks}	Delayed rectifier, slow	Phase 3	Voltage, depolarization	KVLQT1	KCNQ1
	I_{K1}	Inward rectifier	Phase 3, 4	Voltage, depolarization	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, hyperpolarization	HCN2/4	HCN2/4

Adapted from Grant (2009). ADP = adenosine diphosphate; AP = action potential; ATP = adenosine triphosphate

In contrast to the relative high yield from genetic testing in long QT syndrome, 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 also play a role in the pathogenesis of other channelopathies, thereby creating 'overlap syndromes' or 'mixed phenotypes' that share features of both Brugada syndrome and other channelopathies (e.g. short QT syndrome or progressive cardiac conduction disease). Only two genes, SCN5A and CACN1AC, account for >5% of positively genotyped individuals with Brugada syndrome (Wilde and Behr, 2013), with SCN5A mutations accounting for 20–30% of all cases (Kapplinger et al, 2010), while the contribution of other genes is even less frequent.

Genetic confirmation of catecholaminergic polymorphic ventricular tachycardia 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 et al, 2011) whereas pathological variants of calsequestrin gene (CASQ2), autosomally recessively inherited, account for 1–2% of the cases (Ackerman et al, 2013). Mutations in other genes are also implicated in catecholaminergic polymorphic ventricular tachycardia, 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

Figure 4. Major ionic currents of the myocardial action potential. Phase 0: inward Na+ current (I_{Na}), rapid depolarization. Phase 1: transient outward K+ current (I_{to}), early repolarization, 'notch'. Phase 2: balance between the inward depolarizing Ca^{2+} (I_{Ca-L}) and the outward delayed rectifier K+ currents (I_{Kr}, I_{Ks}), repolarization '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.

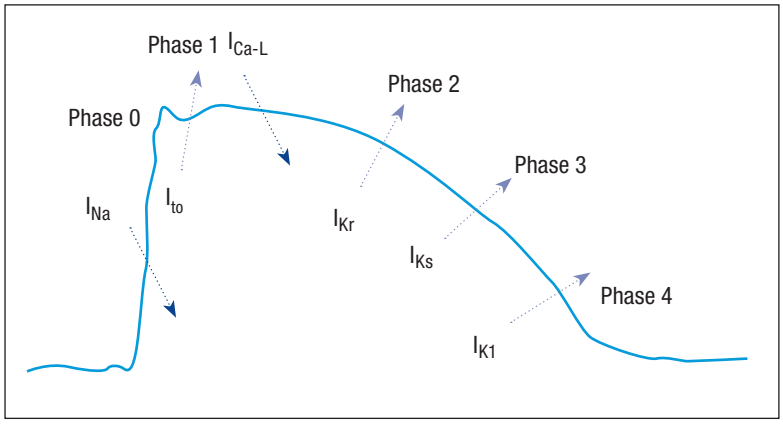


Table 3. Genes associated with cardiac channelopathies

Condition	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			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 ß4 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 $\alpha 1$	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%

AD = autosomal dominant; AR = autosomal recessive; NA = not ascertained or applicable

loss of function mutations may be responsible for Brugada syndrome, familial atrial fibrillation, progressive cardiac conduction disease and sick sinus syndrome. Similarly, K+ channel mutations can delay repolarization (long QT syndrome), lead to Andersen–Tawil syndrome (LQT7), speed up repolarization (short QT syndrome) or trigger atrial fibrillation. Abnormal changes in intracellular Ca2+ handling can cause Timothy syndrome (LQT8), Brugada syndrome, short QT syndrome and catecholaminergic polymorphic ventricular tachycardia.

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 sudden cardiac death. This is caused by the incomplete penetrance and variable expressivity of these conditions. Catecholaminergic polymorphic ventricular tachycardia 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 and Ackerman, 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 long QT syndrome 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 et al, 2013) and some are determinants of the repolarization reserve (Varro and Baczko, 2011). Individual differences in autonomic tone, in the magnitude of catecholaminergic response to stress, and also in the capacity to compensate for functional or inherited impairment of repolarization 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.

Table 3. Genes associated with cardiac channelopathies (continued)

Condition	Gene	Locus	Inheritance	Protein	Functional effect	Phenotype	Frequency in disease
Brugada syndrome	SCN5A	3p22.2	AD	$Na_v1.5$	Loss of function	BrS1	20–30%
	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/β1 subunit	Loss of function	BrS10	<1%
	HCN4	15.q24.1	NA	K/Na hyperpolarization 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 sub-family M member 4	Loss of function	BrS14	6%
Catecholaminergic polymorphic ventricular tachycardia	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

AD = autosomal dominant; AR = autosomal recessive; NA = not ascertained or applicable

Repolarization reserve

The cardiac repolarization 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 repolarization 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 to also tolerate alterations to a certain degree. This 'buffer capacity' is known as the repolarization 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 repolarization 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 repolarization reserve capacity (Xiao et al, 2008).

The concept originally suggested a static nature for the relationship between the main ionic current, I_{Kr} determining repolarization 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, 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 long QT syndrome 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 electrocardiogram. 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 et al, 2009). In childhood, males have also been found to have a higher risk of 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 electrocardiogram. 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 repolarization 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 et al, 2009).

In LQT3 syndrome long isoelectric ST segments are followed by short symmetrical T waves on the surface electrocardiogram. 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, 2008).

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

Genetic testing for primary arrhythmia syndromes in clinical practice

Comprehensive or targeted genetic testing is recommended for patients with a strong clinical suspicion of long QT syndrome or catecholaminergic polymorphic ventricular tachycardia, and represents a class I indication. Given the lower yield of genetic testing in Brugada syndrome 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 et al, 2011).

Targeted post-mortem genetic analysis should be considered in all sudden death victims in whom an inheritable channelopathy is suspected (Priori 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 sudden arrhythmic death syndrome victim results in the diagnosis of an ion channel disorder, most commonly long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia, in up to 50% of cases, including paediatric relatives (Giudici 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' 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:sequence variation of unknown/uncertain significance 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 catecholaminergic polymorphic ventricular tachycardia and long QT syndrome, which means a relatively low rate of false positivity compared to a less desirable ratio of 10:1 for Brugada syndrome (Ackerman 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 Brugada syndrome or short QT syndrome.

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 long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, prophylactic treatment and lifestyle 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 inherited channelopathies (e.g. long QT syndrome, catecholaminergic polymorphic ventricular tachycardia) 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.

Conclusions

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 Brugada syndrome and short QT syndrome to 75–80% for long QT syndrome. Its diagnostic impact is reasonably well established in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia compared to Brugada syndrome, but the effect on prognosis and therapy is only valuable in long QT syndrome 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 consideration of the ethical aspects of predictive testing. **BJHM**

KEY POINTS

- Inheritable cardiac channelopathies are rare genetic disorders associated with an increased risk of ventricular arrhythmia and sudden death, often in a previously asymptomatic and ostensibly healthy young individual with a structurally normal heart.
- The common clinical end point of the different cardiac channelopathies is a predisposition to development of ventricular tachyarrhythmias that results from an imbalance in ionic currents of cardiac repolarization, mainly caused by mutations in genes encoding ion channels and associated structures.
- Channelopathies are genetically heterogenous conditions with variable expressivity and incomplete penetrance.
- Genetic testing in cardiac channelopathies may have diagnostic, therapeutic and prognostic values, but these are very much disease-dependent. The highest yield is in long QT syndrome with 75–80% diagnostic confirmation of the disease, and may have therapeutic and prognostic implications.
- Interpretation of genetic test results may be challenging and requires expertise.
- 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.

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