Rev Port Cardiol. 2018;37(2):179–199

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

REVIEW ARTICLE

Cardiac channelopathies: The role of sodium channel mutations☆

Diana João Fonseca*, **Manuel Joaquim Vaz da Silva**

Faculdade de Medicina da Universidade do Porto, Porto, Portugal

KEYWORDS
Mutations;
Sodium channels;
Heart diseases;
Heart arrhythmias;
Sudden cardiac death

Abstract
Introduction and objectives: The importance of sodium channels for the normal electrical activity of the heart is emphasized by the fact that mutations (inherited or de novo) in genes that encode for these channels or their associated proteins cause arrhythmogenic syndromes such as the Brugada syndrome and the long QT syndrome (LQTS). The aim of this study is to conduct a review of the literature on the mutations in the sodium channel complex responsible for heart disease and the implications of a close relationship between genetics and the clinical aspects of the main cardiac channelopathies, namely at the level of diagnosis, risk stratification, prognosis, screening of family members and treatment.
Methods: The online Pubmed® database was used to search for articles published in this field in indexed journals. The *MeSH database* was used to define the following query: ''Mutation [Mesh] AND Sodium Channels [Mesh] AND Heart Diseases [Mesh]'', and articles published in the last 15 years, written in English or Portuguese and referring to research in human beings were included.
Conclusions: In the past few years, significant advances have been made to clarify the genetic and molecular basis of these syndromes. A greater understanding of the underlying pathophysiological mechanisms showed the importance of the relationship between genotype and phenotype and led to progress in the clinical approach to these patients. However, it is still necessary to improve diagnostic capacity, optimize risk stratification, and develop new specific treatments according to the genotype-phenotype binomial.

☆ Please cite this article as: Fonseca DJNdO, Silva MJLVd. Canalopatias cardíacas: o papel das mutações nos canais de sódio. Rev Port Cardiol. 2018;37:179–199.

* Corresponding author.
E-mail address: mimed11120@med.up.pt (D.J. Fonseca).

PALAVRAS-CHAVE
Mutações;
Canais de Sódio;
Doenças cardíacas;
Arritmias cardíacas;
Morte súbita cardíaca

Canalopatias cardíacas: o papel das mutações nos canais de sódio

Resumo
Introdução e objetivos: A importância dos canais de sódio para a normal atividade elétrica do coração é enfatizada pelo facto de as mutações (hereditárias ou de novo) nos genes que codificam esses canais ou as proteínas a esses associadas provocarem síndromes arritmogénicas como a síndrome de Brugada e a síndrome do QT longo. O objetivo deste trabalho é proceder a uma revisão bibliográfica sobre as mutações no complexo dos canais de sódio responsáveis por doença cardíaca e as implicações da relação estrita entre a genética e a clínica das principais canalopatias cardíacas, nomeadamente no nível do diagnóstico, da estratificação do risco, do prognóstico, do rastreio de parentes e terapêutica.
Métodos: Foi usada a base de dados online Pubmed® para pesquisar os artigos publicados nessa área, em revistas indexadas. Recorreu-se à *MeSH Database* para definir a seguinte *query*: ''Mutation [Mesh] AND Sodium Channels [Mesh] AND Heart Diseases [Mesh]'' e incluíram-se artigos publicados nos últimos 15 anos, escritos em inglês ou português e referentes à investigação em humanos.
Conclusões: Nos últimos anos, grandes avanços foram feitos no esclarecimento da base genética e molecular dessas síndromes. A maior compreensão dos mecanismos fisiopatológicos subjacentes demonstrou a importância da relação entre o genótipo e o fenótipo e permitiu efetuar progressos na abordagem clínica desses pacientes. Todavia, é ainda necessário melhorar a capacidade de diagnóstico, aprimorar a estratificação do risco e desenvolver novas terapêuticas específicas de acordo com o binómio genótipo-fenótipo.

List of abbreviations

AF	atrial fibrillation
AP	action potential
BrS	Brugada syndrome
Ca^{2+}	calcium ion
CAV3	caveolin-3
CCD	cardiac conduction disease
CPVT	catecholaminergic polymorphic ventricular tachycardia
DCM	dilated cardiomyopathy
ECG	electrocardiogram
EPS	electrophysiological study
HR	heart rate
I_{Ca}	calcium current
I_K	potassium current
I_{Na}	sodium current
$I_{Na\ late}$	late, persistent or sustained sodium current
$I_{Na\ peak}$	peak sodium current
K^+	potassium ion
LQTS	long QT syndrome
LQTS1	long QT syndrome type 1
LQTS2	long QT syndrome type 2
LQTS3	long QT syndrome type 3
ms	milliseconds
Na^+	sodium ion
NaC	sodium channels
PVS	programmed ventricular stimulation
PVT	polymorphic ventricular tachycardia
QTc	QT interval corrected for heart rate
SCD	sudden cardiac death
SD	sudden death
SNP	single nucleotide polymorphism
SNTA1	syntrophin
SQTS	short QT syndrome
TdP	Torsade de pointes
VF	ventricular fibrillation
VT	ventricular tachycardia

Introduction

Cardiac channelopathies constitute a heterogeneous group of inherited cardiac diseases caused by mutations in genes that encode for the ion channels expressed in the heart (involved in Na^+ [I_{Na}], K^+ [I_K] and Ca^{2+} [I_{Ca}] currents) and/or the proteins that regulate their function.[1–3] These mutations result in different phenotypes according to the abnormalities induced in the sodium current and in other ion currents, leading to a greater likelihood of occurrence of syncope, seizures and arrhythmias, although most of the time there are no underlying structural heart defects.[4] This shows the importance of ion channels, namely sodium channels (NaC), in the genesis and propagation of the action potential (AP), and consequently in heart excitability.[2,3,5–7]

Table 1 Main genes associated with hereditary arrhythmias.

Pathology	Genes (% of involvement)	Prevalence
Hereditary arrhythmias in the absence of structural heart defects		
Brugada syndrome	SCN5A (20-30%)	1:3300 to 1:10 000*
Long QT syndrome	KCNQ1 (30-35%), KCNH2 (25-30%), SCN5A (5-10%)	1:2500*
Catecholaminergic polymorphic ventricular tachycardia	RYR2 (60-65%), CASQ2 (<5%)	1:10 000*
Cardiac conduction disease	SCN5A (5%)	
Short QT syndrome	None of the 3 known genes represents >5% of the disease	
Atrial fibrillation	None of the known genes represents >5% of the disease	
Hereditary arrhythmias in the presence of structural heart defects		
Right ventricular arrhythmogenic cardiomyopathy/Right ventricular arrhythmogenic dysplasia	PKP2 (25-40%), DSG2 (5-10%), DSP (2-12%), DSC2 (2-7%)	
Dilated cardiomyopathy	TTN (≈25%)	
Hypertrophic cardiomyopathy	MYBPC3 (30-40%), MYH7 (20-30%), TNNT2 (10%), TNNI3 (7%)	

Extracted and adapted from Mizusawa (2016).[9],
* Imbrici et al. (2016)[12] and Ackerman et al. (2011).[53]

Induced arrhythmias are potentially fatal, and sudden cardiac death (SCD) frequently constitutes the first manifestation of these diseases.[4,8] Sudden death (SD) is one of the most common causes of death due to cardiovascular pathologies and, in the adult Western population, cardiac channelopathies (1-2%) are one of the most frequently diagnosed predisposing pathologies together with cardiomyopathies (10-15%) and coronary disease (75%).[9] In reality, some studies show that cardiac channelopathies are responsible for approximately 1/3 of the SD cases in young people with a negative autopsy, and up to 50% of the cases of arrhythmic SCD.[10,11]

The main hereditary arrhythmias caused by ion channel dysfunctions are Brugada syndrome (BrS), long QT syndrome (LQTS), short QT syndrome (SQTS) and catecholaminergic polymorphic ventricular tachycardia (PVT).[4,12] However, their prevalence in the general population is difficult to estimate.[11,13–15] In addition to the pathologies mentioned above, pre-excitation syndrome, idiopathic ventricular fibrillation (VF) and rare cases of familial cardiomyopathies are also associated with ion channel mutations.[4,12]

In the last two decades, the knowledge about the genetic and molecular mechanisms underlying arrhythmias (especially those of hereditary nature – Table 1) has vastly increased, and various mutations and/or genetic variants have been described.[16,17]

Although many mutations in different ion channels affect the heart's electrical currents, we only cover what concerns sodium currents in this literature review. In particular, we cover the structure of the NaC and their role in heart excitability, mutations in the NaC complex, the associated phenotypes and the implications of the relationship between genetic and clinical aspects at the level of diagnosis, risk stratification, prognosis and treatment, namely of LQTS and BrS.

Methods

A narrative review of the literature covering the topic *Cardiac channelopathies: the role of sodium channel mutations* was conducted. The online Pubmed® database was used to search for articles published in this field, and the *MeSH database* was used to select the MeSH terms and to define the following query: ''Mutation [Mesh] AND Sodium Channels [Mesh] AND Heart Diseases [Mesh]''.

Applying the predefined inclusion criteria, only articles published in the last 15 years, written in English or in Portuguese, and referring to research in human beings were included. Additionally, the impact factor was taken into consideration.

Other references were also included, some with a publication date prior to 2002, with the aim of widening the relevant content cited in the initially searched articles.

Structure and function of sodium channels

The NaC are transmembrane proteins consisting of an α subunit together with one or two β subunits (Figure 1).[2] There are various types of α subunits, which are differentially expressed according to the type of tissue and are encoded by a family of 10 different genes (Table 2).[18,19] The main α subunit expressed in the heart is called Nav1.5 (like the sodium channel it is part of) and is encoded by the SCN5A (*sodium*

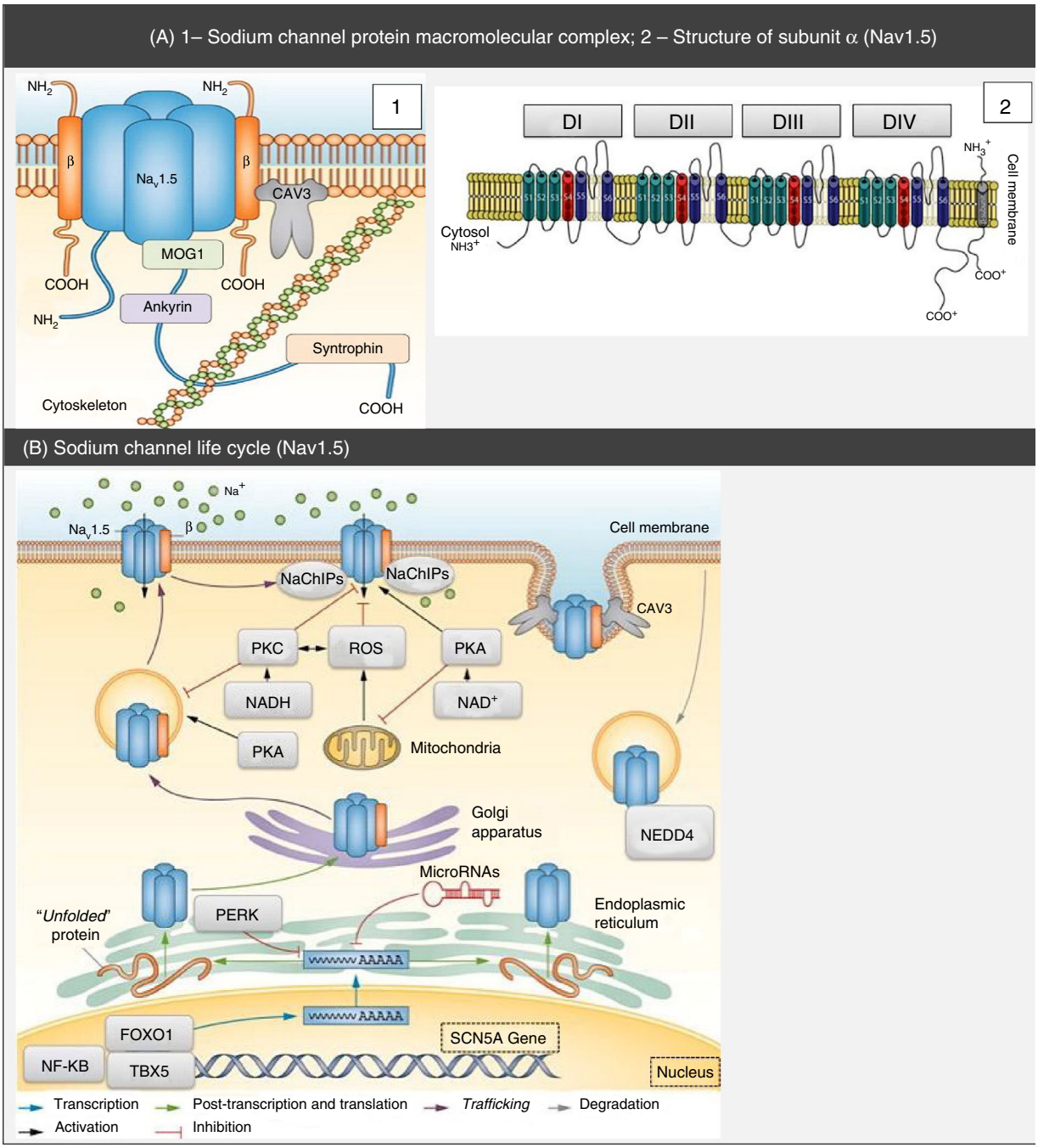

Figure 1 Protein macromolecular complex, α subunits and life cycle of the Nav1.5 sodium channels. **(A)** The Nav1.5 channel is part of a macromolecular complex interacting with various proteins such as: β subunits, caveolin-3, MOG1, ankyrin, syntrophin and cytoskeleton. Extracted and adapted from Liu et al. (2014)[7] and Amin et al. (2010).[22] **(B)** The life cycle of Nav1.5 starts in the nucleus, where transcription of the SCN5A gene and the respective regulation by transcription factors (FOXO1, NF-KB and TBX5) occur. However, microRNAs also regulate mRNA levels. In the endoplasmic reticulum proteins are translated and, after appropriate protein folding and assembly, they are transported to the cell membrane (trafficking). Mutations or splicing variants may lead to a misfolded Nav1.5 protein, which may activate the PERK pathway for downregulation of their mRNA levels. PKA, PKC, oxidative stress (ROS) and metabolic states (NADH and NAD^+) may modulate channel trafficking. NEDD4 regulates ubiquitin-mediated degradation. Extracted and adapted from Liu et al. (2014).[7]

CAV3: caveolin-3; FOXO1: forkhead box protein O1; MOG1: Ran guanine nucleotide release factor; NaChIP: Na^+-channel-interacting protein; NEDD4: E3 ubiquitin-protein ligase NEDD4; NF-κB: nuclear factor NF-κB; PERK: eukaryotic translation initiation factor 2α-kinase 3; PKA: AMPc-dependent protein kinase (protein kinase A); PKC: protein kinase C; ROS: reactive oxygen species; TBX5: T-box transcription factor TBX5.

Table 2 Sodium channel α subunits.

Protein	Tissue with major expression	Gene	Chromosome
Nav1.1	CNS and PNS	SCN1A	2q24
Nav1.2	CNS and PNS	SCN2A	2q23-24
Nav1.3	CNS and PNS	SCN3A	2q24
Nav1.4	Skeletal muscle	SCN4A	17q23-25
Nav1.5	Heart	SCN5A	3p21
Nav1.6	CNS and PNS	SCN8A	12q13
Nav1.7	PNS	SCN9A	2q24
Nav1.8	PNS	SCN10A	3p21-24
Nav1.9	PNS	SCN11A	3p21-24
Nav2.1 (Nax)	Glial cells	SCN6/7A	2q21-23

CNS: central nervous system; PNS: peripheral nervous system. Extracted and adapted from England and Groot (2009).[19]

channel, voltage gated, type V alpha subunit) gene, which includes 28 exons and spans more than 100 kb in chromosome 3p22.[18,20]

Regulation of transcription of the SCN5A gene is influenced by many factors, including: presence of three promoters, transcription factors and microRNAs with post-transcriptional activity. More than 10 isoforms resulting from splicing of this gene have been described, and the most abundant isoform in the human heart is SCN5A-003 (adult isoform).[7,18,20]

The α subunit has about 227 kDa and consists of a transmembrane protein with four homologous domains (DI-DIV) connected by cytoplasmic loops, each of them with six α-helix transmembrane segments (S1-6) connected by intra- and extracellular loops. It also has a C terminus (carboxy) and an N terminus (amino), both being cytoplasmic.[5,6,21]

The central pore is formed by the four S5 and S6 segments of subunit α, namely by the extracellular loops that connect them. It is selectively permeable to sodium, which travels through it according to the electrochemical gradient. Segments S1 to S4 act as voltage sensors. However, the latter has the peculiarity of having a positive charge.[2,5,18,21]

Like the other voltage-gated channels, the NaC show conformational changes during a process called gating that enables defining three functional states for the channel (open, inactive or closed), according to membrane potential. These alterations occur in the α subunit, which is the main one responsible for regulation of depolarization of excitable cells membranes.[2,18,22]

The subunits are proteins of approximately 30-40 kDa, with a single transmembrane segment, an intracellular C terminus and an extracellular N terminus.[5] These subunits associate with the α subunit of the NaC (Figure 1), thus not only modulating their expression on the cell surface and the gating process, but also enabling connection with the cytoskeleton and other interaction proteins. In effect, the subunits are capable of increasing the channels traffic to the cell membrane, with subsequent increase in I_{Na}.[5,18]

There are four types of β subunits (β1, β2, β3 and β4), encoded by the SCN1B, SCN2B, SCN3B and SCN4B genes, respectively. These are preferentially associated with different α subunits according to the type of tissue where they are expressed.[5,18,20,23]

In addition to the β subunits, there are other proteins with the ability to interfere and modulate Nav1.5 function (ankyrin-G, calmodulin, caveolin-3, syntrophin α1, plakophilin-2, Ran guanine nucleotide release factor [MOG1], glycerol-3-phosphate dehydrogenase 1-like [GPD1L], fibroblast growth factor homologous factor 1B [FHF-1B] and Nedd4-like ubiquitin ligases, among others) that integrate a macromolecular complex (Figure 1).[5,6,18,20,21,24,25]

The role of sodium channels in heart excitability

The heart AP is generated by depolarizing (I_{Na}; I_{Ca}) and repolarizing (I_K) ion currents.[22] NaC play an essential role in AP initiation through the generation of I_{Na}, and they are expressed in the membrane of atrial and ventricular cardiomyocytes and in specialized conduction tissue.[21–23] However, although their expression is abundant in the bundle of His, bundle branches and Purkinje fibers, their expression is low or absent in the sinus and atrioventricular nodes.[6,21]

In the ventricular myocardium, during diastole, the transmembrane electrical potential (at rest) is approximately -85 mV, and the NaC are closed. When a stimulus depolarizes the membrane, the S4 segments of the four domains move simultaneously outside, the channel opens and there is Na^+ movement to the intracellular medium, according to the electrochemical gradient.[5,6,18,22] In addition, I_{Na}, the main agent responsible for the rapid AP depolarization phase (phase 0), is thus generated and then rapidly increases until it reaches its peak ($I_{Na\ peak}$) and decreases milliseconds later.[18,23]

In NaC inactivation, the loop between domains III and IV (inactivation gate) works as a ''lid'' and the channels gradually close in about 1 ms.[18,26] It should be noted that the NaC undergo various conformational changes that translate into different inactivation states (rapid, intermediate and slow inactivation) which, in turn, have different recovery times.[18,22] However, at the end of phase 0, the majority (≈99%) of the NaC are inactivated, precluding ion traffic. They remain like this until the cell membrane is repolarized, when they recover from inactivation and again become available to be activated during phase 4.[5,18]

Nevertheless, during AP phase 2, a small fraction of the NaC (<1% of the total NaC available) may maintain conductibility for Na^+ and reopen, and thus a small I_{Na} called late current persists ($I_{Na\ late}$).[5,18,27] Moreover, some channels may reactivate during the repolarization phase (phase 3), when inactivation is not yet completed but the AP enables their reactivation, generating a current called window current.[18,22] This current corresponds to less than 1% of the sodium current peak.[22] An important role in the ventricular arrhythmogenesis present in certain cardiac pathologies, some of them covered in this review, has been attributed to these two currents.[5,18,22,27]

Under physiological conditions, the NaC activation and inactivation processes are strictly regulated in order to ensure normal cardiac electrical activity. Anomalies in the NaC cause significant abnormalities in heart electrophysiology and potentiate arrhythmogenesis, which may result from

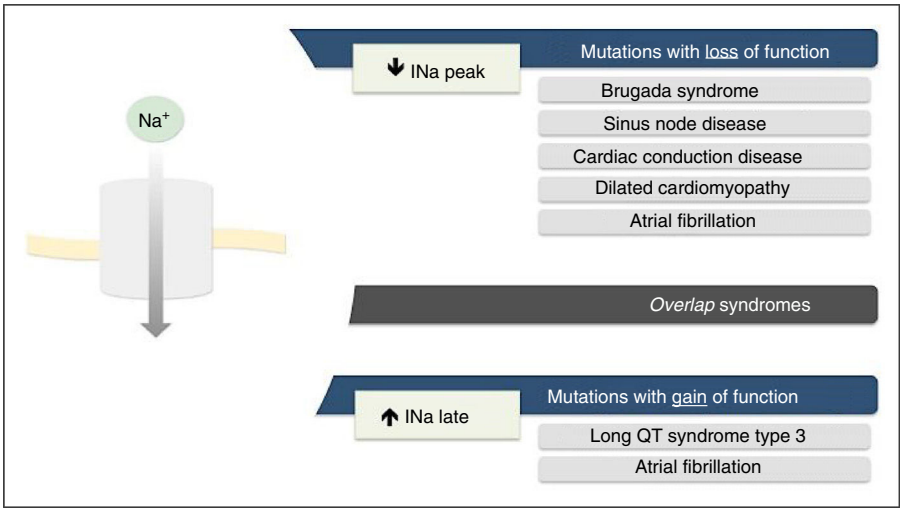

Figure 2 Clinical phenotypes associated with mutations in Nav1.5 sodium channels.
Extracted and adapted from Liu et al. (2014).[7]

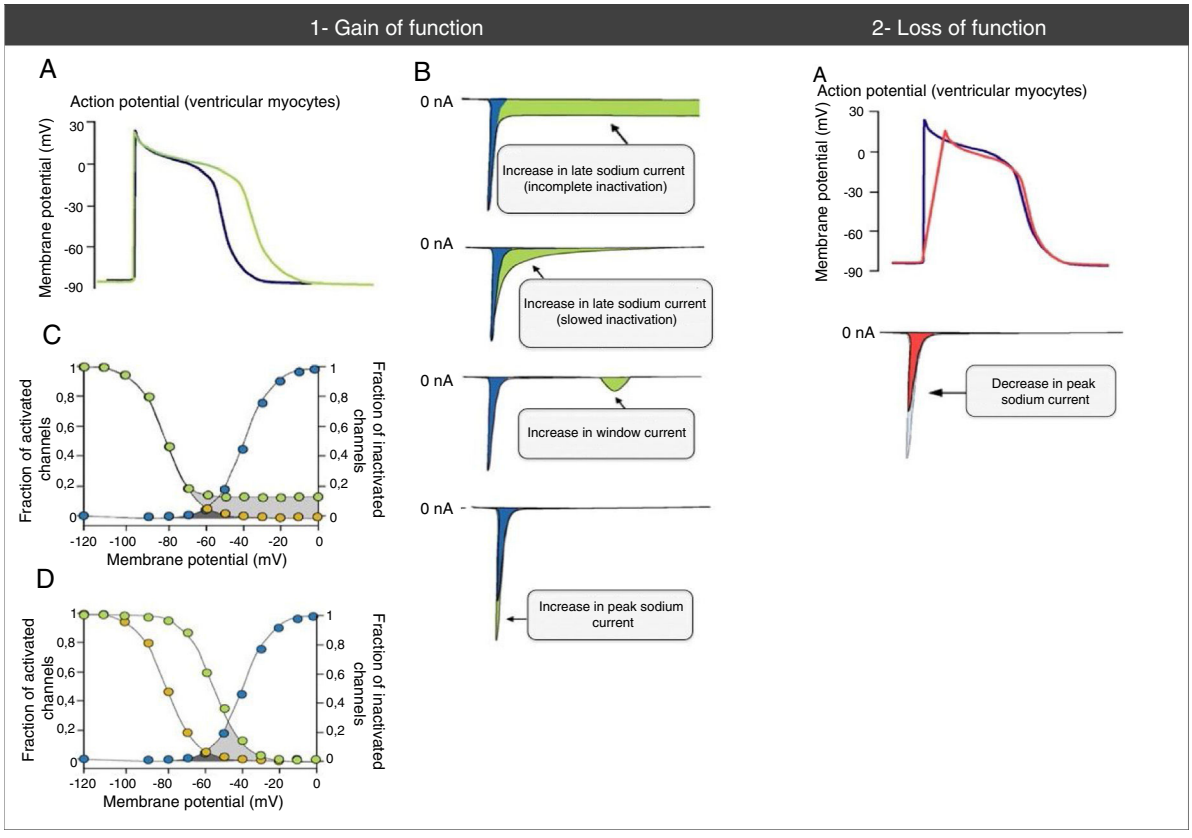

Figure 3 Abnormalities in action potential and sodium currents associated with gain- and loss-of-function mutations in Nav1.5 channels. **(1A)** Gain-of-function mutations are associated with an increase in the duration of the action potential and may trigger arrhythmic events. **(1B)** Various mechanisms may be associated with gain of function in the sodium current. The most common mechanism is increased late sodium current (abnormally sustained increase of INa during the AP phase 2 with prolonged membrane depolarization and delayed repolarization), which may be due to incomplete or slowed inactivation. Other less common mechanisms are increased window current and increased INa peak (increase in influx of Na^+ in AP phase 0). **(1C)** The mechanism of sodium current increase more frequently results from incomplete inactivation of the sodium channels (green circles). **(1D)** In the mechanism of window current increase (green circles), inactivation occurs in more positive AP states, ''delaying'' and broadening the amplitude of voltages during which NaC may be reactivated. **(2A)** In loss-of-function mutations, decreased peak sodium current decreases the upstroke speed of the AP phase 0, slowing down electrical conduction in the heart.
Extracted and adapted from Amin et al. (2010).[22]

alterations in gating properties or in I_{Na} kinetics. These alterations change channel availability, the amplitude of the $I_{Na\ peak}$ or prevent adequate channel inactivation, with maintenance of a persistent I_{Na} during the AP plateau. Therefore, the importance of the NaC in heart excitability is emphasized by the occurrence of potentially fatal arrhythmias (e.g., ventricular tachycardia and VF) in the presence of hereditary or acquired dysfunction in these channels.[18,21,22]

Mutations in sodium channels

Mutations in subunit α

In the last few decades, the knowledge about the function of the SNC5A gene at the molecular and electrophysiological level has greatly increased, and various genetic studies show that mutations in this gene are associated with many heart diseases, namely hereditary cardiac arrhythmias.[1,5,16,18,21,22,28] In most cases, the pathologies associated with NaC mutations are caused by mutations that alter channel permeability or the gating process.[6,21]

Mutations in the SCN5A gene leading to dysfunction of the Nav1.5 NaC may be due to gain of function, loss of function or both.[7,18]

The loss-of-function mutations result in decreased I_{Na} and are associated with BrS, sinus node disease (SND), atrial fibrillation (AF), Lev-Lenégre disease and dilated cardiomyopathy (DCM) (Figure 2).[7,18] The mechanism most frequently involved is decreased $I_{Na\ peak}$ (Figure 3).[7,18,23]

Gain-of-function mutations result in increased I_{Na} and are associated with LQTS3 (Figure 2). There are also some gain-of-function mutations associated with AF and DCM.[7,18] The most frequently involved mechanism consists of increased $I_{Na\ late}$.[7,18,23] However, there are other mechanisms such as increased I_{Na} peak, decreased inactivation rate or increased window current (Figure 3).[18,22]

Rarely, the mutations may simultaneously cause reduced $I_{Na\ peak}$ and increased $I_{Na\ late}$, occurring with loss and gain of function, respectively.[7,23]

Mutations in β subunits

Mutations in the β1 subunits were identified in patients with BrS, AF and cardiac conduction disease (CCD) (Table 3). The mechanism involved in these phenotypes is believed to occur with a decrease in I_{Na} density (loss of function). However, given the limited number of patients with these mutations, the mechanism involved or the genotype-phenotype relationship cannot be completely determined.[20,23,25]

The prevalence of potentially pathogenic variants of the genes for the β subunits is similar to that of other minor genes involved in BrS.[29,30] Indeed, even though in recent years the knowledge of the underlying mechanisms of BrS focuses mainly on the SCN5A gene, the screening of the four β subunits may lead to a potential increase in the genetic diagnosis of the syndrome, up to approximately 5.4%.[30]

Mutations in the β1 and β2 subunits are associated with AF, and the mechanism consists of alterations in gating and decreased I_{Na}.[6,31] In 2011, Olesen et al.[32] described mutations associated with AF, also in the β3 subunit. These mutations decrease I_{Na}, increasing the susceptibility for AF through one of two mechanisms: conduction delay or decrease in the refractory period (promoting the possibility of reentry circuits).[32] Moreover, mutations in SCN3B are also associated with BrS (Table 3).[8,23]

Mutations in β4 subunit have already been described in LQTS10 and confer gain of function, whose most likely mechanism consists of increased $I_{Na\ late}$.[23,25,30,33]

Mutations in proteins associated with sodium channels

The NaC are part of a macromolecular complex that includes various proteins that participate in cell adhesion, signal transduction pathways and the cytoskeleton (Figure 1).[6,7,11] These proteins are directly or indirectly bound to the NaC and have the ability to modulate their expression, traffic and function.[6,19,23] Therefore, their dysfunction contributes to the pathophysiology of the cardiac channelopathies.[6,22,23,28]

In fact, mutations in several of these proteins are associated with LQTS or BrS (Table 3).[5,22,34–36] Caveolin-3 (CAV3) is an important protein in membrane traffic and in the positioning of the ion channels in the sarcoplasmatic membrane, which regulates various ion currents in the heart such as I_{Na}. Syntrophin α1 (SNTA1) is a cytoskeleton protein that interacts with the NaC (Figure 1). Gain-of-function mutations described in CAV3 are associated with LQTS9, whereas those described for SNTA1 are associated with a phenotype similar to LQTS3.[6,15,22,28,37] On the other hand, mutations in ankyrin-B, whose function is to bind membrane proteins to cytoskeleton structures (Figure 1), are associated with LQTS4 and AF, among others.[15]

Mutations in the GPD1L gene, which encodes the glycerol-3-phosphate dehydrogenase 1-like protein, or in the MOG1 gene, which encodes a molecule that affects protein traffic, have already been described in BrS.[6,15,23,25] In addition, mutations in plakophilin-2, a desmosomal protein, may decrease I_{Na} and therefore lead to a phenotype similar to BrS.[15,38,39]

''Cardiac'' phenotypes associated with dysfunction in sodium channels and interacting proteins

The numerous ''cardiac'' phenotypes associated with mutations in the genes encoding for the NaC and the proteins that make up its macromolecular complex are described in Table 4. The most prevalent cardiac channelopathies are LQTS (1:2500) and BrS (1:3300 to 1:10 000), which are partially associated with NaC dysfunction.[12] Therefore, we will now cover only these two entities.

Brugada syndrome

BrS was first described in 1992 as a syndrome characterized by a typical electrocardiographic pattern, absence of structural heart anomalies and family history of SD. Since then, progress has been made in understanding its pathophysiology and in identifying its genetic basis.[1,40,41]

BrS is a rare hereditary syndrome with an estimated prevalence of 1/3300 to 1/10 000, and ethnic and

Table 3 Mutations in proteins of the sodium channel macromolecular complex.

Gene	Protein	Normal effect on I_{Na}	Mutations	Mutation effect	Phenotype
SCN1B	β1	(↓) I_{Na} late	Trp179X	(Ø-) Activation, (Ø-) SSI, (Ø↑) I_{Na} peak	BrS, CCD
		(↑) Rec.R	E87Q	(Ø-) Activation, (Ø↑) I_{Na} peak	BrS, CCD
		(↑) I_{Na} peak	R85H	(+) Activation, SSI, (Ø↑) I_{Na} peak	Familial AF
			D153N	(Ø↑) I_{Na} peak	Familial AF
			R214Q	(Ø↑) I_{Na} peak	BrS, Familial AF
SCN2B	β2	State of sialylation	R28Q	(+) Activation, (↓) I_{Na} peak	Familial AF (↑) PR, (↑) RP.ST
		(↑) Late current	R28W	(+) SSI, (+) Activation, (↓) I_{Na} peak	Familial AF (↑) PR, (↑) RP.ST
SCN3B	β3	(↑) I_{Na}, (↑)	R6K, L10P and M161T	Mixed, (↓) I_{Na} peak, (-) SSI, (↓) Rec.R	Familial AF BrS
		Rec.R, (+)	A130V	(↓) I_{Na} peak	Familial AF
		SSI, (↑)	V54G	(↓) I_{Na} peak (↓) Trafficking	Idiopathic VF, ISDS
		Ref.P	V36M	(↓) I_{Na} peak (↑) I_{Na} late	ISDS
SCN4B	β4	(↑) Speed of AP upstroke	S206L	(↑) I_{Na} late	ISDS
		(+) SSI	L179F	(↑) Window current	LQTS10
CAV3	Caveolin 3	Scaffolding, (↓) I_{Na}	F97C, S141R	(↑) I_{Na} late	LQTS9
		late	V14L, T78M and L79R	(↑) I_{Na} late	ISDS
GPD1L	GPD1L	(↑) I_{Na} by	A280V	(↓) I_{Na} peak	BrS
		phosphorylation	E83K, I124V, R273C	(↓) I_{Na} peak	ISDS
RANGRF	MOG1	(↑) Surface density,(↑) I_{Na} peak	E83D	(↓) I_{Na} peak (↓) Trafficking	BrS
SNTA1	Syntrophin α1	Scaffolding	A390V	(↑) I_{Na} peak, (↑) I_{Na} late	LQTS12
			S287R, T372M, G460S	(↑) I_{Na} peak, (↑) I_{Na} late, (+) SSI	ISDS

Ø: failure; (↑): increase; (↓): decrease; (+): depolarizing shift; (-): hyperpolarizing shift; AF: atrial fibrillation; BrS: Brugada syndrome; CCD: cardiac conduction disease; ISDS: infant sudden-death syndrome; LQTS: long QT syndrome; Rec.R: recovery rate; Ref.P: refractory period; RP.ST: ST segment in right precordial leads; SSI: steady state inactivation; VF: ventricular fibrillation.

Extracted and adapted from Adsit et al. (2013).[23]

Table 4 ''Cardiac'' phenotypes associated with dysfunction of sodium channels and related proteins.

Gene	Protein	Abnormalities in I_{Na}	''Cardiac'' phenotype
Sodium channel			
SCN5A	$Na_v1.5$	(↓) I_{Na} by different mechanisms	Type 1 BrS
		(↑) I_{Na} late	Type 3 LQTS
		(↓) I_{Na} by different mechanisms	CCD
		(↓) I_{Na} by different mechanisms	Lev-Lenégre disease
		(↓) I_{Na} by different mechanisms	Congenital AV block
		(↓) I_{Na}	SND
		(↓) I_{Na}	Atrial standstill
		Different and mismatched molecular phenotypes	AF
		Different and mismatched molecular phenotypes	DCM
		(↑) I_{Na} late/(↓) I_{Na}	ISDS
		Combination of molecular phenotypes present in other clinical entities	Overlap Syndrome
Proteins of sodium channel macromolecular complex			
SCN1B	Subunit β1	(↓) I_{Na} peak	Type 5 BrS
		(↓) I_{Na} peak	CCD
		(↓) I_{Na} peak	AF
SCN2B	Subunit β2	(↓) I_{Na} peak	AF
		(↓) I_{Na} peak	Type 7 BrS
SCN3B	Subunit β3	(↓) I_{Na} peak	AF
		(↓) I_{Na} peak	CCD
		(↓) I_{Na} peak/(↑) I_{Na} late	ISDS
		(↓) I_{Na} peak	Idiopathic VF
SCN4B	Subunit β4	(↑) I_{Na} late	Type 10 LQTS
		(↑) I_{Na} late	ISDS
SNTA	Syntrophin α1	(↑) I_{Na} late/(↑) I_{Na}peak	Type 12 LQTS
		(↑) I_{Na} late/(↑) I_{Na}peak	ISDS
RANGRF	MOG1	(↓) I_{Na} peak	Type 8 BrS
CAV3	Caveolin-3	(↑) I_{Na} late	Type 9 LQTS
		(↑) I_{Na} late	ISDS
GPD1L	Glycerol-3-phosphate dehydrogenase 1-like	(↓) I_{Na} peak	Type 2 BrS
		(↓) I_{Na} peak	ISDS
PTPH1	Tyrosine phosphatase H1		–
NEDD4L	Nedd4-2/Nedd4-like		–
CALM	Calmodulin		–
CAMK2D	Calcium/Calmodulin-dependent protein kinase II delta		–
SAP97	SAP97		–
YWHAH	14-3-3-a		–
FGF13	FGF13		–
ANK3	Ankyrin-G		–
ACTN2	Actinin α2		–
PKP2	Plakophilin-2		Arrhythmogenic cardiomyopathy
DSG2	Desmoglein-2		Arrhythmogenic cardiomyopathy
TCAP	Telethonin		–
ZASP	Z band		–

AF: atrial fibrillation; AV: atrioventricular; BrS: Brugada syndrome; CCD: cardiac conduction disease; DCM: dilated cardiomyopathy; ISDS: infant sudden death syndrome; LQTS: long QT syndrome; SND: sinus node disease.
Extracted and adapted from Wilde and Brugada (2011),[5] Remme (2013),[6] Abriel (2010)[15] and Adsit et al. (2013).[23]

Table 5 Drugs used in provocation tests to ''unmask'' Brugada syndrome.

Drug	Dose and duration	Route of administration
Ajmaline	1 mg/kg for 5 minutes	IV
Flecainide	2 mg/kg for 10 minutes	IV
	400 mg	PO
Pilsicainide	1 mg/kg for 10 minutes	IV
Procainamide	10 mg/kg for 10 minutes	IV

IV: intravenous; PO: *per os*.
Extracted and adapted from Antzelevitch et al. (2005).[45]

geographic differences have already been described.[12,14,42] It affects relatively young adults (<40 years old), more frequently males, with a family history of SD in 20-50% of the cases.[21,43,44] Moreover, it is estimated that BrS is responsible for at least 4% of all SD cases and for at least 20% of all SD cases in individuals without structural heart abnormalities.[8,45]

The absence of structural heart anomalies was classically a characteristic of BrS.[41] However, mild structural anomalies in the right and left ventricles have been described in various studies.[46]

Most individuals are asymptomatic at the time of diagnosis, which is made following a routine ECG in approximately 58% of cases or as a result of family screening in approximately 37% of cases.[44] However, SCD may be the first sign of the disease since these individuals are at increased risk for developing tachyarrhythmias, namely PVT and VF.[22,47]

It is estimated that the rate of arrhythmia events per year in symptomatic individuals is about 0.5%, occurring more frequently at rest and while sleeping, but also in the presence of fever or after a heavy meal.[1,44,48] In fact, fever is one of the factors that may cause or exacerbate the electrocardiographic pattern of BrS, triggering potentially fatal arrhythmias in about 27% of cases.[21,49]

Diagnosis is made using clinical criteria, presence of a typical pattern of electrocardiographic abnormalities and exclusion of other etiologies that may mimic BrS, namely because they trigger ST-segment elevation (Figure 4).[45,50,51] Provocation tests with NaC-blocking agents (Table 5) may be performed to provoke the electrocardiographic abnormalities seen in BrS (Figure 5), which enables diagnosing those individuals with transient electrocardiographic pattern.[14,41,45,52] In these cases, Holter may also be used and, through prolonged monitoring, it may enable diagnosing intermittent abnormalities.[1]

Genetic tests (broad or specific for the SCN5A gene) may also be useful for diagnosis in any case where there is strong clinical suspicion of BrS according to the family and medical history and the ECG.[53] It should be noted that after identifying a pathogenic mutation in a BrS *case index*, specific genetic screening of family members is indicated.[53,54]

BrS presents high genetic complexity and there are various genes that may be mutated in this syndrome, although only a few are associated with abnormalities in I_{Na} (Table 6).[43,54,55] As of today, more than 300 mutations reducing I_{Na} amplitude through different mechanisms have been described.[16,43,54,56] The mutations occur more frequently in the SCN5A gene, and usually occur in transmembrane segments S1-S4 and in the segments involved in pore formation (S5-S6).[16,55] However, only a few (approximately 10-30%) of the total number of individuals diagnosed with BrS are positive for a mutation in this gene.[21,43,56–58] Other genes (Table 6) are involved in fewer than 5% of the cases.[55]

In fact, only 30-35% of the individuals with a clinical diagnosis have a genetic diagnosis as well (positive genotype).[8] Therefore, the majority of the individuals affected (approximately 65%) remains genetically undetermined (negative genotype) and for this reason identifying new susceptibility genes for BrS is necessary.[16,56,59]

Recently, the SCN10A gene was identified as a susceptibility gene for BrS, although its real prevalence has yet to be determined.[56,60] The expression level and function of the Nav1.8 NaC in the heart are still controversial. However, a study published in 2014 shows that the variants of this gene influence the duration of the PR and QRS interval, heart rate (HR) and also the risk of arrhythmias.[56]

A few recessive forms with homozygous or compound heterozygous mutations have been described, but most of the known pathogenic mutations in the SCN5A gene present an autosomal dominant transmission pattern with variable, and frequently incomplete, penetrance.[18,43,45]

The mechanism most frequently implicated is decreased $I_{Na\ peak}$ due to mutations in the SCN5A gene (loss of function) and consequent slowing of cardiac conduction (Figure 3).[7,18,60,61] Nevertheless, there are many hypotheses for the pathophysiological mechanisms of BrS that involve depolarization and repolarization abnormalities; however, the latter are not covered in this article.[40,51,54]

The genotype of individuals with BrS does not currently carry relevant implications for prognosis or treatment (Table 7).[9] Nonetheless, its influence in the risk of arrhythmia and in prognosis is still under debate.[54] In reality, genetic data may constitute a complementary tool for risk stratification.[43,61] Nonsense mutations, which result in truncated proteins, have been associated with a poorer prognosis compared with other types of mutations with less marked repercussions in NaC function.[40,43,59,61] A retrospective study published in 2009 shows that the phenotype is more severe in individuals with mutations associated with more significant I_{Na} reductions compared with individuals with mutations associated with lower reductions.[61] The same is seen when the mutation is located in a transmembrane region of the NaC.[61] Another study published in 2013 shows that different mutations in the SCN5A gene have a different impact on I_{Na}, emphasizing the role of mutation characterization in the risk assessment for non-affected family members.[62] However, it is still not clear to what extent different mutations confer a risk for arrhythmia events or SCD, thus the risk is currently stratified only with clinical parameters.[53,54]

The only treatment available proven capable of preventing SCD in patients with BrS was the implementation of an implantable cardioverter defibrillator (ICD).[1,9,44,46] This procedure, however, results in a considerable risk of complications, which occur in approximately 9% of patients/year and, although rarely life-threatening, they are psychologically harmful.[9,54] Therefore, a careful assessment of risks (namely the risk of arrhythmia) and benefits is a key process in this decision.[44,54]

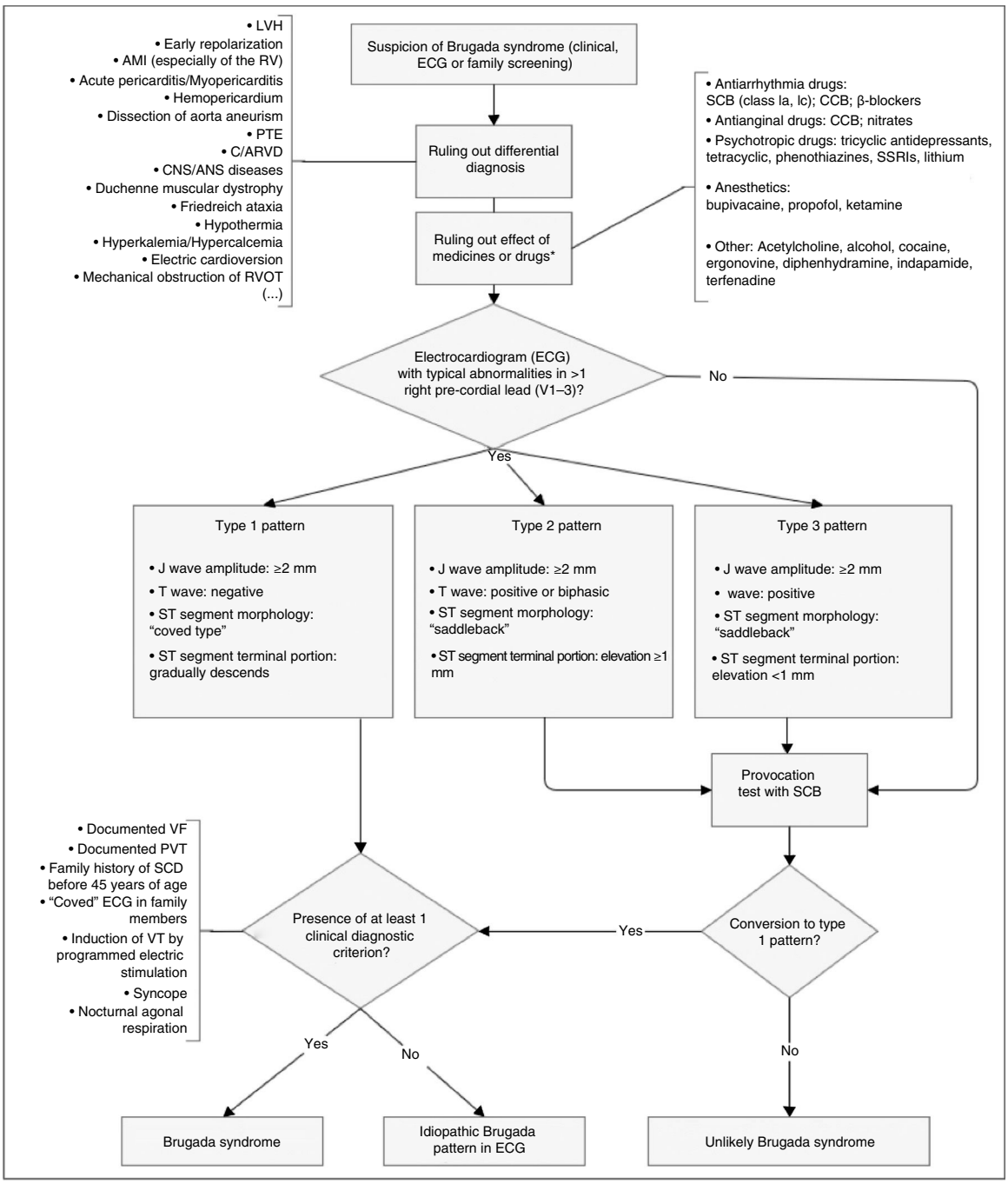

Figure 4 Diagnostic algorithm for Brugada syndrome. There are three patterns of electrocardiographic abnormalities in the right precordial leads (V1-V3). Type 1 is considered to be diagnostic, unlike types 2 and 3 (in presence of which provocation tests with SCB must be performed). Other electrocardiographic abnormalities that may be present in BrS are: prolongation of the PR interval and right branch block. A definitive diagnosis is made in presence of type 1 ST-segment elevation in at least one V1-V3 lead and when one of the clinical criteria presented in the figure is met. AMI: acute myocardial infarction; ANS: autonomic nervous system; C/ARVD: cardiomyopathy/arrhythmogenic right ventricular dysplasia; CCB: calcium channel blockers; CNS: central nervous system; ECG: electrocardiogram; LVH: left ventricular hypertrophy; PTE: pulmonary thromboembolism; RV: right ventricle; RVOT: right ventricular outflow tract; SCB: sodium channel blockers; SSRIs: selective serotonin reuptake inhibitors; VF: ventricular fibrillation; VT: ventricular tachycardia; β-blockers: beta blockers. *May unmask genetic susceptibility to BrS.
Extracted and adapted from Berne and Brugada (2012).[51]

A 2003 study that included 547 individuals diagnosed with BrS, showing a diagnostic electrocardiographic pattern but no prior ''aborted'' SCD, was conducted with the aim of assessing the prognostic value of clinical, electrocardiographic and electrophysiological variables. The authors observed that the group with lower risk (incidence of events:

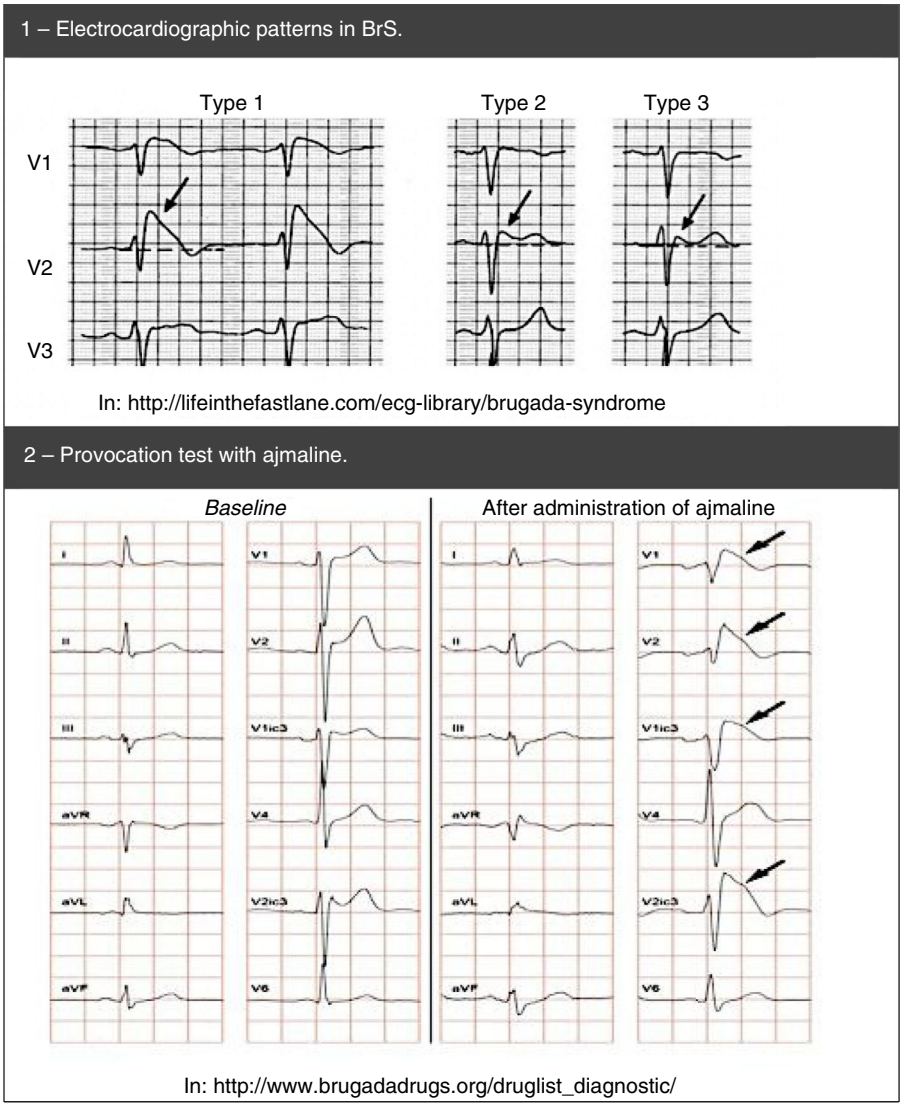

Figure 5 Electrocardiographic patterns in BrS: spontaneous **(1)** and after provocation test with ajmaline **(2)**.

0.5%) is characterized by absence of syncope episodes, an electrocardiographic pattern only triggered by antiarrhythmics and absence of arrhythmia during programmed ventricular stimulation (PVS). However, the group with higher risk (incidence of events: 27.2%) is characterized by prior history of syncope episodes, spontaneously abnormal ECG and presence of arrhythmias induced by PVS. Moreover, individuals with inducibility of arrhythmias in PVS have a six-fold higher risk of SCD or VF during the subsequent two years than those who do not have it.[63]

Although some are controversial, there are many risk factors for arrhythmia events, and among them, symptoms are one of the most important.[42,46,54,64] In fact, individuals diagnosed after an ''aborted'' SCD are at the highest risk, and in approximately 60% of these cases there is a new event 10 years after the diagnosis.[54] Individuals with syncope episodes have a rate of arrhythmia events of 1.9%/year, and the simultaneous presence of a type 1 electrocardiographic pattern is associated with a poor prognosis.[46,54] Additionally there are other electrocardiographic parameters that are associated with a poorer prognosis, for example, presence of QRS-interval fragmentation in the ECG, identified in 30-40% of the patients.[54]

Long QT syndrome

Congenital LQTS is an arrhythmia syndrome with a genetic/hereditary etiology and incomplete penetrance, whose prevalence in Caucasians is approximately 1:2500, a value much higher than what was previously expected.[12,13,65] It represents a heterogeneous group of diseases and, classically, it is divided into two variants: Romano-Ward syndrome and Jervell and Lange-Nielsen syndrome (Table 8).[1,43,65]

In 1995 and 1996, the three main genes conferring susceptibility to LQTS were identified: KCNQ1, KCNH2 and SCN5A.[66–68] These genes constitute about 75% of the clinically defined LQTS and the remainder collectively represents only 5% of these cases.[43,69] It should be noted that LQTS is

Table 6 Mutated genes in Brugada syndrome.

Phenotype	Gene	Locus	Protein	Effect on function	Inheritance	Frequency
Sodium channels and associated proteins						
BrS1	SCN5A	3p21	Nav1.5	(-)	AD	11-28%
BrS18	SCN10A	3p22.2	Nav1.8	(-)	AD	5.0-16.7%
BrS5	SCN1B	19q13.12	Subunit β1	(-)	AD	1.1%
BrS17	SCN2B	11q23.3	Subunit β2	(-)	AD	<1%
BrS7	SCN3B	11q24.1	Subunit β3	(-)	AD	<1%
BrS2	GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1-like	(-)	AD	<1%
BrS11	RANGRF	17p13.1	*MOG1*	(-)	AD	<1%
BrS15	SLMAP	3p14.3	Protein associated with sarcolemma	(-)	AD	<1%
BrS20	PKP2	12p11	Plakophilin 2	I_{Na} deficit[#]	AD	<1%
BrS19	HEY2	6q22	Nav1.5	(-)		
Calcium channels						
BrS3	CACNA1C	12p13.33	α1c subunit of voltage-gated L-type calcium channel (Cav1.2)	(-)	AD	6.6%
BrS4	CACNB2B	10p12.33-p12.31	β2 subunit of voltage-gated L-type calcium channel (Cav β2)	(-)	AD	4.8%
BrS10	CACNA2D1	7q21.11	α2/δ1 subunits of voltage-gated calcium channel (Cavα2δ1)	(-)	AD	1.8%
BrS16	TRPM4	19q13.33	*''Transient receptor potential cation channel subfamily M member 4''*	(-)	AD	<1%
Potassium channels						
BrS13	KCND3	1p13.2	*Voltage-gated potassium channel subfamily D member 3*	(+)	AD	<1%
BrS6	KCNE3	11q13.4	*Voltage-gated potassium channel subfamily E member 3*	(+)	AD	<1%
BrS9	KCNJ8	12p12.1	Inward rectifier potassium channel 8 sensitive to ATP	(+)	AD	2%
BrS14	HCN4	15q24.1	*''Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4''*	(+)	AD	<1%
BrS12	KCNE5	Xq22.3	Voltage-gated potassium channel subfamily E ''regulatory β'' subunit 5	(+)	X-linked	<1%
BrS8	KCNH2	7q35	*Kv11.1, IKr*	(+)		1-2%
BrS21	ABCC9	12p12.1	SUR2A (subunit 2A of the sulfonylurea receptor), IK-ATP	(+)		4-5%

AD: autosomal dominant.
[#] Plakophilin causes I_{Na} deficit.
Extracted and adapted from Sarquella-Brugada-et al. (2016),[8] Sieira et al. (2016)[54] and Juang and Horie (2016).[60]

Table 7 Recommendations for the treatment of Brugada syndrome.

General measures for lifestyle alterations			
Avoid drugs that may induce or worsen ST segment elevation in RPCld			(Class I)
Avoid excessive alcohol consumption			(Class I)
In presence of fever, promptly medicate with antipyretic drug			(Class Ia)
Risk stratification and specific treatment			
Symptomatic individuals[a]		Asymptomatic individuals	
''aborted'' SCD	ICD (Class I)	Spontaneous type 1 electrocardiogram (ECG) pattern	Quinidine (Class IIb)
Documented spontaneous VT, with or without syncope	ICD (Class I)	Spontaneous type 1 ECG pattern + VT/VF induced by EPS	ICD (Class IIb)
Syncope + Spontaneous type 1 ECG pattern	ICD (Class IIa)		
Electrical/arrhythmic storm[b]	Isoprenaline[c] (Class IIa) Quinidine[d] (Class IIa)	Type 1 ECG pattern induced by drugs and family history of SCD	ICD (Class III)
Individuals who are eligible for ICD but present a contraindication or refuse ICD and/or present with a history of supraventricular arrhythmias that require treatment			Quinidine (Class IIa)
Individuals diagnosed with BrS and history of electrical/arrhythmic storms or (appropriate) repetition shocks due to ICD			Catheter ablation – RF (Class IIb)

BrS: Brugada syndrome; ICD: implantable cardioverter defibrillator; RF: radiofrequency; RPCld: right precordial leads; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

[a] The clinical manifestations associated with BrS may include ventricular fibrillation, ''aborted'' sudden death, syncope, palpitations, chest discomfort and nocturnal agonal breathing.

[b] Defined as more than 2 VT/VF episodes in 24 hours.

[c] May be useful to suppress electrical/arrhythmic storms.

[d] May be useful in individuals diagnosed with BrS and history of electrical/arrhythmic storms.

Adapted from Priori et al. (2013)[46] and Steinfurt et al. (2015).[64]

associated with abnormalities in sodium currents only for types 3, 9, 10 and 12.[22,69]

LQTS is characterized by a delay in ventricular repolarization, which translates echocardiographically as QT interval prolongation (Figure 6).[22,65] The duration of the QT interval depends on NaC inactivation, the alteration of which may trigger arrhythmias.[26]

Mutations in the SCN5A gene associated with LQTS3 (gain of function) usually affect NaC inactivation, which is slower, unstable or incomplete.[6,18,22,26] Consequently, there is an increase in $I_{Na\ late}$ with prolongation of membrane depolarization and delay in repolarization.[18,26,65,70] Other mechanisms potentially involved are: increased window current, slower inactivation and increased $I_{Na\ peak}$ (Figure 3).[6,18,22]

The first mutation associated with LQTS3 is found in the loop between domains III and IV, corresponding to the inactivation gate.[26] Since then, multiple mutations causing abnormalities in inactivation have been identified and functionally characterized. They may be located at different sites in the NaC structure, namely in the C terminus, to which a relevant function in this process has been attributed.[22,26]

Congenital LQTS occurs mainly in young, healthy individuals without concomitant structural heart abnormalities and is associated with an increased risk of syncope and potentially fatal heart arrhythmias such as *Torsade de Pointes* (TdP), which degenerates into VF and causes cardiac arrest.[6,18,66] In LQTS3 (unlike LQTS1 and LQTS2 – Figure 6), arrhythmias usually occur at rest, particularly while sleeping (low HR).[6,22,43,70] It should be noted that $I_{Na\ late}$ is higher with slower stimulation frequencies, suggesting that the intensity of this current may be a strong factor in determining the occurrence of arrhythmias.[22]

The first cardiac event (more frequently syncope) usually occurs in adolescents (16±10 years old in LQTS3) and earlier among males.[9,71] However, in approximately 5-10% of cases, SCD is the initial event of the disease and, actually, LQTS is one of the main causes of SCD with negative autopsy.[10,72]

Diagnosis is mainly based on medical history and ECG (Figures 6 and 7).[65,70] In ECGs, the QT interval is the most relevant parameter (Table 9), and is measured from the beginning of the QRS complex to the end of the T wave in the DII and V5 or V6 leads.[65,73] The longest value is used, generally corrected for HR (QTc) with the *Bazett formula* (despite its limitations for particularly rapid or slow HR).[1,46,65,73]

Additionally, secondary causes for QT interval prolongation (acquired LQTS) must be ruled out, for example: drugs, myocardial ischemia, cardiomyopathy, hypokalemia, hypomagnesemia and hypothermia, among others.[46,65] Once

Table 8 Subtypes of congenital LQTS.

Name	Gene	Protein	Current	Effect on function	Frequency
Autosomal dominant inheritance (Romano-Ward)					
LQTS1	KCNQ1	$K_V7.1$	I_{Ks}	(-)	40-55%*
LQTS2	KCNH2	$K_V11.1$	I_{Kr}	(-)	30-45%*
LQTS3	SCN5A	$Na_V1.5$	I_{Na}	(+)	5-10%*
LQTS4	ANKB	Ankyrin B	NCX exchanger, ATPase Na^+/K^+	(-)	Rare*
LQTS5	KCNE1[a]	MinK	I_{Ks}	(-)	Rare*
LQTS6	KCNE2	MiRP1	I_{Kr}	(-)	Rare*
LQTS7 (ATS)	KCNJ2	Kir2.1	I_{Kl}	(-)	Rare*
LQTS8 (TS)	CACNA1C	$Ca_V1.2\alpha1$	$I_{Ca,L}$	(+)	Rare*
LQTS9	CAV3	Caveolin-3	I_{Na}	(+)	Rare*
LQTS10	SCN4B	Subunit β4	I_{Na}	(+)	Very rare*
LQTS11	AKAP9	Yotiao	I_{Ks}	(-)	Very rare*
LQTS12	SNTA1	Syntrophin-α1	I_{Na}	(+)	Very rare*
LQTS13	KCNJ5	Kir 3.4	$I_{K\text{-}Ach}$	(-)	Very rare*
LQTS14	CALM1	Calmodulin 1	Reduction of affinity for Ca^{2+} **	Rare*	
LQTS15	CALM2	Calmodulin 2	Reduction of affinity for Ca^{2+} **	Rare*	
Autosomal recessive inheritance (Jervell and Lange-Nielsen)					
JLN1	KCNQ1	$K_V7.1$	I_{Ks}	(-)	Rare
JLN2	KCNE1[a]	MinK	I_{Ks}	(-)	Rare

(-): loss of function; (+): gain of function; ATS: Andersen-Tawil syndrome; $I_{Ca,L}$: Ca^{2+} currents through voltage-gated type-L calcium channels; $I_{K\text{-}Ach}$: K^+ current regulated by acetylcholine receptors; I_{Kl}: K^+ entry current, rectifying; I_{Kr}: rapid component (internal rectification – K^+ channels are open when potential is negative and closed when potential is less negative or positive) of the K^+ ''delayed rectifier'' current (I_{Kr}); I_{Ks}: slow component of the K^+ ''delayed rectifier'' current (I_{Kr}); I_{Na}: voltage-gated Na^+ current; NCX: Na^+/Ca^{2+} exchanger; TS: Timothy syndrome.

[a] Mutations in the KCNE1 gene may cause Romano-Ward syndrome (autosomal dominant; LQTS5) or, if homozygous or compound heterozygous, Jervell and Lange-Nielsen syndrome (autosomal recessive).

** Calmodulin dysfunction may alter the inactivation of Ca^{2+}-gated L-type Ca^{2+} channels (increasing the depolarizing current during phase 2 of the action potential), but some calmodulin mutations may also be associated with an abnormality in the regulation of sodium channels.

Extracted and adapted from Nakano and Shimizu (2016),[34] **Makita et al. (2014)[36] and *Mizusawa (2014).[69]

Table 9 Assessment of the QT interval.

1 – Method for correction of QT interval (formulas)

Bazett	$QT/RR^{1/2}$
Fridericia	$QT/RR^{1/3}$
Framingham	QT + 0.154 (1 - RR)
Hodges	QT + 1.75 (HR - 60)

2 – Normal, borderline and prolonged QTc values calculated with the Bazett formula

	Normal	*Borderline*	Prolonged
1-15 years	<440 ms	440-460 ms	>460 ms
Adult (♂)	<430 ms	430-450 ms	>450 ms
Adult (♀)	<450 ms	450-470 ms	>470 ms

♂: male; ♀: female; HR: heart rate; RR: RR interval.

Extracted and adapted from Goldenberg et al. (2006).[73]

ruled out, the presence of a repetition of a QTc value ≥500 ms (or 480-499 ms if conducted after an unexplained syncope episode) in an electrocardiogram is considered to be diagnostic.[43,46] However, LQTS types 1, 2 and 3 may occur with normal QTc in the ECG at rest in 36%, 19% and 10% of cases, respectively.[69]

A scoring system considering various clinical and electrocardiographic parameters was created for diagnosis and provides the likelihood for LQTS (Figure 6).[43,46,70] In addition, Holter monitoring and the ECG obtained during an effort test or after adrenaline infusion may be useful in some particular cases.[1,46,53,65,69]

A Characteristics of the most common congenital LQTS (according to genotype)

Genotype	LQTS1	LQTS2	LQTS3
Frequency	35%	30%	10%
Gene	KCNQ1	KCNH2	SCN5A
Effect on ion currents	↓I_{Ks}	↓I_{Kr}	↑I_{Na}
Effect on AP (duration – ms)	Phase 3>2	Phase 2>3	Phase 0 (slower)
Main triggers	Exercise Sympathetic tone	Auditory stimulus and emotion	*Sleep, rest without stimulation*
Cardiac events triggered by exercise*	62%	13%***	13%***
Patients at higher risk	♂ before adolescence	♀ after adolescence	♂ after adolescence
Response to β-blocker	+++	++	+

B Criteria for the diagnosis of congenital LQTS (Schwartz score)

Findings in the ECG		Points
A QTc	≥ 480 ms	3
	460-479 ms	2
	450-459(♂)ms	1
B	QTc in the 4th minute of recovery after exercise test ≥ 480 ms	1
C	*Torsade de pointes*#	2
D	T wave "*alternans*"	1
E	*3-lead entailed T wave*	1
F	HR low for age**	0.5
Medical history		
A	Syncope# With *stress*	2
	Syncope# Without *stress*	1
B	Congenital deafness	0.5
Family history		
A	Family members with LQTS⊙	1
B	Unexplained scd in family Members aged <30 years⊙	0.5

C Relationship between myocyte AP phases and abnormalities in ion channel function (gain or loss of function) leading to prolonged AP duration and QT interval in the ECG

D LQTS 1 to 3: abnormalities in QT interval in the ECG and associated clinical aspects

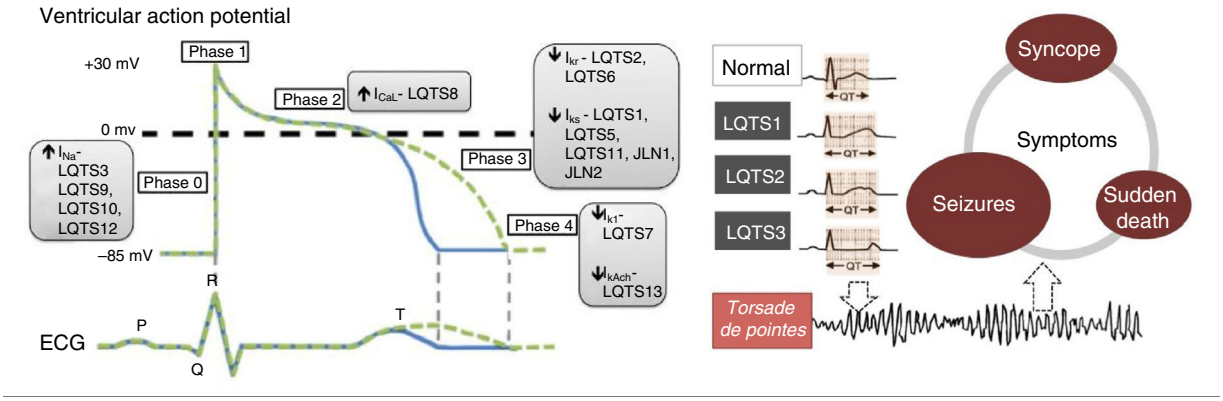

Figure 6 Long QT syndrome – main characteristics and diagnostic criteria. **(B)** Scoring system used in the diagnosis of LQTS based on the findings in the electrocardiogram, medical history (symptoms) and family history. QTc is calculated using the Bazett formula. Scoring: ≤1 – low likelihood of LQTS; 1.5 to 3 – intermediate likelihood of LQTS; ≥3.5 – high likelihood of LQTS. LQTS is diagnosed in individuals with a score ≥3.5 in whom there are no secondary causes for QT interval prolongation.
♂: male individuals; ♀: female individuals; HR: heart rate.
#Mutually exclusive. ⊙Both cannot be accounted for in the same family.
**HR at rest below the 2nd percentile for age.
***The low risk associated with exercise in LQTS2 and LQTS3 patients is explained by the fact that both have a normal IK current, stimulated by activation of the sympathetic nervous system, which in turn results in shortening of the ventricular repolarization whenever the heart rate increases, thus avoiding the likelihood of ventricular tachyarrhythmias during exercise.
(A) Extracted and adapted from Furst and Aziz (2016)[75] and *Schwartz et al. (2001)[74]; **(B)** Extracted and adapted from Schwartz et al. (2013)[43]; **(C)** and **(D)** Extracted and adapted from Giudicessi and Ackerman (2013).[70]

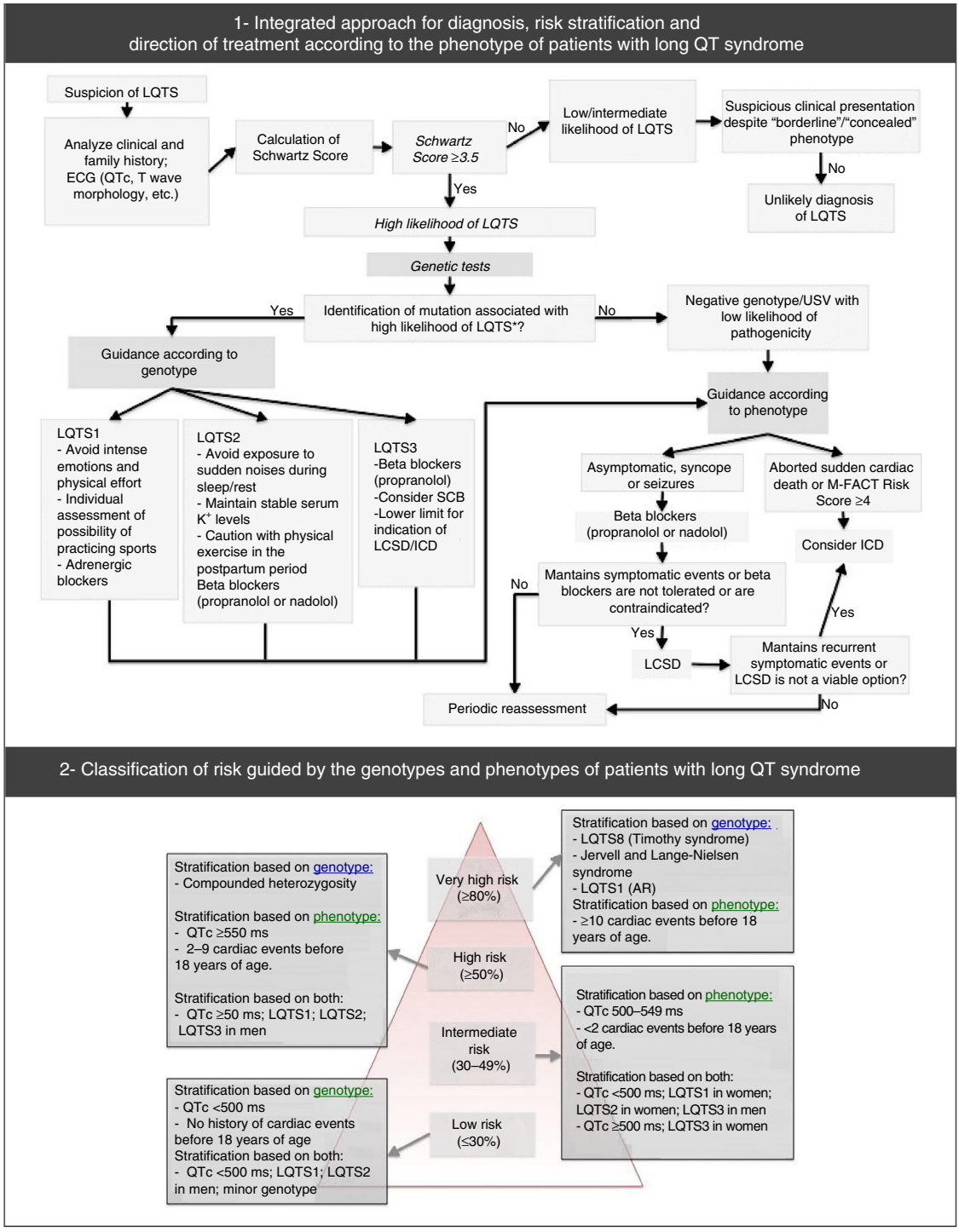

Figure 7 Diagnostic approach, risk stratification and guidance for the treatment of long QT syndrome. USV: undetermined significance variant. Extracted and adapted from Giudessi and Ackerman (2013).[70]

Once the diagnosis is made or given the occurrence of unexplained SD in a young individual, first-degree family members must be screened for LQTS.[1,65,72] However, LQTS cannot be ruled out in family members with a normal ECG.[43] In fact, after identifying a pathogenic mutation in an *index case*, family members should undergo a genetic test specific for the mutation in question, with the aim of identifying individuals with a normal QT interval.[43,53] This is important given the risk of arrhythmias, which is estimated to occur in 10% of asymptomatic carriers.[1]

Moreover, genetic tests specific for LQTS (broad or specific for the three main genes) are recommended for any patient when there is a strong clinical suspicion of LQTS (based on the medical and family history and the ECG), or for any asymptomatic patient with QT interval prolongation in the absence of other clinical conditions that may prolong

Table 10 Recommendations for the treatment of long QT syndrome.

General measures for lifestyle alterations	
Avoid drugs that prolong the QT interval	(Class I)
Identify and correct hydroelectrolytic disorders	(Class I)

Risk stratification and specific treatment			
Symptomatic individuals		Asymptomatic individuals	
Syncope	β-blockers(Class I)	QTc ≥470 ms	β-blockers (Class I)
Documented VT/VF	β-blockers(Class I)	QTc ≤470 ms	β-blockers(Class IIa)
''aborted'' SCD	ICD (Class I)	Not treated with β-blockers*	ICD (Class III)
Recurrent syncope episodes during treatment with β-blockers	ICD (Class IIa)		
Individuals with a diagnosis of LQTS who present with events during treatment with β-blockers/ICD	LCSD (Class IIa)		
High-risk individuals with a diagnosis of LQTS who refuse ICD or for whom it is contraindicated and/or when β-blockers are not effective in preventing syncope/arrhythmias, are not tolerated, are contraindicated or are refused			LCSD (Class I)
Individuals with type 3 LQTS and QTc >500 ms that decrease >40 ms after acute oral test with an SCB			SCB (Class IIa)

ICD: implantable cardioverter defibrillator; LCSD: left cardiac sympathetic denervation; SCB: sodium channel blocker; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.
* Except under special circumstances, the ICD is not indicated in asymptomatic individuals not undergoing treatment with β-blockers.
Adapted from Priori et al. (2013).[46]

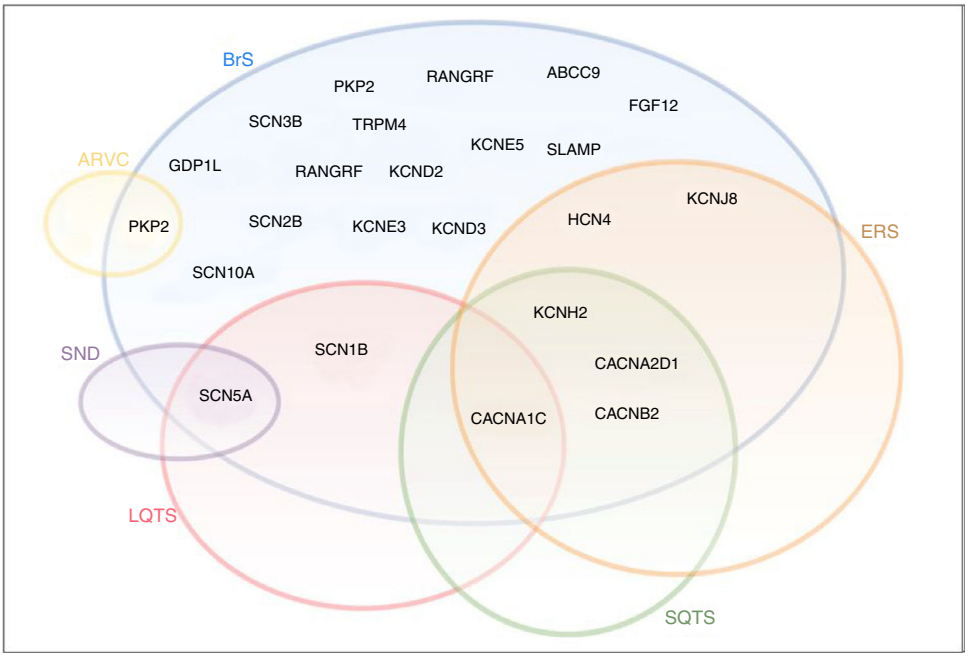

Figure 8 Diagram illustrating the overlap between BrS, LQTS, SQTS, SND, ERS and ARVC. The sodium channel macromolecular complex genes are in bold.
ARVC: arrhythmogenic right ventricular cardiomyopathy; ERS: early repolarization syndrome; LQTS: long QT syndrome; SND: sinus node disease; SQTS: short QT syndrome.
Extracted and adapted from Sarquella-Brugada (2016)[8] and Fernandez-Falgueras (2017).[35]

this interval.[53] In reality, genetic tests play an important role, not only in the diagnosis of LQTS (namely of asymptomatic carriers) and in ruling out disease for first-degree family members, but also in risk stratification, prognosis and treatment (according to the genotype – Figure 7).[1,43,69,70,72]

Risk stratification takes into account phenotype and genotype and is conducted for all patients with regular clinical assessments (Figure 7).[46,65,70] Risk varies according to genotype and, additionally, in the most common genetic types, it is influenced by the specific type and location of the mutations, as well as by the degree of dysfunction that they cause.[43,46]

Priori et al. (2003)[71] followed up 647 individuals with mutations in the genes for LQTS types 1, 2 and 3, for an average period of 28 years. The authors found that 42% of the individuals with LQTS3 developed a first cardiac event (occurrence of syncope, cardiac arrest or SCD) before turning 40 years old and before starting treatment. The incidence of cardiac arrest or SCD in patients with LQTS3 was about 16%, and men presented with symptoms earlier than women. However, given the small study sample, no conclusions could be reached about this finding. Additionally, the authors found that the QTc interval of patients with cardiac events was significantly longer than that of asymptomatic patients (LQTS3 subgroup: 523±55 ms vs. 481±38 ms, p=0.003). They also concluded that only a QTc value higher than 498 ms is associated with a markedly increased likelihood of cardiac events. However, the percentage of individuals in the LQTS3 subgroup with a normal QT interval and carrying a silent mutation was 10%.[71]

The result of the genetic tests is also important in the treatment and counseling of affected individuals and family members (Figure 7; Table 10).[9,43] It should be noted, for example, that LQTS1 involves higher risk during physical activity compared with LQTS2 and LQTS3.[43,74,75]

Mexiletine, flecainide or ranolazine constitute ''specific'' therapeutic options for LQTS3 (Table 10), for which β-blockers may not be so effective, since the adrenergic stress in this type is a trigger with less influence.[1,43,70,76] Mexiletine may be used as an add-on to β-blockers.[9,43,46,50] However, its effect depends on the type of mutation and may not be beneficial for all individuals with LQTS3.[9,12,70]

In fact, of the three main types of LQTS, type 3 is the one that involves a higher arrhythmia recurrence rate in individuals receiving treatment with β-blockers (10-15%).[70] This justifies the need for individuals with LQTS3 to undergo other invasive procedures, such as left cardiac sympathetic denervation and/or ICD implantation more frequently (Table 10).[70]

Conclusions

Cardiac channelopathies are not common in clinical practice (although they are more common than once thought), but they have a significant impact on quality of life and survival.[1,13] The clinical approach constitutes a challenge, owing to their high clinical and genetic heterogeneity.[1,76]

Although they were initially considered to be separate clinical entities with distinct phenotypes, these syndromes may have overlapping clinical and genetic presentations

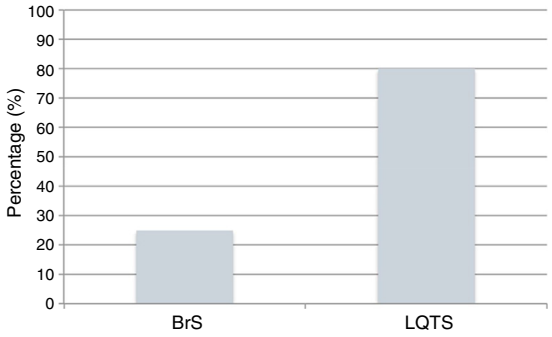

Figure 9 Cardiac channelopathies: positivity of the genetic tests in individuals clinically diagnosed with BrS and LQTS. Data presented in the charts from Schwartz and Dagradi (2016).[78]

(Figure 8).[21] In fact, in addition to strictly loss- or gain-of-function mutations, there is a wide spectrum of mutations associated with various anomalies with different repercussions in NaC function.[25] In some cases, a single mutation in the SCN5A gene may result in multiple rhythm disorders, and various phenotypes may thus coexist in the same family.[6,25]

Moreover, some studies have recently reported structural heart anomalies secondary to mutations in this gene (namely DCM), although the underlying mechanism is unknown.[6,18,22,77]

The power of the genetic tests to identify mutations is currently 25% for BrS and 80% for LQTS (Figure 9).[43,78] The impact of genetics in clinical approach varies considerably depending on the underlying channelopathies, and is more marked in LQTS, where influence at the level of diagnosis, prognosis and treatment is recognized.[9,43,78]

Great progress has been made in understanding the genotype-phenotype relationship and its implications.[43] However, despite increased scientific knowledge in this field, the genotype of a considerable number of affected individuals remains undetermined, some mechanisms still need to be clarified and the treatment options currently available are still limited.[12,18,72] A better understanding of molecular principles may contribute not only to increasing knowledge of these aspects, but also to developing new specific treatment approaches for the gene or mutation.[12,43]

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Cerrone M, Cummings S, Alansari T, et al. A clinical approach to inherited arrhythmias. Circ Cardiovasc Genet. 2012;5:581–90.
2. George AL Jr. Inherited disorders of voltage-gated sodium channels. J Clin Invest. 2005;115:1990–9.
3. Cerrone M, Napolitano C, Priori SG. Genetics of ion-channel disorders. Curr Opin Cardiol. 2012;27:242–52.
4. Ackerman MJ, Zipes DP, Kovacs RJ, et al. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 10: The Cardiac Channelopathies: A Scientific Statement From the American Heart

Association and American College of Cardiology. Circulation. 2015;132:e326–9.
5. Wilde AA, Brugada R. Phenotypical manifestations of mutations in the genes encoding subunits of the cardiac sodium channel. Circ Res. 2011;108:884–97.
6. Remme CA. Cardiac sodium channelopathy associated with SCN5A mutations: electrophysiological, molecular and genetic aspects. J Physiol. 2013;591:4099–116.
7. Liu M, Yang KC, Dudley SC Jr. Cardiac sodium channel mutations: why so many phenotypes? Nat Rev Cardiol. 2014;11:607–15.
8. Sarquella-Brugada G, Campuzano O, Arbelo E, et al. Brugada syndrome: clinical and genetic findings. Genet Med. 2016;18:3–12.
9. Mizusawa Y. Recent advances in genetic testing and counseling for inherited arrhythmias. J Arrhythm. 2016;32:389–97.
10. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. J Am Coll Cardiol. 2007;49:240–6.
11. Abriel H, Rougier JS, Jalife J. Ion channel macromolecular complexes in cardiomyocytes: roles in sudden cardiac death. Circ Res. 2015;116:1971–88.
12. Imbrici P, Liantonio A, Camerino GM, et al. Therapeutic approaches to genetic ion channelopathies and perspectives in drug discovery. Front Pharmacol. 2016;7:121.
13. Schwartz PJ, Stramba-Badiale M, Crotti L, et al. Prevalence of the congenital long-QT syndrome. Circulation. 2009;120:1761–7.
14. Meregalli PG, Wilde AA, Tan HL. Pathophysiological mechanisms of Brugada's syndrome: depolarization disorder, repolarization disorder, or more? Cardiovasc Res. 2005;67:367–78.
15. Abriel H. Cardiac sodium channel Na(v)1.5 and interacting proteins: physiology and pathophysiology. J Mol Cell Cardiol. 2010;48:2–11.
16. Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada's syndrome genetic testing. Heart Rhythm. 2010;7:33–46.
17. Kapplinger JD, Giudicessi JR, Ye D, et al. Enhanced classification of Brugada's syndrome-associated and long-QT's syndrome-associated genetic variants in the SCN5A-encoded Na(v)1.5 cardiac sodium channel. Circ Cardiovasc Genet. 2015;8:582–95.
18. Veerman CC, Wilde AA, Lodder EM. The cardiac sodium channel gene SCN5A and its gene product NaV1.5: role in physiology and pathophysiology. Gene. 2015;573:177–87.
19. England S, de Groot MJ. Subtype-selective targeting of voltage-gated sodium channels. Br J Pharmacol. 2009;158:1413–25.
20. Rook MB, Evers MM, Vos MA, et al. Biology of cardiac sodium channel Nav1.5 expression. Cardiovasc Res. 2012;93:12–23.
21. Remme CA, Bezzina CR. Sodium channel (dys)function and cardiac arrhythmias. Cardiovasc Ther. 2010;28:287–94.
22. Amin AS, Asghari-Roodsari A, Tan HL. Cardiac sodium channelopathies. Pflugers Arch. 2010;460:223–37.
23. Adsit GS, Vaidyanathan R, Galler CM, et al. Channelopathies from mutations in the cardiac sodium channel protein complex. J Mol Cell Cardiol. 2013;61:34–43.
24. Liu M, Sanyal S, Gao G, et al. Cardiac Na^+ current regulation by pyridine nucleotides. Circ Res. 2009;105:737–45.
25. Ruan Y, Liu N, Priori SG. Sodium channel mutations and arrhythmias. Nat Rev Cardiol. 2009;6:337–48.
26. Glaaser IW, Osteen JD, Puckerin A, et al. Perturbation of sodium channel structure by an inherited long QT's syndrome mutation. Nat Commun. 2012;3:706.
27. Poulet C, Wettwer E, Grunnet M, et al. Late sodium current in human atrial cardiomyocytes from patients in sinus rhythm and atrial fibrillation. PLOS ONE. 2015;10:e0131432.
28. Campuzano O, Beltran-Alvarez P, Iglesias A, et al. Genetics and cardiac channelopathies. Genet Med. 2010;12:260–7.
29. Ricci MT, Menegon S, Vatrano S, et al. SCN1B gene variants in Brugada's syndrome: a study of 145 SCN5A-negative patients. Sci Rep. 2014;4:6470.
30. Peeters U, Scornik F, Riuro H, et al. Contribution of cardiac sodium channel beta-subunit variants to Brugada's syndrome. Circ J. 2015;79:2118–29.
31. Watanabe H, Darbar D, Kaiser DW, et al. Mutations in sodium channel beta1- and beta2-subunits associated with atrial fibrillation. Circ Arrhythm Electrophysiol. 2009;2:268–75.
32. Olesen MS, Jespersen T, Nielsen JB, et al. Mutations in sodium channel beta-subunit SCN3B are associated with early-onset lone atrial fibrillation. Cardiovasc Res. 2011;89:786–93.
33. Medeiros-Domingo A, Kaku T, Tester DJ, et al. SCN4B-encoded sodium channel beta4 subunit in congenital long-QT's syndrome. Circulation. 2007;116:134–42.
34. Nakano Y, Shimizu W. Genetics of long-QT's syndrome. J Hum Genet. 2016;61:51–5.
35. Fernandez-Falgueras A, Sarquella-Brugada G, Brugada J, et al. Cardiac channelopathies and sudden death: recent clinical and genetic advances. Biology (Basel). 2017;6.
36. Makita N, Yagihara N, Crotti L, et al. Novel calmodulin mutations associated with congenital arrhythmia susceptibility. Circ Cardiovasc Genet. 2014;7:466–74.
37. Vatta M, Ackerman MJ, Ye B, et al. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT's syndrome. Circulation. 2006;114:2104–12.
38. Cerrone M, Delmar M. Desmosomes and the sodium channel complex: implications for arrhythmogenic cardiomyopathy and Brugada's syndrome. Trends Cardiovasc Med. 2014;24:184–90.
39. Cerrone M, Lin X, Zhang M, et al. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada's syndrome phenotype. Circulation. 2014;129:1092–103.
40. Brugada P. Brugada's syndrome: more than 20 years of scientific excitement. J Cardiol. 2016;67:215–20.
41. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992;20:1391–6.
42. Benito B, Brugada R, Brugada J, et al. Brugada syndrome. Prog Cardiovasc Dis. 2008;51:1–22.
43. Schwartz PJ, Ackerman MJ, George AL Jr, et al. Impact of genetics on the clinical management of channelopathies. J Am Coll Cardiol. 2013;62:169–80.
44. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada1s syndrome: results from the FINGER Brugada's Syndrome Registry. Circulation. 2010;121:635–43.
45. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005;111:659–70.
46. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10:1932–63.
47. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. Circulation. 1998;97:457–60.
48. Sieira J, Ciconte G, Conte G, et al. Asymptomatic Brugada's syndrome: clinical characterization and long-term prognosis. Circ Arrhythm Electrophysiol. 2015;8:1144–50.

49. Andorin A, Behr ER, Denjoy I, et al. Impact of clinical and genetic findings on the management of young patients with Brugada's syndrome. Heart Rhythm. 2016;13:1274–82.
50. Lieve KV, Wilde AA. Inherited ion channel diseases: a brief review. Europace. 2015;17 Suppl 2, ii1–6.
51. Berne P, Brugada J. Brugada's syndrome 2012. Circ J. 2012;76:1563–71.
52. Brugada R, Brugada J, Antzelevitch C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation. 2000;101:510–5.
53. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8:1308–39.
54. Sieira J, Dendramis G, Brugada P. Pathogenesis and management of Brugada's syndrome. Nat Rev Cardiol. 2016;13:744–56.
55. Crotti L, Marcou CA, Tester DJ, et al. Spectrum and prevalence of mutations involving BrS1- through BrS12-susceptibility genes in a cohort of unrelated patients referred for Brugada's syndrome genetic testing: implications for genetic testing. J Am Coll Cardiol. 2012;60:1410–8.
56. Hu D, Barajas-Martinez H, Pfeiffer R, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada's syndrome. J Am Coll Cardiol. 2014;64:66–79.
57. Probst V, Wilde AA, Barc J, et al. SCN5A mutations and the role of genetic background in the pathophysiology of Brugada's syndrome. Circ Cardiovasc Genet. 2009;2:552–7.
58. Garcia-Molina E, Lacunza J, Ruiz-Espejo F, et al. A study of the SCN5A gene in a cohort of 76 patients with Brugada's syndrome. Clin Genet. 2013;83:530–8.
59. Brugada P. Commentary on the Brugada ECG pattern: a marker of channelopathy, structural heart disease, or neither? Toward a unifying mechanism of the Brugada's syndrome. Circ Arrhythm Electrophysiol. 2010;3:280–2.
60. Juang JJ, Horie M. Genetics of Brugada's syndrome. J Arrhythm. 2016;32:418–25.
61. Meregalli PG, Tan HL, Probst V, et al. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. Heart Rhythm. 2009;6:341–8.
62. Calloe K, Refaat MM, Grubb S, et al. Characterization and mechanisms of action of novel NaV1.5 channel mutations associated with Brugada's syndrome. Circ Arrhythm Electrophysiol. 2013;6:177–84.
63. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada's syndrome and no previous cardiac arrest. Circulation. 2003;108:3092–6.
64. Steinfurt J, Biermann J, Bode C, et al. The diagnosis, risk, and stratification and treatment of Brugada's syndrome. Dtsch Arztebl Int. 2015;112:394–401.
65. Goldenberg I, Moss AJ. Long QT syndrome. J Am Coll Cardiol. 2008;51:2291–300.
66. Wang Q, Shen J, Splawski I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long-QT's syndrome. Cell. 1995;80:805–11.
67. Curran ME, Splawski I, Timothy KW, et al. A molecular basis for cardiac arrhythmia: HERG mutations cause long-QT's syndrome. Cell. 1995;80:795–803.
68. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet. 1996;12:17–23.
69. Mizusawa Y, Horie M, Wilde AA. Genetic and clinical advances in congenital long-QT's syndrome. Circ J. 2014;78:2827–33.
70. Giudicessi JR, Ackerman MJ. Genotype- and phenotype-guided management of congenital long-QT's syndrome. Curr Probl Cardiol. 2013;38:417–55.
71. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT's syndrome. N Engl J Med. 2003;348:1866–74.
72. Schwartz PJ. The congenital long-QT's syndromes from genotype to phenotype: clinical implications. J Intern Med. 2006;259:39–47.
73. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is ''normal''. J Cardiovasc Electrophysiol. 2006;17:333–6.
74. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT's syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103:89–95.
75. Furst ML, Aziz PF. The evolution of sports participation guidelines and the influence of genotype-phenotype correlation in long-QT's syndrome. Trends Cardiovasc Med. 2016;26:690–7.
76. Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. Circulation. 2011;123:1021–37.
77. Zaklyazminskaya E, Dzemeshkevich S. The role of mutations in the SCN5A gene in cardiomyopathies. Biochim Biophys Acta. 2016;1863 Pt B:1799–805.
78. Schwartz PJ, Dagradi F. Management of survivors of cardiac arrest – the importance of genetic investigation. Nat Rev Cardiol. 2016;13:560–6.