Cardiac Arrhythmias Related to Sodium Channel Dysfunction

Eleonora Savio-Galimberti, Mariana Argenziano, and Charles Antzelevitch

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Abstract

The voltage-gated cardiac sodium channel ($Na_v1.5$) is a mega-complex comprised of a pore-forming α subunit and 4 ancillary β-subunits together with numerous protein partners. Genetic defects in the form of rare variants in one or more sodium channel-related genes can cause a loss- or gain-of-function of sodium channel current (I_{Na}) leading to the manifestation of various disease phenotypes, including Brugada syndrome, long QT syndrome, progressive cardiac conduction disease, sick sinus syndrome, multifocal ectopic Purkinje-related premature contractions, and atrial fibrillation. Some sodium channelopathies have also been shown to be responsible for sudden infant death syndrome (SIDS). Although these genetic defects often present as pure electrical diseases, recent studies point to a contribution of structural abnormalities to the electrocardiographic and arrhythmic manifestation in some cases, such as dilated cardiomyopathy. The same rare variants in *SCN5A* or related genes may present with different clinical phenotypes in different individuals and sometimes in members

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of the same family. Genetic background and epigenetic and environmental factors contribute to the expression of these overlap syndromes. Our goal in this chapter is to review and discuss what is known about the clinical phenotype and genotype of each cardiac sodium channelopathy, and to briefly discuss the underlying mechanisms.

Keywords
Atrial fibrillation · Brugada syndrome · Dilated cardiomyopathy · Early repolarization syndrome · Inherited cardiac arrhythmia syndromes · J wave syndromes · Long QT syndrome · Multifocal ectopic Purkinje-related premature contractions · Overlap syndromes · Progressive conduction disease · Sick sinus syndrome · Sudden infant death syndrome

1 Introduction

In the heart, voltage-gated sodium channels (Nav) are responsible for initiation and propagation of the action potential (AP). During the upstroke (or phase 0) of the AP, sodium channels open rapidly, generating an inward depolarizing current (I_{Na}), after which they quickly inactivate and enter into a nonconductive state. Inactivated sodium channels cannot respond to another stimulus and therefore cannot initiate a second AP (or after-depolarizations) until the channels recover from inactivation. Recovery from inactivation is time- and voltage-dependent. The sequential activation and inactivation of sodium channels work as a security mechanism, guaranteeing the directionality of the cardiac electrical activity through the myocardial syncytium, thus preventing the occurrence of pro-arrhythmic events that can trigger arrhythmias.

Nine different isoforms of voltage-gated sodium channel have been identified within the human body (Catterall et al. 2005). Although Nav 1.5 is the canonical cardiac sodium channel (Rogart et al. 1989; Gellens et al. 1992a, b; George et al. 1995), cardiac muscle expresses several other voltage-gated sodium channels, including neuronal sodium channels Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.4, Nav 1.6, and Nav1.8 (Maier et al. 2004; Kaufmann et al. 2013; Westernbroek et al. 2013). Nav 1.8 (encoded by *SCN10A* gene) has been identified in human hearts (Facer et al. 2011; Yang et al. 2012) as well as in intracardiac neurons (Verkerk et al. 2012). *SCN10A* rare variants have been associated with alterations in the PR interval, QRS duration, and alterations in ventricular conduction (Chambers et al. 2010; Sotoodehnia et al. 2010a, b). Eukaryotic voltage-gated sodium channels share a similar structure that is highly preserved even when compared with the prokaryotic sodium channel. The channel is constituted by a single transmembrane copy of a protein of 2016 amino acids (~220 kDa) that comprises a cytoplasmic N-terminus, four homologous transmembrane domains (DI-DIV), and a cytoplasmic C-terminal domain (Fig. 1). Each one of the domains is similar to a prokaryotic subunit and is comprised of six α-helical transmembrane segments (termed S1 through S6) connected by extracellular and cytoplasmic loops. Segments S1 through S4 form the voltage-sensing domain and segments S5 and S6 comprise the pore-forming domain (Payandeh et al. 2011, 2012; Catterall 2014). The loop between S5 and S6

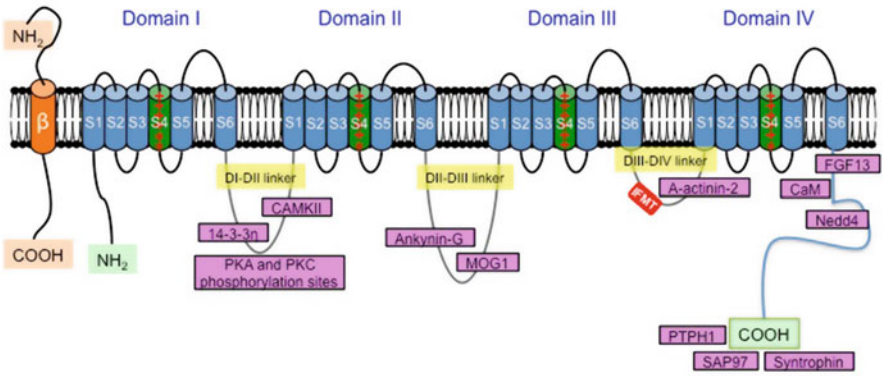

Fig. 1 Schematic representation of the α- and β-subunits of the VGSC. The four homologous domains (I–IV) of the α-subunit are represented; S5 and S6 are the pore-lining segments and S4 is the core of the voltage sensor. In the cytoplasmic linker between domains III and IV the IFMT (isoleucine, phenylalanine, methionine, and threonine) region is indicated. This is a critical part of the "inactivation particle" (inactivation gate), and substitution of amino acids in this region can disrupt the inactivation process of the channel. The "docking site" consists of multiple regions that include the cytoplasmic linker between S4 and S5 in domains III and IV, and the cytoplasmic end of the S6 segment in domain IV (*). Depending on the subtype of β-subunit considered they could interact (covalently or non-covalently) with the α-subunit. Some of the protein partners that can directly interact with the Nav1.5 are also shown in the figure (see also Table 1) (modified from Savio-Galimberti et al. 2012)

forms the selectivity filter. The S4 segment is heavily charged (arginine enriched region) and plays a central role in voltage sensing to increase channel permeability (activation of the channel) during depolarization of the cell.

The C-terminus and the linkers between domains contain interaction sites with which several protein partners ["sodium channel partners" or "Channel interactive proteins" (ChIP)] that regulate Nav 1.5 activity directly interact (Table 1 and Fig. 1). Other proteins that may indirectly interact with the Nav 1.5 include caveolin-3 (a scaffolding protein located within caveolar membranes) (Lu et al. 1999; Rybin et al. 2000; Yarbrough et al. 2002; Vatta et al. 2006), connexin-43 (Sato et al. 2011), telethonin (Valle et al. 1997; Mayans et al. 1998; Furukawa et al. 2001; Knoll et al. 2002; Haworth et al. 2004; Kojic et al. 2004; Mazzone et al. 2008), plakophilin-2 (Sato et al. 2009), ankyrin-B/ankyrin-2 (Jenkins and Bennett 2001; Garrido et al. 2003; Lemaillet et al. 2003; Mohler et al. 2004), glycerol-3-phosphate dehydrogenase 1-like protein (GPD1L), and Z-band-alternatively spliced-PDZ motif protein (ZASP) (Li et al. 2010; Remme 2013). The activity of the α-subunit of Nav 1.5 is also modulated by regulatory β-subunits (~30 kDa) of which there are four (β1-4). The stoichiometry between α- and β-subunits in the heart remains largely unknown. β-subunits can also act as cell adhesion molecules (CAMs) as well as modulate cell surface expression of Na_Vs, enhancing sodium channel density and therefore cell excitability (Patino and Isom 2010; Savio-Galimberti et al. 2012). Mutations in the genes that encode several members of

Table 1 *SCN5A* protein partners

Nav 1.5 channel protein	Interacting proteins	Function	References
IQ motif (C-terminal)	Calmodulin (CaM)	Ubiquitous Ca-binding protein that may confer sensitivity to intracellular Ca levels	Tan et al. (2002); Shy et al. (2013)
PY motif (C-terminal)	Ubiquitin-protein Ligase Nedd 4-2	Ubiquitynation of Na channel	Van Bemmelen et al. (2004); Rougier et al. (2005)
PDZ domain-binding motif	PTPH1		Gavillet et al. (2006); Jespersen et al. (2006); Petitprez et al. (2011)
	SAP97		
	Syntrophins		
Other regions of C-terminus	Fibroblast growth factor homologous factor 13 (FGF13)	Delay fast inactivation of the channel	Dover et al. (2010); Wang et al. (2011)
Cytosolic DI–DII linker	14-3-3n; PKA and PKC phosphorylation sites; interaction site for CAMKII	Modulation of steady-state inactivation of the channel; Regulatory effects of Na channel availability and persistent current (late I_{Na}) magnitude	Allouis et al. (2006); Wagner et al. (2006); Ashpole et al. (2012)
DII–DIII linker	Ankyrin-G	Regulation of cell surface expression of Na channels	Lemaillet et al. (2003); Mohler et al. (2004); Kattygnarath et al. (2011)
	MOG1		
DIII–DIV linker	α-Actinin-2 (F-actin cross-linking protein family)	Increase of sodium current density with no effect on gating properties	Ziane et al. (2010)
Extracellular connecting loops between S5 and S6 segments	β1–β4 subunits	Modulation of Nav 1.5 channel density and kinetics	Malhotra et al. (2001); McEwen and Isom (2004); Ko et al. (2005); Meadows and Isom (2005); Medeiros-Domingo et al. (2007)

the ChIP group including *ANK2* (which encode Ankyrin-B/2 protein) and *SCN1B-3B* genes (that encode β1, β2, β3, and β4 subunits) have been associated with cardiac arrhythmia syndromes like long QT syndrome, structural heart disease (*ANK2*) (Swayne et al. 2017), Brugada syndrome (BrS; *SCN1B*, *SCN2B*, *SCN3B*) (Hu et al. 2009, 2010, 2012; Swayne et al. 2017), and atrial fibrillation (AF; *SCN1B, SCN2B, SCN3B*) (Olesen et al. 2011a, b, 2012a, b, c).

SCN5A mRNA transcription is regulated by several enhancers and repressors located near or within the promoter of the *SCN5A* gene (Arnolds et al. 2012; Van den Boogaard et al. 2012; Remme 2013). Transcriptional regulation of *SCN5A* can also be affected by gene-to-gene interaction. Van den Boogaard et al. (2012, 2014) reported that a common genetic variant within the intronic region of *SCN10A*

modulates cardiac *SCN5A* expression (Van den Boogaard et al. 2012). Using high-resolution 4C-seq analysis of the *Scn10a-Scn5a* locus in murine heart tissue they showed that a cardiac enhancer located in *Scn10a*, encompassing *SCN10A* functional variant rs6801957, interacts with the promoter of *Scn5a*. An engineered transgenic mouse where they deleted the enhancer within *Scn10a* revealed that the enhancer was essential for Scn5a expression in cardiac tissue. Furthermore, in humans, the *SCN10A* variant rs6801957, which correlates with slowed conduction, was associated with decreased *SCN5A* expression (Van den Boogaard et al. 2012). These observations notwithstanding, the majority of *SCN10A* variants associated with BrS are exonic and not intronic as presumed in the *SCN5A-SCN10A* gene interaction hypothesis (Hu et al. 2014). Hu and coworkers presented evidence in support of the hypothesis that Nav1.5 encoded by *SCN5A* and $Na_v1.8$ encoded by *SCN10A* are physically associated in the cell membrane and that a mutation in *SCN10A* can lead to a major loss-of-function of Nav1.5 current, thus providing a mechanism to explain the association of *SCN10A* variants with BrS (Hu et al. 2014). Debate continues as to these two putative mechanisms.

2 *SCN5A* Mutations and Cardiac Arrhythmias

Gellens et al. (1992a, b) were the first to clone and characterize *SCN5A*. Three years later, George et al. (1995) mapped the *SCN5A* human gene to chromosome 3p21 by fluorescence in situ hybridization (FISH). In 1996 Wang et al. reported the genomic organization of the gene that contains 28 exons (Wang et al. 1996).

The first mutation in *SCN5A* was reported in a long QT syndrome (LQTS) type 3 by Mark Keating and his group in 1995 (Wang et al. 1995). Mutations in *SCN5A* (most of which are autosomal dominant) have been associated with a wide range of cardiac arrhythmia syndrome. These can be divided into three categories, based on minor allele frequency and gene location of the variant: rare *SCN5A* exonic variants, common exonic variants, and intronic noncoding variants.

2.1 Rare *SCN5A* Exonic Variants

2.1.1 Long QT Syndrome (LQTS)

Sixteen genes have been associated with LQTS to date (Table 2). Two forms have been identified: (1) Jervell and Lange-Nielsen syndrome (J-LN) is associated with deafness, and (2) the Romano-Ward syndrome (R-W) (Bennett et al. 1995; Schwartz et al. 2012). LQT1, 2, and 3 account for 90% of genotyped cases of LQTS. The prevalence of LQT3 among genotype-positive LQTS patients is 5–10%; LQT1 associated with loss-of-function mutations in *KCNQ1* gene accounts for 40–55%, and LQT2 associated with loss-of-function mutations in *KCNH2* gene accounts for 30–45% (Schwartz et al. 2012). Type 3 LQTS (LQT3) is associated with mutations in *SCN5A* giving rise to late or persistent sodium channel current (late I_{Na}) that effects the prolongation of the AP (Fig. 3) (Bennett et al. 1995;

Table 2 Genetic defects associated with the long QT syndrome

Chromosome		Gene	Ion channel	
LQT1	11	*KCNQ1, KvLQT1*	↓ I_{Ks}	90%
LQT2	7	*KCNH2, HERG*	↓ I_{Kr}	
LQT3	3	*SCN5A, $Na_v1.5$*	↑ Late I_{Na}	
LQT4	4	*Ankyrin-B, ANK2*	↑ Ca_i, ↑ Late I_{Na} ?	
LQT5	21	*KCNE1, minK*	↓ I_{Ks}	
LQT6	21	*KCNE2, MiRP1*	↓ I_{Kr}	
LQT7[a]	17	*KCNJ2, Kir2.1*	↓ I_{K1}	
LQT8[b]	6	*CACNA1C, $Ca_v1.2$*	↑ I_{Ca}	
LQT9	3	*CAV3, Caveolin-3*	↑ Late I_{Na}	
LQT10	11	*SCN4B, NavB4*	↑ Late I_{Na}	
LQT11	7	*AKAP9, Yotiao*	↓ I_{Ks}	
LQT12	20	*SNTA1, α-1 Syntrophin*	↑ Late I_{Na}	
LQT13	11	*KCNJ5, Kir3.4*	↓ $I_{K\text{-}ACh}$	
LQT14	14	CALM1, Calmodulin	↑ I_{Ca}, ↑ Late I_{Na}	
LQT15	2	CALM2, Calmodulin	↑ I_{Ca}, ↑ Late I_{Na}	
LQT16	19	CALM3, Calmodulin	↑ I_{Ca}, ↑ Late I_{Na}	

Augmentation of late I_{Na} is observed in variants associated with 8 of the 16 LQTS-susceptibility genes
[a]Andersen–Tawil syndrome
[b]Timothy syndrome

Schwartz et al. 2012). Variants in 8 of the 16 LQTS susceptibility genes have been shown to produce a gain-of-function in late I_{Na}, thus contributing to AP and QT prolongation (Table 2), which can be reversed with agents that block late I_{Na}, including ranolazine and mexiletine (Antzelevitch et al. 2014).

Clinical manifestation of LQTS includes syncopal episodes, frequently associated with cardiac arrest and leading to sudden cardiac death (SCD). The syncopal episodes are the consequence of an atypical polymorphic ventricular tachycardia known as torsade de pointes (TdP). SCD results when TdP degenerates into ventricular fibrillation. Most arrhythmic events in congenital LQT1 occur during physical or emotional stress, at rest or in association with sudden auditory stimulation in LQT2, and during sleep or rest in LQT3 patients (Priori et al. 2013). These phenotypic distinctions are consistent with the differential effects of catecholamines in the three genotypes (Fig. 2).

Ion channel dysfunctions associated with LQTS result in an inward shift in the balance of current leading to prolongation of the ventricular action potential and QT interval. The reduced repolarization reserve can lead to development of early afterdepolarizations (EADs). When EADs reach the threshold for activation of the inward calcium current, they generate triggered extrasystoles. Differences in the degree of AP prolongation among the three cell types that comprise the ventricular wall lead to development of transmural dispersion of repolarization (TDR), thus creating a vulnerable window across the ventricular wall and other regions of the ventricular myocardium, which can lead to development of reentrant arrhythmias. When an EAD-induced triggered response falls within this vulnerable window, the result is TdP (Antzelevitch 2007a, b) (Fig. 3).

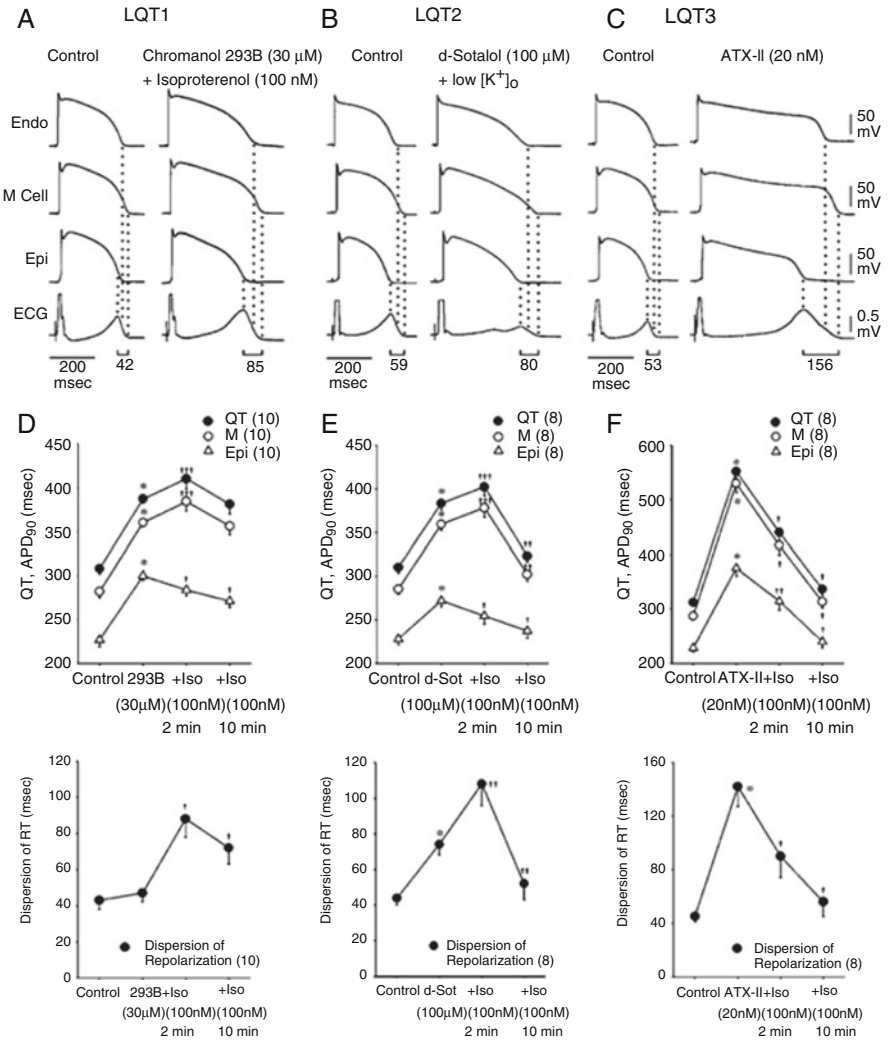

Fig. 2 Transmembrane action potentials (AP) and transmural electrocardiograms (ECG) in LQT1 (**a**), LQT2 (**b**), and LQT3 (**c**) models of long QT syndrome (LQTS) generated in arterially perfused canine left ventricular wedge preparations. Isoproterenol + chromanol 293B (an I_{Ks} blocker), d-sotalol + low $[K^+]_o$, and ATX-II – an agent that slows inactivation of late I_{Na} are used to mimic the LQT1, LQT2, and LQT3 syndromes, respectively. Panels (**a–c**) depict action potentials simultaneously recorded from endocardial (Endo), M, and epicardial (Epi) sites together with a transmural ECG. Basic cycle length = 2,000 ms. Transmural dispersion of repolarization (TDR) across the ventricular wall, defined as the difference in the repolarization time between M and Epi cells, is denoted below the ECG traces. Panels (**d–f**) show the effect of isoproterenol (Iso) in the LQT1, LQT2, and LQT3 models. In LQT1, Iso produces a persistent prolongation of the APD90 of the M cell and of the QT interval (at both 2 and 10 min), whereas the AP duration of 90(APD90) of the epicardial cell is always abbreviated, resulting in a persistent increase in TDR (**d**). In LQT2, Iso initially prolongs (2 min) and then abbreviates the QT interval and the APD90 of the M cell to the control level (10 min), whereas the APD90 of Epi cell is always abbreviated, resulting in a

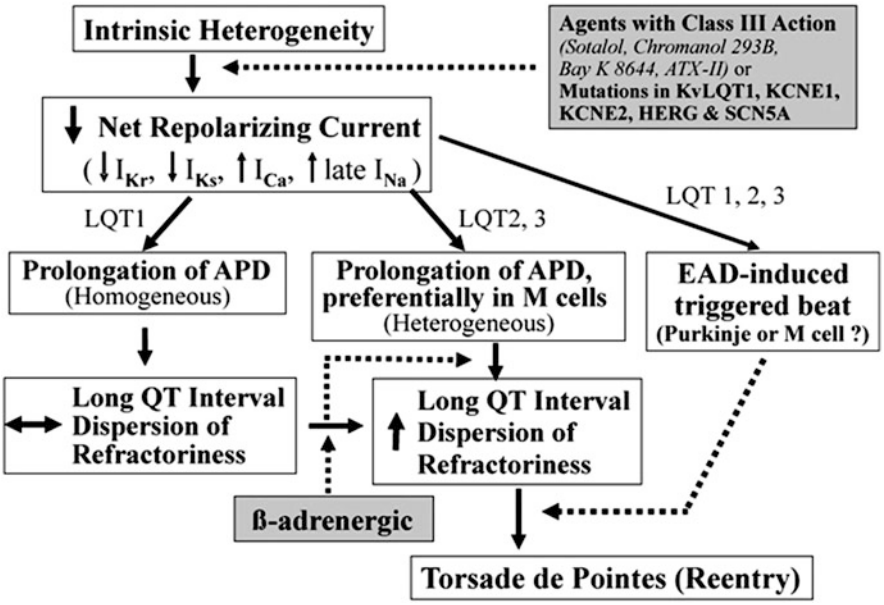

Fig. 3 Cellular and ionic mechanism underlying the development of Torsade de Pointes in the long QT syndrome. *APD* action potential duration, *EAD* early after-depolarization. Modified from Antzelevitch (2007a, b), with permission

2.1.2 J-Wave Syndromes: Brugada and Early Repolarization Syndrome

A prominent J wave is encountered in several life-threatening cardiac arrhythmia syndromes, including the Brugada (BrS) and early repolarization (ERS) syndromes. BrS and ERS differ with respect to the magnitude and lead location of abnormal J waves and are thought to represent a continuous spectrum of phenotypic expression termed J wave syndromes (JWSs). Both are associated with vulnerability to polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) leading to SCD in young adults with apparently structurally normal hearts. Both syndromes characteristically display prominent J waves in the ECG that are thought to be a consequence of the presence of a transmural voltage-gradient caused by heterogeneous transmural distribution of I_{to} (Yan and Antzelevitch 1996). Both syndromes are predominantly observed in young males in their third and fourth decades of life, their electrical phenotype can be attenuated by quinidine, isoproterenol, milrinone, cilostazol, and tachypacing, and exacerbated by an increase in the vagal tone, and both can evolve into polymorphic ventricular tachycardia (VT)/ventricular

Fig. 2 (continued) transient increase in TDR (**e**). In LQT3, isoproterenol produced a persistent abbreviation of the QT interval and the APD90 of both M and Epi cells (at both 2 and 10 min), resulting in a persistent decrease in TDR (**f**). *RT* repolarization time $*p < 0.0005$ vs. control; $\dagger p < 0.0005$, $\dagger\dagger p < 0.005$, $\dagger\dagger\dagger p < 0.05$, vs. 293B, d-sotalol (d-Sot) or ATX-II. Modified from Shimizu and Antzelevitch (1997, 1998, 2000), with permission

fibrillation (VF) with increased risk for sudden cardiac death (SCD) (Antzelevitch and Yan 2015; Antzelevitch et al. 2016). The region most affected by BrS is the anterior right ventricular outflow tract (RVOT), accounting for why J waves and ST-segment elevation are limited to the right precordial leads. The region most affected in ERS is the inferior wall of the left ventricle (LV), accounting for why the appearance of J waves or early repolarization in the inferior ECG leads is associated with the highest risk for development of arrhythmias and SCD. BrS and ERS have been linked to mutations in genes affecting ion channels leading to an outward shift in the balance of current during the early phase of the epicardial action potential (AP), thus causing accentuation of the AP notch, loss of the AP dome, and leading to the development of phase 2 reentry and polymorphic VT (Fig. 4).

BrS has been associated with variants in 19 different genes, whereas ERS has been associated with variants in seven genes (Table 3). Variants in 10 of the 19 BrS-susceptibility genes and 2 or the 7 ERS-susceptibility genes have been associated with a loss-of-function of I_{Na}. Loss-of-function mutations in *SCN5A* have been identified in 11–28% of probands with BrS in different regions of the world (Kapplinger et al. 2010).

BrS and ERS are strongly male dominant syndromes with a male:female ratio as high as 10:1 in the expression of the disease phenotype in the case of BrS (Antzelevitch and Yan 2010). Higher testosterone-mediated expression of I_{to} in the right ventricular epicardium is thought to be responsible (Antzelevitch 2003;

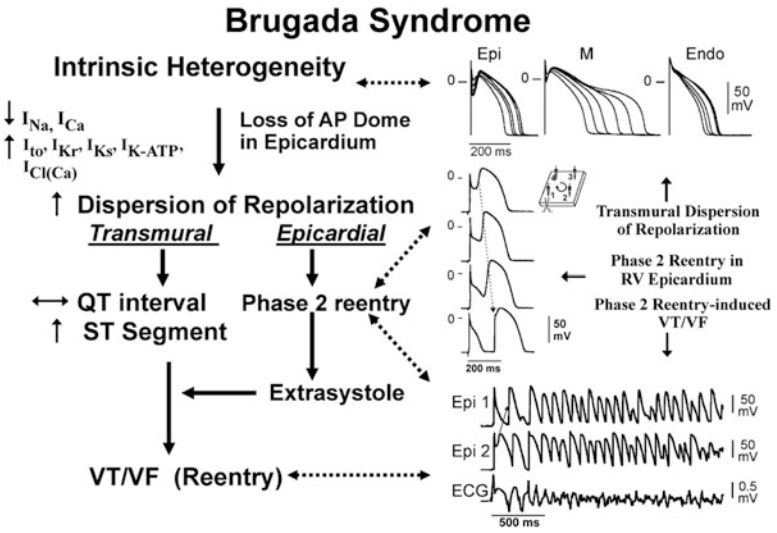

Fig. 4 Proposed mechanism for the Brugada syndrome. An outward shift in the balance of currents serves to amplify existing heterogeneities by causing loss of the action potential dome at some epicardial, but not endocardial sites. A vulnerable window develops as a result of the dispersion of repolarization and refractoriness within epicardium as well as across the wall. Epicardial dispersion leads to the development of phase 2 reentry, which provides the extrasystole that captures the vulnerable window and initiates VT/VF via a circus movement reentry mechanism. Modified from Antzelevitch (2001), with permission

Table 3 Genetics of Brugada and early repolarization syndromes

		Locus	Ion channel	Gene/protein
BrS	BrS1	3p21	$\downarrow I_{Na}$	*SCN5A*, $Na_V1.5$
	BrS2	3p24	$\downarrow I_{Na}$	*GPD1L*
	BrS3	12p13.3	$\downarrow I_{Ca}$	*CACNA1C*,$Ca_V1.2$
	BrS4	10p12.33	$\downarrow I_{Ca}$	*CACNB2b*, $Ca_v\beta2b$
	BrS5	19q13.1	$\downarrow I_{Na}$	*SCN1B*, $Na_V\beta1$
	BrS6	11q13-q14	$\downarrow I_{Ca}$	*KCNE3*. MiRP2
	BrS7	11q23.3	$\downarrow I_{Na}$	*SCN3B*, Navb3
	BrS8	12p11.23	$\uparrow I_{K\text{-}ATP}$	*KCNJ8*, Kir6.1
	BrS9	7q21.11	$\downarrow I_{Ca}$	*CACNA2D1*, $Ca_v\alpha2\delta1$
	BrS10	1p13.2	$\uparrow I_{to}$	*KCND3*, $K_v4.3$
	BrS11	17p13.1	$\downarrow I_{Na}$	*RANGRF*, MOG1
	BrS12	3p21.2-p14.3	$\downarrow I_{Na}$	*SLMAP*
	BrS13	12p12.1	$\uparrow I_{K\text{-}ATP}$	*ABCC9*, SUR2A
	BrS14	11q23	$\downarrow I_{Na}$	*SCN2B*, $Na_v\beta2$
	BrS15	12p11	$\downarrow I_{Na}$	*PKP2*, Plakophillin2
	BrS16	3q28	$\downarrow I_{Na}$	*FGF12*, FHAF1
	BrS17	3p22.2	$\downarrow I_{Na}$	*SCN10A*, $Na_v1.8$
	BrS18	6q	$\uparrow I_{Na}$	*HEY2 (transcriptional factor)*
	BrS19	1p3633	$\uparrow I_{to}$	*KCNAB2*, *Kv* ß2
ERS	ERS1	12p11.23	$\uparrow I_{K\text{-}ATP}$	*KCNJ8*, Kir6.1
	ERS2	12p13.3	$\downarrow I_{Ca}$	*CACNA1C*, $Ca_v1.2$
	ERS3	10p12.33	$\downarrow I_{Ca}$	*CACNB2b*, $Ca_v\beta2b$
	ERS4	7q21.11	$\downarrow I_{Ca}$	*CACNA2D1*, $Ca_v\alpha2\delta1$
	ERS5	12p12.1	$I_{K\text{-}ATP}$	*ABCC9*, SUR2A
	ERS6	3p21	$\downarrow I_{Na}$	*SCN5A*, $Na_v1.5$
	ERS7	3p22.2	$\downarrow I_{Na}$	*SCN10A*, $Na_v1.8$

Matsuo et al. 2003; Cordeiro et al. 2008; Ezaki et al. 2010). Barajas-Martinez and coworkers have also presented evidence in support of gender-related differences in transmural distribution of I_{Na} as the basis for the male predominance (Barajas-Martinez et al. 2009).

2.1.3 Progressive Cardiac Conduction Disease (PCCD or Lenegre-Lev Disease)

Familial PCCD is an inherited cardiac disease that may be associated with structural heart disease or may present as a primary electrical disease or channelopathy. In structurally normal hearts it is associated with genetic variants in the ion channel genes *SCN5A*, *SCN1B*, *SCN10A*, *TRPM4*, and *KCNK17*, as well as in genes coding for cardiac connexin proteins (Baruteau et al. 2015). Mutations in genes coding for cardiac transcriptional factors, including *NKX2.5* and *TBX5*, involved in the development of the cardiac conduction system and in cardiac morphogenesis, have been also been implicated in PCCD as well as in various congenital heart defects.

PCCD is clinically characterized by a progressive slow conduction through the His-Purkinje system, with right and/or left bundle branch block and widening of the QRS complex, leading to complete atrio-ventricular node block. PCCD can cause syncope and SCD and for this reason is the most frequent indication for implantation of permanent pacemakers globally (0.5 implantations/1,000 inhabitants/year in developed countries) (Scott et al. 1999). Scott and coworkers first reported a mutation in *SCN5A* that segregated with PCCD in an autosomal dominant manner in a French family in 1999 (Scott et al. 1999). Numerous loss-of-function *SCN5A* mutations, including splice-site, frameshift, nonsense, and missense mutations, have since been identified in association with PCCD (Barc and Bezzina 2014).

2.1.4 Sick Sinus Syndrome (SSS)

SSS is a disorder characterized by the dysfunction of the sinoatrial node. Patients affected by SSS exhibit sinus bradycardia, sinus arrest, and a reduced chronotropic response (Benson et al. 2003; Butters et al. 2010; Abe et al. 2014). Sinus node dysfunction has been associated with mutations in *SCN5A* (Benson et al. 2003; Makita et al. 2005), *HCN4* (Schulze-Bahr et al. 2003; Hategan et al. 2017), *CACNA1D* (Baig et al. 2011), and *GNB2* (Baig et al. 2011; Stallmeyer et al. 2017), which encodes the Gβ2 subunit of the heterotrimeric G-protein complex.

Like PCCD and J Wave syndrome, *SCN5A* mutations causing SSS are associated with loss-of-function of sodium channel current (Arnold et al. 2008). Although *SCN5A* is poorly expressed in central cells in the sinus node, mutations in this gene have a small impact on individual primary peacemaker cells. However, loss-of-function mutations in *SCN5A* reduced excitability in the cells located in the periphery of the sinus node thus slowing conduction and causing conduction block.

2.1.5 Sudden Infant Death Syndrome (SIDS)

SIDS is defined as sudden death of an infant <1-year old without any preceding symptoms. Based on the definition of SIDS, the historical era, demographics, and ethnicity of the population evaluated, SIDS affects ~2 infants per 1,000 live births, with a peak incidence between the ages of 2 and 5 months (Kinney and Thach 2009; Tester and Ackerman 2012). *SCN5A* mutations reported using candidate gene approaches account for 2–10% of SIDS cases (Ackerman et al. 2001). Although functional electrophysiological studies report a wide range of effects of *SCN5A* variants in SIDS cases, a gain-of-function mechanism is the most commonly associated (Schwartz et al. 2000). The first direct molecular link between SIDS and a cardiac arrhythmia was reported by Schwartz and coworkers and involved a gain-of-function missense mutation in *SCN5A* (S941N) that prolonged the QT interval via an increase in late I_{Na} (Schwartz et al. 2000).

2.1.6 Atrial Fibrillation (AF)

AF is the most frequent cardiac arrhythmia encountered and diagnosed in the clinic. It is characterized as a very rapid atrial activation and rapid and irregular ventricular rates (Brugada and Kaab 2008). Approximately 35% of AF cases have a positive family history suggesting a heritable basis for the arrhythmia (Wyse et al. 2014).

The Framingham Study showed that ~27% of individuals with AF have a first-degree relative with AF confirmed by ECG, and that familial AF is associated with a 40% increased risk of AF for other family members over a subsequent 8-year period, even after adjustment for established AF clinical risk factors (Lubitz et al. 2010). Linkage analysis and candidate gene approach have been used to identify mutations in *SCN5A* and its beta subunits (*SCN1B*, *SCN2B*, and *SCN3B*) in the AF population (McNair et al. 2004; Olson et al. 2005a, b; Laitinen-Forsblom et al. 2006; Ellinor et al. 2008; Makiyama et al. 2008a, b; Olesen et al. 2011a, b).

To date, rare variants in 32 genes have been associated with AF (Hayashi et al. 2017). Nineteen encode ion channel proteins and of these six affect sodium channel activity. Rare variants associated with AF exert a wide spectrum of effects on the biophysical properties of the sodium channel resulting in a loss-of-function with a consequent shortening of the APD (Ellinor et al. 2008; Watanabe et al. 2009a, b) as well as a gain-of-function (Makiyama et al. 2008a, b; Li et al. 2009). *SCN5A* and *SCN1B* variants are reported to show either a gain-of-function or a loss-of-function of I_{Na} (Olson et al. 2005a, b; Darbar et al. 2008; Makiyama et al. 2008a, b; Olesen et al. 2012a, b, 2012c; Hayashi et al. 2015), whereas rare variants in *SCN2B*, *SCN3B*, and *SCN4B* show loss-of-function effects (Watanabe et al. 2009a, b; Wang et al. 2010; Olesen et al. 2011a, b). Gain-of-function of I_{Na}, particularly of late I_{Na}, can promote ectopic activity and increase dispersion of repolarization and refractoriness, whereas loss-of-function can promote AF by abbreviating the refractory period and slowing of conduction, which provide the substrate for the development of reentrant arrhythmias. Rare variants in *SCN10A*, the gene that encodes $Na_v1.8$, have also been reported to be associated with AF (Savio-Galimberti et al. 2014; Jabbari et al. 2015).

2.1.7 Dilated Cardiomyopathy Disease (DCM)

DCM is a disorder characterized by ventricular dilatation and impaired systolic function, which usually results in the development of heart failure. Valvular heart disease, excess alcohol ingestion, hypertension, pregnancy, and infections are the most common underlying etiologic factors. Idiopatic DCM (IDCM) represents a subgroup of DCM patients where the etiology has not been determined, and where genetic, autoimmune, viral, and metabolic causes have been implicated as potential pathophysiological mechanisms of the disease. Approximately 40% of DCM has a positive family history for the disease displaying autosomal dominant inheritance, although X-linked, autosomal recessive, and mitochondrial inheritance have also been described as well, although less frequently. Mutations in numerous candidate genes (>40) have been identified in patients with IDCM. Rare genetic variants associated with DCM affect a range of diverse cellular structures and functions. Truncating variants in *titin* represent the single largest genetic cause of IDCM (Tayal et al. 2017). Two main forms of IDCM have been described: DCM with and without conduction system disease. Linkage analysis has been used to identify *SCN5A* mutations in the combined form. The first *SCN5A* mutation implicated in IDCM (D1275N) was independently discovered by McNair and coworkers and Olson and coworkers (McNair et al. 2004; Olson et al. 2005a, b) in a DCM family

that was originally reported by Greenlee et al. in 1986 (Greenlee et al. 1986). Other *SCN5A* mutations (T220I, D1595H, 2550-2551 instTG, R814W) have been reported in IDCM patients (Olson et al. 2005a, b), in most cases these are loss-of-function mutations. The mechanisms by which sodium channel variants lead to DCM remain poorly understood.

2.1.8 Multifocal Ectopic Purkinje-Related Premature Contractions (MEPPC)

MEPPC is a cardiac arrhythmia recently linked to variants in *SCN5A* mutations. It was previously associated with both AF and DCM. Five families have been described with MEPPC. All presented with the same missense mutation in *SCN5A* (p.R222Q) involving the voltage sensor of the sodium channel in domain I causing an increase in the excitability of the channel (Laurent et al. 2012; Mann et al. 2012, Nair et al. 2012). The mutation is a rare variant, inherited as a dominant trait, with complete penetrance (McNair et al. 2011; Laurent et al. 2012; Mann et al. 2012; Nair et al. 2012).

2.1.9 Overlap Syndromes

SCN5A mutations can lead to a wide range of phenotypes. Although these entities may occur as isolated syndromes, in most cases an exhaustive investigation reveals their involvement in multiple "overlap syndromes" (Fig. 5). Loss-of-function *SCN5A* rare variants can be associated with multiple overlapping clinical manifestations including progressive conduction disease, BrS, AF, SSS, and DCM. Gain-of-function rare variants can be associated with LQTS, AF, and MEPCC. The particular phenotype expressed often depends on the genetic background, including modulating rare and common variants, as well as epigenetic and environmental factors.

2.2 Common *SCN5A* EXONIC Variants

Genetic screening of the exonic regions of *SCN5A* in patients with cardiac arrhythmias as well as in control populations often reveals the common occurrence of missense variants (polymorphisms) in the general population (common variants). The interest in these variants derives from the fact that they can potentially modulate the severity of disease phenotypes. This modulation is possible either because they affect the biophysics of the wild-type channel when they occur in the *trans* configuration (different allele from the one with the mutation) or because they can attenuate or exacerbate the biophysical behavior of the mutated channel when they occur in the *cis* configuration (on the same allele with the mutation). Viswanathan and coworkers were the first to introduce the concept that interaction between polymorphisms and mutations can exert important effects on the functional consequences of a mutation (Viswanathan et al. 2003). This has been referred as "trans-complementation effect" (Barc and Bezzina 2014), and there are several examples reported for *SCN5A* variants where this interaction has been confirmed (Viswanathan et al. 2003; Poelzing et al. 2006).

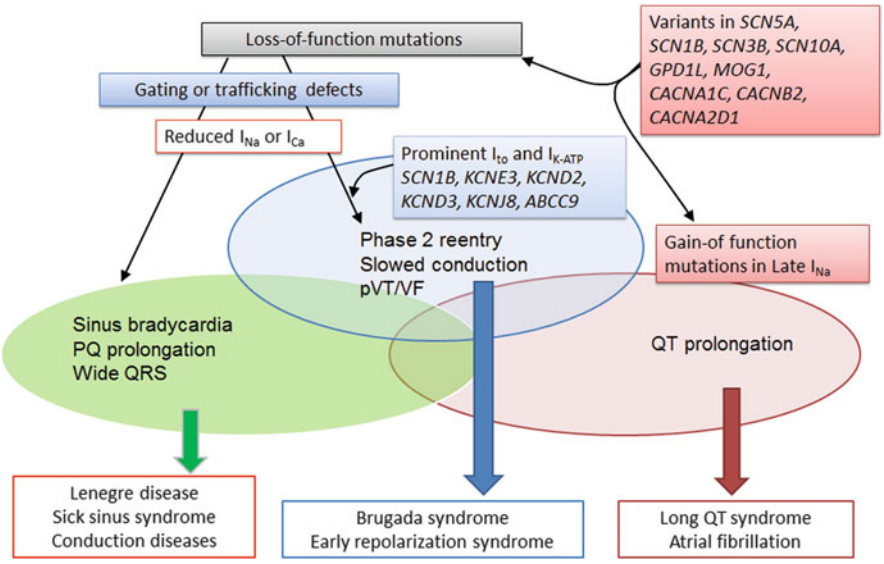

Fig. 5 Schematic showing overlap between Brugada and other inherited cardiac arrhythmia syndromes resulting from genetic defects secondary to loss-of-function of sodium (I_{Na}) and/or calcium (I_{Ca}) channel current. In the absence of prominent I_{to} or $I_{K\text{-}ATP}$, loss-of-function mutations in the inward currents result in various manifestations of conduction disease. In the presence of prominent I_{to} or $I_{K\text{-}ATP}$, loss-of-function mutations in inward currents cause conduction disease as well as the J wave syndromes (Brugada and Early repolarization syndromes). Early repolarization syndrome is believed to be caused by loss-of-function mutations of inward current in the presence of prominent I_{to} in certain regions of the left ventricle (LV), particularly the inferior wall of the LV. The genetic defects that contribute to BrS and ERS can also contribute to the development of long QT and conduction system disease, in some cases causing multiple expression of these overlap syndromes. In some cases, structural defects contribute to the phenotype. Modified from Antzelevitch et al. (2016), with permission

2.3 Common *SCN5A* Intronic Variants (*SCN5A-SCN10A* Interaction/Regulation)

Genetic screening studies (candidate gene approach, GWAS) conducted in control and diseased (BrS) populations have uncovered the role of genetic variation in the noncoding (intronic) regions of *SCN5A* in the regulation of cardiac electrophysiology. These variants (single nucleotide polymorphisms, SNP) may modulate the clinical phenotype by affecting the Nav 1.5 expression level as well as its biophysical properties of either the wild-type (WT) or the mutated channel. Bezzina and coworkers were the first to examine the first noncoding region in the *SCN5A* gene. They identified a haplotype including multiple polymorphisms in the promoter region of the *SCN5A* that are common in an Asian population (Bezzina et al. 2006).

The noncoding region surrounding *SCN5A* has also been studied in GWAS studies conducted in the general population. These studies set out to identify common variants that can modulate conduction and repolarization parameters on

the ECGs (Kolder et al. 2012; Marsman et al. 2014). Several common variants in *SCN5A* and in and around *SCN10A* have been associated with changes in PR interval, QRS duration, and QT interval corrected (QTc) in the general population (Newton-Cheh et al. 2009; Pfeufer et al. 2009, 2010; Chambers et al. 2010; Holm et al. 2010; Sotoodehnia et al. 2010a, b; Smith et al. 2011).

Several groups have provided important information about the presence of regulatory elements (e.g., enhancers) within the noncoding regions of the genome. Also, much information has emerged concerning the potential interaction between regulatory regions between genes, like the interaction between *SCN10A* and *SCN5A* and its regulatory consequences in the context of cardiac arrhythmias like BrS (Arnolds et al. 2012; Van den Boogaard et al. 2012). Christoffels, Nobrega, Barnett, and Moscowitz groups have shown that the G to A nucleotide change identified at SNP rs6801957 is located in a consensus T-box transcription factor binding site within a cardiac enhancer located in the *SCN10A* gene. This change from G to A has at least three effects:

1. It reduces the T-box binding to the enhancer,
2. It affects the stimulation and repression by TBX5 and TBX3, respectively, of a reporter in in vitro assays, and
3. It reduces the activity of the enhancer in vivo (Van den Boogaard et al. 2012).

Moreover, the haplotype tagged by rs6801957 was associated with reduced *SCN5A* expression in human hearts (Van den Boogaard et al. 2012).

3 Summary

Consistent with the central role of *SCN5A* in cardiac electrophysiology, we describe a series of cardiac arrhythmia syndromes in which variants in this gene as well as the genes that encode its protein partners play a key role in the pathogenesis of disease. This pertains not only to the rare variants identified in coding (exonic) regions but also for the variants identified in the noncoding (intronic) regions; the latter generally involving intricate gene-to-gene interactions.

Conflict of Interest None

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