Physiological and Pathophysiological Insights of Nav1.4 and Nav1.5 Comparison

Gildas Loussouarn, Damien Sternberg, Sophie Nicole, Céline Marionneau, Francoise Le Bouffant, Gilles Toumaniantz, Julien Barc, Olfat A. Malak, Véronique Fressart, Yann Péréon, et al.

frontiers in Pharmacology

REVIEW
published: 14 January 2016
doi: 10.3389/fphar.2015.00314

Physiological and Pathophysiological Insights of Nav1.4 and Nav1.5 Comparison

Gildas Loussouarn[1, 2, 3]*, *Damien Sternberg*[4, 5, 6, 7, 8, 9], *Sophie Nicole*[4, 5, 6, 7], *Céline Marionneau*[1, 2, 3], *Francoise Le Bouffant*[1, 2, 3], *Gilles Toumaniantz*[1, 2, 3], *Julien Barc*[1, 2, 3], *Olfat A. Malak*[1, 2, 3], *Véronique Fressart*[9], *Yann Péréon*[10, 11], *Isabelle Baró*[1, 2, 3] and *Flavien Charpentier*[1, 2, 3, 12]

[1] Institut National de la Santé et de la Recherche Médicale, UMR 1087, l'Institut du Thorax, Nantes, France, [2] Centre National de la Recherche Scientifique, UMR 6291, Nantes, France, [3] Université de Nantes, Nantes, France, [4] Institut National de la Santé et de la Recherche Médicale, U1127, Paris, France, [5] Sorbonne Universités, Université Pierre-et-Marie-Curie, UMR S1127, Paris, France, [6] Centre National de la Recherche Scientifique, UMR 7225, Paris, France, [7] Institut du Cerveau et de la Moelle Épinière, ICM, Paris, France, [8] Assistance Publique – Hôpitaux de Paris (AP-HP), Centres de Référence des Canalopathies Musculaires et des Maladies Neuro-musculaires Paris-Est, Paris, France, [9] Assistance Publique – Hôpitaux de Paris (AP-HP), Hôpital de la Pitié Salpêtrière, Service de Biochimie Métabolique, Unité de Cardiogénétique et Myogénétique, Paris, France, [10] Centre Hospitalier Universitaire de Nantes, Centre de Référence Maladies Neuromusculaires Nantes-Angers, Nantes, France, [11] Atlantic Gene Therapies - Biotherapy Institute for Rare Diseases, Nantes, France, [12] Centre Hospitalier Universitaire de Nantes, l'Institut du Thorax, Nantes, France

OPEN ACCESS

Edited by:
Mohamed Chahine, Laval University, Canada

Reviewed by:
Anselm Zdebik, University College London, UK
Adrien Moreau, Centre de Recherche de l'Institut Universitaire en Santé, Canada

***Correspondence:**
Gildas Loussouarn
gildas.loussouarn@inserm.fr

Specialty section:
This article was submitted to Pharmacology of Ion Channels and Channelopathies, a section of the journal Frontiers in Pharmacology

Received: *05 November 2015*
Accepted: *21 December 2015*
Published: *14 January 2016*

Citation:
Loussouarn G, Sternberg D, Nicole S, Marionneau C, Le Bouffant F, Toumaniantz G, Barc J, Malak OA, Fressart V, Péréon Y, Baró I and Charpentier F (2016) Physiological and Pathophysiological Insights of Nav1.4 and Nav1.5 Comparison. Front. Pharmacol. 6:314. doi: 10.3389/fphar.2015.00314

Mutations in Nav1.4 and Nav1.5 α-subunits have been associated with muscular and cardiac channelopathies, respectively. Despite intense research on the structure and function of these channels, a lot of information is still missing to delineate the various physiological and pathophysiological processes underlying their activity at the molecular level. Nav1.4 and Nav1.5 sequences are similar, suggesting structural and functional homologies between the two orthologous channels. This also suggests that any characteristics described for one channel subunit may shed light on the properties of the counterpart channel subunit. In this review article, after a brief clinical description of the muscular and cardiac channelopathies related to Nav1.4 and Nav1.5 mutations, respectively, we compare the knowledge accumulated in different aspects of the expression and function of Nav1.4 and Nav1.5 α-subunits: the regulation of the two encoding genes (*SCN4A* and *SCN5A*), the associated/regulatory proteins and at last, the functional effect of the same missense mutations detected in Nav1.4 and Nav1.5. First, it appears that more is known on Nav1.5 expression and accessory proteins. Because of the high homologies of Nav1.5 binding sites and equivalent Nav1.4 sites, Nav1.5-related results may guide future investigations on Nav1.4. Second, the analysis of the same missense mutations in Nav1.4 and Nav1.5 revealed intriguing similarities regarding their effects on membrane excitability and alteration in channel biophysics. We believe that such comparison may bring new cues to the physiopathology of cardiac and muscular diseases.

Keywords: Nav1.4, Nav1.5, physiopathology, associated/regulatory proteins, missense mutations

Voltage-gated sodium channels (Nav) constitute a family of 10 members in mammals, Nav1.1 to Nav1.9 and Nax, expressed in a large variety of tissues. In excitable cells such as striated myocytes, they initiate action potentials that, in heart as well as in skeletal muscles, trigger, and regulate the contraction. Because of their key role in this function, mutations impacting their activity have tremendous consequences. This review compares the knowledge accumulated in different aspects of the expression and function of Nav1.4 and Nav1.5 α-subunits, and focuses on "homologous" mutations *i.e.,* in the same (aligned) amino acids of the skeletal muscle Nav1.4 and of the cardiac Nav1.5 leading to a large range of muscular and cardiac disorders also called channelopathies.

CLINICAL DESCRIPTION OF THE MAIN Nav1.4 AND Nav1.5 RELATED PATHOLOGIES

Clinical Description of Nav1.4 Related Channelopathies

Nav1.4, which is encoded by the *SCN4A* gene, is the pore-forming subunit of the main sodium channel present in skeletal muscles. Nav1.4 related channelopathies that affect skeletal muscle excitability (Vicart et al., 2005; Jurkat-Rott et al., 2010; Nicole and Fontaine, 2015) are dominant diseases classified in two opposite groups as defined by the prevalent clinical symptoms: muscle stiffness and hypertonia (myotonia) episodes [non dystrophic myotonias (NDM)], and muscle weakness resulting in paralysis episodes (periodic paralyses; PP). It should be noted that similar clinical pattern are also associated with other channelopathies involving chloride channels (NDM) or calcium channels (PP). **Table 1** summarizes the main classes of Nav1.4-related skeletal muscle channelopathies. Detailed clinical, electromyographic (Fournier et al., 2004, 2006), genetic and, *in fine*, pathophysiological analyses have led to distinguish several entities among skeletal muscle sodium channelopathies.

Nav1.4-Related non Dystrophic Myotonias

Myotonia may occur at the beginning of effort and be alleviated (myotonia, with warm-up effect), or aggravated (paradoxical myotonia, also named paramyotonia) by continuing effort. Those myotonic or paramyotonic symptoms are associated with myotonic discharges analyzed with electromyographic investigations. NDM are opposed to dystrophic myotonias as observed in Steinert (Myotonic Dystrophy type 1, DM1) and PROMM (PROximal Myotonic Myopathy or Myotonic Dystrophy type 2, DM2) diseases. Among NDM, at least two entities differ clinically and electromyographically (Trip et al., 2009; Raja Rayan and Hanna, 2010).

- Paramyotonia congenita (PC) consists of cold-induced stiffness often associated with some weakness of face and extremities muscles, and paradoxical myotonia; it is associated with a progressive decrease of compound muscle action potential (CMAP) amplitude during repetitive short efforts test at EMG (pattern I according to Fournier, Fournier et al., 2004).
- Sodium channel myotonias (SCM) regroup the remaining dominant sodium channel-related myotonias that are not significantly cold-sensitive or paradoxical, and do not exhibit any change of CMAP amplitude during repetitive short efforts test at EMG (pattern III according to Fournier); this SCM entity was initially termed "potassium-aggravated myotonia" as potassium load triggers myotonia in some cases. This group was further subdivided into three types: *myotonia*

TABLE 1 | Main classes of Nav1.4 skeletal muscle channelopathies (Trip et al., 2009; Raja Rayan and Hanna, 2010).

	Clinical manifestations	Triggers	Paraclinics	EMG canonical pattern	First intention treatment	Most frequently mutated residues	References
PC	Stiffness followed by weakness Paradoxical myotonia	Cold		Myotonia Type I (repeated short effort test)	Mexiletine	T1313 (ID III-IV), R1448 (DIV S4)	McClatchey et al., 1992b; Ptácek et al., 1992; Hayward et al., 1996; Featherstone et al., 1998; Bouhours et al., 2004
SCM	Stiffness at exertion (most often), permanently at rest (*myotonia permanens*), or acetazolamide-responsive myotonia	Exertion Acetazolamide		Myotonia Type III (repeated short effort test)	Mexiletine	G1306 (ID III-IV), G1306A/V: *myotonia fluctuans* G1306E: *myotonia permanens*	Lerche et al., 1993; Rüdel et al., 1993; Ricker et al., 1994; Hayward et al., 1996
HyperPP	Short episodes (minutes)	Fasting	Normal or high potassium level during episodes	Some myotonia Type IV (long effort test)	Acetazolamide	T704 (DIIS5), M1592 (DIV S6)	Ptácek et al., 1991; Rojas et al., 1991; Yang et al., 1994; Iaizzo et al., 1995
HypoPP	Long-lasting episodes (hours, days)	Glucide-rich meals Rest after exercise Prolonged rest	Markedly low potassium levels during episodes	No myotonia Type V (long effort test)	Acetazolamide	R669, R672 (DII S4)	Bulman et al., 1999; Jurkat-Rott et al., 2000; Bendahhou et al., 2001; Sternberg et al., 2001

PC, Paramyotonia Congenita; SCM, Sodium channel Myotonia; Hypo, Normo, Hyper PP, Hypo, Normo, Hyper-kalemic Periodic Paralysis.

permanens, *myotonia fluctuans,* and acetazolamide-responsive myotonia. While this classification is not used in clinics, it has some relevance: *myotonia permanens* designates myotonia that is present permanently, even at rest; *myotonia fluctuans* designates myotonia that appears and disappears at some moment, with no systematic concomitance with exertion, a peculiar circumstance being exercise-induced delayed-onset myotonia, that occurs some time after exertion has stopped; acetazolamide-responsive myotonia is a treatment-related designation, that underlines the fact that some SCM are treatable by acetazolamide.

Nav1.4-Related Periodic Paralysis

Among PP, two distinct entities are recognized (Raja Rayan and Hanna, 2010): hypokalemic periodic paralysis (HypoPP) is characterized by a marked hypokalemia concomitant with paralysis episodes, and, on the opposite, hyperkalemic periodic paralysis (HyperPP) is associated with a tendency to high blood potassium levels during the paralysis episodes. From the electromyographic point of view, both are characterized by a marked decrease of CMAP amplitude after a 5 min-long effort (long effort test, also referred to as McManis test).

Overlap, borderline or mixed syndromes between PP and NDM or between their subtypes have been reported (McClatchey et al., 1992a; Sugiura et al., 2003; Webb and Cannon, 2008; Yoshinaga et al., 2012). The age at onset is usually in early to late childhood. Neonatal symptoms are not classically reported in the most frequent Nav1.4 channelopathies, but dominant *de novo* mutations are reported in moderate to severe neonatal clinical presentations such as severe neonatal episodic laryngospasm (SNEL) (Lion-Francois et al., 2010). In a general way, respiratory symptoms are not common in PP and NDM, however a small number of patients are exposed to laryngeal or diaphragmatic weakness or myotonia that may be symptomatic.

The minimal prevalence of skeletal muscle Nav1.4 channelopathies has been recently estimated to be 0.4:100,000 in England (Horga et al., 2013) and 1.4:100,000 in France. Mutations in Nav1.4 are mostly missense or rarely in-frame deletions or insertions, usually with a dominant effect. However exceptional recessive homozygosity (Arnold et al., 2015) and a possible recessive compound heterozygosity (Tsujino et al., 2003) have been reported in congenital myasthenic syndromes. A small number of canonical mutations account for a significant percentage of cases (**Table 1**), e.g., T1313M and R1448C/H for PC, T704M for HyperPP, V445M (Rosenfeld et al., 1997), V1293I (Koch et al., 1995), and G1306A/V/E for SCM, mutations of domains II and III S4 arginines (IIS4 and IIIS4) at position 669 (R>H), 672 (R>H/G/C/S), 1132 (R>Q) (Carle et al., 2006), 1135 (R>H) for HypoPP (Matthews et al., 2009). Mutations at IIS4 arginine 675 (R>Q/G/W) result in a special type of PP with both features of HyperPP and HypoPP (Vicart et al., 2004). However, beside those frequent canonical mutations, more than 70 different missense mutations at more than 55 different positions in different domains of the protein have been reported in the literature as causative mutations for Nav1.4 channelopathies. The penetrance of Nav1.4 dominant mutations is variable for each mutation: it is high for HyperPP (T704M), PC (T1313M/A and R1448C/H) and SCM (V445M and V1293I) mutations, and lower, with cases of gender-related non-penetrance in pedigrees, for some other mutations such as HypoPP mutations at position 669 or 672 (Ke et al., 2013).

Clinical Description of Nav1.5 Related Channelopathies

Nav1.5, which is encoded by the *SCN5A* gene, is the pore-forming subunit of the main cardiac sodium channel. Nav1.5 related channelopathies affecting cardiac excitability are dominant diseases that, similarly to Nav1.4 in the skeletal muscles, impact cardiac excitability through loss of function or gain of function effects on Nav1.5 activity. **Table 2** summarizes the Nav1.5 related channelopathies that are discussed in this review, which only considers pathologies provoked by mutations in the same, i.e., aligned amino acids in Nav1.4 and Nav1.5 (cf. Part Comparison of Missense Mutations. Are there (dys-)Functional Homologies between Nav1.4 and Nav1.5?): the Brugada syndrome (BrS), the long QT syndrome (LQTS), and arrhythmic dilated cardiomyopathy. The latter includes a novel form of cardiac arrhythmia characterized by multifocal ectopic Purkinje-related premature contractions (MEPPCs), associated or not with atrial fibrillation and dilated cardiomyopathy. Consequently, **Table 2** is not an exhaustive list of Nav1.5 related channelopathies.

The Brugada Syndrome

The BrS is a primary electrical disorder that is characterized by a specific ECG pattern consisting of ST-segment elevation followed by a negative T-wave in the right precordial leads (Brugada and Brugada, 1992), indicating abnormal electrical activity in the upper part of the right ventricle (right ventricular outflow tract). This ECG pattern is associated with an increased risk of sudden cardiac death (SCD) resulting from polymorphic ventricular tachyarrhythmias or ventricular fibrillation. The incidence of BrS in the general population is currently estimated at 1:2000 (Antzelevitch et al., 2005). This syndrome is 8–10 times more prevalent in males than in females and typically manifests during adulthood, with a mean age of SCD of 41 $\pm$ 15 years (Antzelevitch et al., 2005). BrS was first described as a monogenic disease, with autosomal dominant transmission. Although more than 20 genes have been proposed as causally related to BrS, mutations in these genes explain less than 30% of the cases (Crotti et al., 2012; Nielsen et al., 2013; Antzelevitch and Yan, 2015; Veerman et al., 2015). Around 25% of BrS patients possess a mutation in *SCN5A*. So far, ≈300 mutations in *SCN5A* have been reported as related to BrS (http://www.ncbi.nlm.nih.gov/clinvar). These mutations lead to a loss of Nav1.5 function and reduce Na^+ current (I_{Na}). Besides BrS, loss-of-function mutations in *SCN5A* also cause isolated cardiac conduction disease and sinus node dysfunction (Remme et al., 2008). ECG signs of conduction defects are also a common feature of BrS. The other genes identified so far are coding for proteins that are involved in generating or regulating the sodium current (Antzelevitch and Yan, 2015), the L-type calcium current (Antzelevitch et al., 2007; Burashnikov et al., 2010; Béziau et al., 2014) or the transient outward potassium current (Delpón et al., 2008; Giudicessi et al., 2011).

TABLE 2 | Nav1.5 cardiac channelopathies.

	Clinical manifestations	Triggers	Paraclinics	ECG canonical pattern	First intention treatment	References
Brugada syndrome (BrS)	Ventricular fibrillation or aborted sudden cardiac death, syncope, nocturnal agonal respiration, palpitations	Rest or sleep, febrile state, vagotonic conditions		ST-segment elevation on right precordial leads (V1 and V2)	Implantable cardioverter-defibrillator (ICD)	Brugada and Brugada, 1992; Antzelevitch et al., 2005
Type 3 Long QT syndrome (LQTS3)	Polymorphic ventricular tachycardia (torsades de pointes), ventricular fibrillation, syncopes, sudden death	Rest or sleep, bradycardia, hypokaliemia, drugs prolonging QT interval		Prolonged QT interval	β-blockers (with or w/o mexiletine)	Wang et al., 1995; Amin et al., 2013; Giudicessi and Ackerman, 2013
Arrhythmic Dilated Cardiomyopathy	Systolic dysfunction, left ventricular enlargement or dilatation. Multiple arrhythmias (text)	For MEPPC: rest (exercise suppresses PVCs)			For MEPPC: Quinidine Amiodarone	McNair et al., 2011; Laurent et al., 2012; Mann et al., 2012; Nair et al., 2012; Beckermann et al., 2014

This list is not exhaustive, but corresponds to pathologies caused by Nav1.5 mutations that are homologous to mutations in Nav1.4 (cf. ***Tables 4****,* ***5****).*

If BrS was first described as a monogenic autosomal dominant disease, there is accumulating evidence suggesting that it follows a more complex genetic model. Concerning *SCN5A*, segregation studies performed in large affected pedigrees demonstrate that mutations in this gene are characterized by a low penetrance (47%). In some instances, a single *SCN5A* mutation can lead to different cardiac arrhythmia phenotypes in the same family or even in a single patient (Kyndt et al., 2001; Probst et al., 2009). Moreover, in some pedigrees, the absence of the familial *SCN5A* mutation is observed in some affected family members, suggesting other origins for the disease (Probst et al., 2009). Recently, a genome-wide association study in a large cohort of BrS patients has provided the proof of concept that common genetic variants outside the *SCN5A* gene, e.g., *SCN10A* and *HEY2* loci in the reported study, may have a large effect on the development of the disease (Bezzina et al., 2013). Altogether, these data suggest that the BrS most probably involves combined contribution of different gene variants of variable impact.

The Long QT Syndrome

Congenital LQTS is defined by several criteria including a prolongation of the QT interval corrected for heart rate, i.e., QTc, to values above 440 ms in males and 460 ms in females, due to prolonged ventricular action potentials. LQTS patients are predisposed to ventricular polymorphic tachyarrhythmias (*torsades de pointes*) that may lead to syncope, seizure or SCD (Amin et al., 2013). The most common form of LQTS (also called Romano-Ward syndrome) is an autosomic dominant disease. Its incidence in the population worldwide is about 1:2000 (Schwartz et al., 2009). To date, genetic defects in 15 different genes have been found in 70% of the LQTS patients (Amin et al., 2013; Giudicessi and Ackerman, 2013). Similar to BrS, the disease penetrance is most often incomplete and highly variable, ranging from 25 to 100% (Priori et al., 1999; Viadero et al., 2011). This suggests that additional genetic and non-genetic factors may modify the clinical manifestations of a given LQTS-causing mutation. In recent years, numerous studies have shown that genetic variants play an important modulatory role in establishing the disease severity (Amin et al., 2013). Among non-genetic factors, hypokalemia, or treatment with drugs inhibiting $K_V11.1$ (hERG) channels as side effect are well known to favor arrhythmic events. Sex is also a well-known modifier of QT interval duration in LQTS. Post-adolescence and pre-menopause women have a lower repolarization reserve than men and are therefore more prone to QT interval prolongation and cardiac events. This is partially explained by the effects of sex hormones on cardiac ion channel expression and function (Tanabe et al., 1999; Zicha et al., 2003; Bai et al., 2005; Gaborit et al., 2010). The most common types of LQTS are LQTS1 (30–35% of patients; Ackerman et al., 2011), LQTS2 (25–40%), and LQTS3 (5–10%), due to defects in *KCNQ1* ($K_V7.1$ channel), *KCNH2* ($K_V11.1$), and *SCN5A* (Nav1.5) genes, respectively. Approximately 80% of all LQTS causal mutations are found in these three genes. Clinically, LQTS3 is characterized by unusually increased duration of the ST segment with a late appearance of the T wave (Moss, 2002). It is often more lethal, although less frequent, than LQTS1 and LQTS2 (Priori et al., 2003). Bradycardia and pauses occurring at rest or more particularly during sleep are often at the origin of the arrhythmias, although fatal tachycardia-induced arrhythmias have also been reported for a third of the patients. Most of the *SCN5A* mutations that were reported to be related to LQTS3 (≈200; http://www.ncbi.nlm.nih.gov/clinvar) alter the fast inactivation process of the channel, leading to persistent inward sodium current causing prolonged membrane depolarizations (Wang et al., 1995; George, 2005).

Arrhythmic Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by systolic dysfunction and, in most patients, left ventricular enlargement or dilatation. It has been associated with the mutations of more than

30 genes, including *SCN5A* (McNair et al., 2011; Hershberger et al., 2013). Sixteen *SCN5A* mutations are linked to familial or sporadic cases with DCM with various types of arrhythmias, for example, sinus node dysfunction, conduction delay, and atrial and/or ventricular tachy-arrhythmias (Amin, 2014). Among arrhythmic DCM, the MEPPC syndrome is a recently-described autosomal dominant form of cardiac arrhythmia (Laurent et al., 2012). It is characterized by frequent premature ventricular contractions (PVCs) originating from various ectopic foci along the fascicular-Purkinje system occasionally associated with dilated cardiomyopathy, non-sustained ventricular tachycardias (NSVTs), and sudden death. A similar phenotype was first reported in 2003 by Bezzina and collaborators in a newborn boy and his diseased sister, both genotyped with Nav1.5 W156X and R225W mutations (Bezzina et al., 2003). Both parents and an elder sibling, each one carrier of one or the other mutation, were asymptomatic. For the sister, arrhythmias being the cause of the DCM is unlikely because persistent arrhythmias were only present for a short period. Two other mutations in Nav1.5 (R222Q and R225P) have been linked to this MEPPC syndrome in several families (Laurent et al., 2012; Mann et al., 2012; Nair et al., 2012; Beckermann et al., 2014). In these families, dilated cardiomyopathy, when present, was suggested as a consequence of severe primary electrical dysfunctions.

Phenotypic and Genotypic Overlap between Cardiac and Skeletal Muscle Sodium Channelopathies?

A recently published study shows that patients carrying (or not) *SCN4A* causative mutations, present with mixed phenotype (BrS and myotonic features) (Bissay et al., 2015). Although *SCN4A* transcripts are present in human ventricles (Péréon et al., 2003), it is difficult to understand how the gain of function *SCN4A* mutations can be compared to the loss of function of *SCN5A* mutations classically associated with Brugada, as discussed in the study of Bissay and collaborators. Another study on a unique family described four patients carrying a *SCN4A* mutation and presenting with PC (Péréon et al., 2003), two of them having slightly prolonged QTc interval. Both PC and LQTS3 are associated with a gain of function of Nav1.4 and Nav1.5, respectively. In this case, it is tempting to hypothesize that the mutant Nav1.4 channels present in the heart are responsible for the QT prolongation. Identifying more families with such overlap phenotypes would help to confirm the potential mutual influence of both channels on the pathogenesis of cardiac and muscular diseases.

CHANNEL MOLECULAR BASES AND GENE EXPRESSION

Voltage-gated sodium channels consist of an α-subunit, constituting the pore, and accessory β-subunits controlling the expression and activity of the pore-forming subunit. Nav1.4, the most frequent Nav α-subunit expressed in the skeletal muscle is a glycosylated transmembrane protein of 1836 amino acids and has an apparent molecular weight of approximately 260 kDa (George et al., 1992a,b). Nav1.5, the most frequent Nav cardiac α-subunit is 2015–2016 amino acid long, depending on the splice variants, and has a similar apparent molecular weight (Gellens et al., 1992; Makielski et al., 2003; Balasuriya et al., 2012).

The *SCN4A* gene which encodes Nav1.4 is composed of 24 exons, all containing coding sequence. No alternative splicing events have been reported in the literature. Nav1.5 is encoded by the *SCN5A* gene, composed of 28 exons, among which exons 2–28 contain the coding sequence. Exon 1 and part of exon 2 encode the 5′ untranslated region (UTR) while exon 28 contains the 3′-UTR (Wang et al., 1996). Intron 2 of *SCN4A* and intron 3 of *SCN5A* are AT-AC type I introns. Intron 21 of *SCN4A* and intron 25 of *SCN5A* are AT-AC type II introns (Wu and Krainer, 1999). All other introns are canonical GT-AG introns. Unlike Nav1.4, mRNA variants of Nav1.5 are detected in the heart of mammals, resulting from alternative splicing. In human and murine hearts, 3′-UTRs present two different splicing variants, generating short or long poly-adenine tails (Shang and Dudley, 2005). In addition, three rare variants were identified only in human, corresponding to alternative splicing of exon 28A by exons 28B–28D coding for truncated and non-functional forms of Nav1.5 (Shang et al., 2007). To date, only the mechanisms of this splice site are understood. They involve interactions with two splicing factors, the RBM25 and LUC7F3 proteins (Gao et al., 2011; Gao and Dudley, 2013). Four and three splice variants, which differ from the canonical non-coding sequence, were described for the 5′UTR of human and mouse *SCN5A* mRNAs, respectively. These transcripts originate from the alternative splicing encompassing exons 1 (designated 1A, 1B, 1C, and 1D) and 2, and are preferentially expressed in the heart as compared with other tissues. Also, a neonatal isoform containing a neonatal exon 6A of 31 nucleotides has been reported. This form presents a difference of seven amino acids in the S3–S4 loop of domain I, in comparison with exon 6 of the adult form (Rook et al., 2012). Ventricular myocardial analysis displayed abnormal splicing of *SCN5A* exon 6, characterized by over-expression of this neonatal isoform, in one patient who present DCM with conduction system disease (Wahbi et al., 2013). These findings suggest a potential implication of mis-splicing of *SCN5A* in the cardiac defect observed in this patient.

Two distinct sodium currents and channels were historically described in skeletal muscle depending upon the developmental and innervation status of the myofiber. SkM1, the TTX-sensitive sodium channel expressed in innervated adult myofibers, corresponds to Nav1.4 and is the main skeletal muscle sodium channel (Trimmer et al., 1989; Kallen et al., 1990). SkM2, the TTX resistant sodium channel expressed in immature and denervated myofibers, corresponds to Nav1.5. In rodents, *SCN4A* expression increases just after birth concomitantly with the decrease of *SCN5A* gene expression (Stocksley et al., 2005). *SCN4A* expression is not sensitive to myofiber denervation by contrast to *SCN5A* gene expression, which was found to be upregulated in response to denervation (Awad et al., 2001).

The *SCN4A* promoter contains distinct positive-acting promoter E-box and negative-acting repressor E-box that cooperate to yield specific gene expression in differentiated skeletal myofibers (Kraner et al., 1998, 1999). It is suggested

that the muscle specificity of *SCN4A* expression result from the binding of two basic helix-loop-helix transcription factors (bHLH) of the muscle-specific MyoD family, myogenin and MRF4 for initiation and maintenance, respectively, to the positive-acting promoter E-box located upstream the translation initiation site. NFI would be another major regulator of *SCN4A* gene expression acting in concert with bHLH factors, especially MRF4 (Hebert et al., 2007). The density of Nav1.4 is around 20 times higher at the neuromuscular junction (NMJ), in part as a result of local mRNA accumulation (Stocksley et al., 2005). Although the promoter element responsible for the transcriptional regulation of subsynaptic genes in response to neuronal factors at the NMJ is the N-box (TTCCGG) (Méjat et al., 2003), no N-box is present within the promoter of *SCN4A,* suggesting the involvement of other regulatory elements.

Similarly to alternative splicing, more is known concerning the regulation of the *SCN5A* promoter, compared with *SCN4A*. After the identification of a first promoter region for human *SCN5A* which includes multiple positive and negative cis-acting elements extending into intron 1 (Yang et al., 2004), two other promoter regions for murine *SCN5A* (designated P2 and P3) containing two distinct cardiac-specific enhancer regions were identified and functionally characterized (Shang and Dudley, 2005). In human and rat, the segment immediately upstream of the major transcription start site contains three GC boxes that could serve as binding sites for the Sp1 transcription factor, which are homologous to the CACC boxes recognized in promoters of muscle restricted genes, and an E-box binding site for bHLH factors (Yang et al., 2004). The human sequence also includes an additional C-rich motif which is recognized as a major regulator of expression in myocytes. Further, Yang and collaborators have characterized a binding site for GATA in intron 1, which is also known as a key regulator of gene expression in the heart. Surprisingly, variants in *SCN10A* (encoding Nav1.8 of which expression is extremely low in heart and undetectable in atrioventricular bundle) are associated with alterations of cardiac conduction parameters and BrS (van den Boogaard et al., 2014). Van den Boogaard and collaborators have shown that the *SCN10A* variants act more likely through an alteration *SCN5A* gene expression level. They have demonstrated that a cis-regulatory element located in *SCN10A* gene -which is immediately located next to *SCN5A*- was able to interact with both *SCN5A* and *SCN10A* promoters. Furthermore, they described, using healthy human heart samples, a direct correlation between the *SCN5A* (but not *SCN10A*) expression and the presence of the rs6801957 risk-associated SNP in the *SCN10A* intronic enhancer. Together, their data provided a genomic mechanism explaining how a common genetic variant at *SCN10A* locus influences cardiac physiology and predispose to Brs.

ASSOCIATED/REGULATORY PROTEINS

Although expression of Nav1.5 or Nav1.4 α-subunits alone results in the generation of functional channels in heterologous expression systems, it is now quite clear that the regulation of gating and/or expression of the Nav subunits substantially relies on a variety of other accessory/regulatory proteins (Abriel, 2010; Rook et al., 2012). Interestingly, the alignment of Nav1.5 and Nav1.4 amino acid sequences could facilitate the identification of novel associated/regulatory proteins of the counterpart channel subunit. In addition, this direct sequence comparison has contributed, as for Navβ1 (Makita et al., 1996), and will certainly continue to contribute to localizing the structural determinants involved in the channel regulation. In this respect, **Table 3** and **Figure 1** recapitulate the Nav1.5 or Nav1.4 amino acid sequences previously identified to mediate interaction with associated/regulatory proteins, and indicates the corresponding sequences in the other Nav α-subunit. Whereas, a number of Nav1.5 interacting proteins, with their binding sites in the channel subunit, have been described in the literature (see references in **Table 3**), very little is known for Nav1.4 (**Figure 1**). Nevertheless, it is interesting to note that the amino acid sequence similarity obtained for some binding sites is high, suggesting the possibility that both channel subunits share the same associated/regulatory proteins. This is the case for example of calmodulin, which associates with the very well conserved (100% sequence similarity) IQ-motif on both Nav1.5 and Nav1.4 C-terminal domains (Tan et al., 2002; Young and Caldwell, 2005). Most of the proteins shown to interact with Nav1.5 on a site conserved in Nav1.4 are ubiquitously expressed (dynamitin, 14-3-3, CaMKII, MOG-1, calmodulin, FGF, PTPH1/PTPN3, SAP97), suggesting that an interaction with Nav1.4 may take place in the skeletal muscle cells (Marfatia et al., 2001; Blair et al., 2006). When not ubiquitously expressed, proteins known to interact with Nav1.5 are also expressed in skeletal muscle (α actinin2) that argue for a possible interaction with Nav1.4 (Foley and Young, 2014). Conversely, weaker sequence similarity may suggest different affinities, sites or absence of interaction/regulation. This is the case for example of Navβ1 for which the region within D1/S5-S6 that confers regulation of Nav1.4 in *Xenopus* oocytes (Makita et al., 1996) is not very well conserved in Nav1.5 (63.1% sequence similarity) which is also regulated by Navβ1, suggesting that the structural determinants of the interaction of Nav1.5 or Nav1.4 with Navβ1 are different. Finally, it is striking to note the complete absence of the PY-motif from the C-terminus of Nav1.4. This suggests that the regulation of Nav1.4 channel internalization and/or degradation is achieved through different mechanisms as compared to Nav1.5 for which cell surface expression is regulated through the ubiquitin-proteasome pathway (van Bemmelen et al., 2004; Rougier et al., 2005). These mechanisms remain to be identified.

COMPARISON OF MISSENSE MUTATIONS. ARE THERE (DYS-) FUNCTIONAL HOMOLOGIES BETWEEN Nav1.4 AND Nav1.5?

Around 300 mutations in *SCN5A* have been identified in patients presenting with BrS, 31% being frameshift, nonsense or splice-site mutations, and 69% being missense or rarely in-frame deletions/insertions (Kapplinger et al., 2010). When studied in

TABLE 3 | Comparison of Nav1.5 and Nav1.4 channel associated/regulatory proteins and corresponding binding sites.

Region	Nav1.4/1.5 interacting proteins	Nav1.5				Nav1.4				% aa sequence similarity
		Binding sites	Mutations	Pathologies	References	Binding sites	Mutations	Pathologies	References	
DI S5–S6 loop	Navβ1	Equivalent sequence: (278–388) HKC—GKI (111 aa)	R282H, V294M, G319S	BrS	Priori et al., 2002	**(278–422) QKC–GKT (145 aa)** (Makita et al., 1996				63.1%
			R282H	BrS	Itoh et al., 2005a					
			G292S	BrS	Niimura et al., 2004					
			K317N	BrS	Yi et al., 2003					
			L325R	BrS	Keller et al., 2005					
			G351V	BrS	Vatta et al., 2002					
			T353I	BrS	Pfahnl et al., 2007					
			D356N	BrS	Makiyama et al., 2005					
			R367C, M369K	BrS	Smits et al., 2002					
			R367H	BrS	Takehara et al., 2004					
			R376H	BrS	Frustaci et al., 2005					
			R376H	BrS	Rossenbacker et al., 2004					
			L276Q, H278D, R282C,	BrS	Kapplinger et al., 2010					
			V300I, L315P, K317-	BrS	Kapplinger et al., 2010					
			T320N, E346X, G351D	BrS	Kapplinger et al., 2010					
			R367C, R367L, M369K	BrS	Kapplinger et al., 2010					
			W374G, G386R, G386E	BrS	Kapplinger et al., 2010					
ID I-II	Dynamitin	**(417–444) EEQ—KKE (28 aa)** Chatin et al., 2014	E428K, H445D, L461V	AF	Darbar et al., 2008	Equivalent sequence: (451–478) AEQ–KKH (28 aa)				85.7%
			E439K	BrS	Kapplinger et al., 2010					
			E446K	DCM	McNair et al., 2011					
			E462K	LQT3	Tester et al., 2005					
	14-3-3	**(417–467) EEQ—PLA (51 aa)** Allouis et al., 2006				Equivalent sequence: (451–482) AEQ—EAD (32aa)				66.7%
	CaMKII	**(417–711) EEQ–GVK (295 aa)** Ashpole et al., 2012				Equivalent sequence: (451–572) AEQ—IIH (122 aa)				87.1% in ID first 31 aa (418–449:452–484) 80.0% in ID last 60 aa (655–714:517–575)
ID II-III	Ankyrin-G	**(1047–1055) VPIAVAESD (9 aa)** Mohler et al., 2004	S941N	LQT3	Schwartz et al., 2000	**(925–933) VPIASEESD (9 aa)** Lemaillet et al., 2003	S804N	SCM	Fournier et al., 2006	77.8%
			R971C	LQT3	Tester et al., 2005					
			A997S	LQT3	Ackerman et al., 2001					
			T1069M	LQT3	Tester et al., 2005					
			R1023H	BrS	Frustaci et al., 2005					
	MOG1	**(940–1200) SSF—CYH (261 aa)** Wu et al., 2008	E1053K, R965C	BrS	Priori et al., 2002	Equivalent sequence: (803–1026) SSF—CFK (224 aa)				50.2%
			D1055G, R965H, A997T	BrS	Kapplinger et al., 2010					
			S1079Y, A1113V, S1140T	BrS	Kapplinger et al., 2010					
			D1114N	LQT3	Splawski et al., 2000					
			A1180V	DCM	Ge et al., 2008					
			R1193Q	LQT3	Wang et al., 2004					

(Continued)

TABLE 3 | Continued

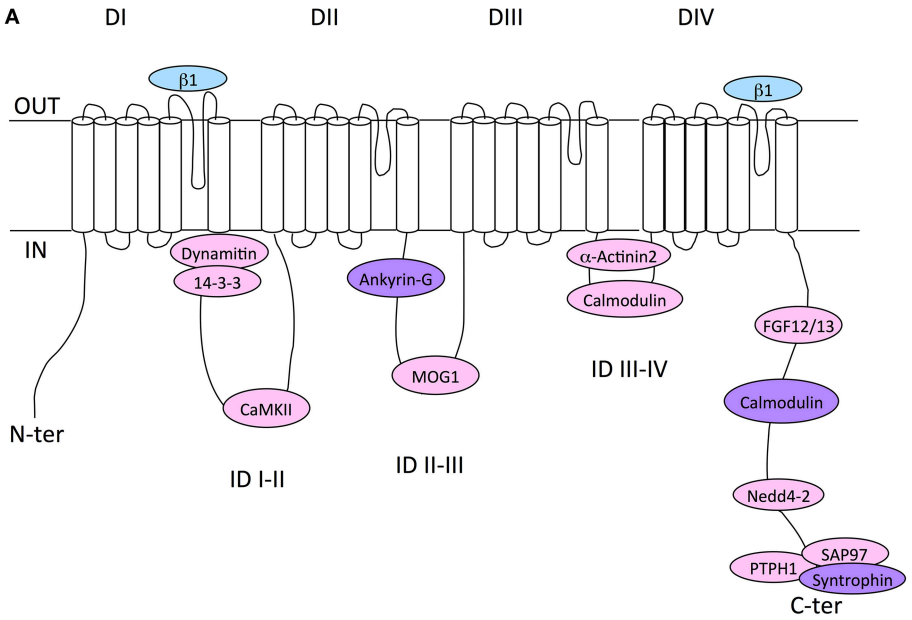
Region	Nav1.4/1.5 interacting proteins	Nav1.5				Nav1.4				% aa sequence similarity
		Binding sites	Mutations	Pathologies	References	Binding sites	Mutations	Pathologies	References	
ID III-IV	α-Actinin-2	**(1471–1523) DNF—IFD (53 aa)** Ziane et al., 2010	G1481E F1486L Y1494N M1498T L1501V	LQT3 LQT3 BrS LQT3 LQT3	Tester et al., 2005 Wang et al., 2007 Tian et al., 2007 Napolitano et al., 2005 Splawski et al., 2000	Equivalent sequence: (1296–1348) DNF—VYD (53 aa)	N1297K G1306E G1306E G1306E	SNDM SCM SNEL PC	Gay et al., 2008 Mitrovic et al., 1995 Lion-Francois et al., 2010 Fleischhauer et al., 1998	94.5%
	Calmodulin	**(1471–1523) DNF—IFD (53 aa)** Potet et al., 2009	L1501V, I1521K G1502S DQKP 1507-1509 R1512W F1520L	BrS BrS LQT3 BrS DCM	Kapplinger et al., 2010 Smits et al., 2005 Keller et al., 2003 Deschênes et al., 2000 McNair et al., 2011	Equivalent sequence: (1296–1348) DNF—VYD (53 aa)	G1306V T1313M T1313A	PC PC PC	Plassart et al., 1994 Fukudome et al., 2003 Bouhours et al., 2004	94.5%
DIV S5-S6 loop	Navβ1	Equivalent sequence: (1720–1748) ILN—AVG (29 aa)	G1712S	BrS	Kapplinger et al., 2010	**(1545–1574) ILN—SIG (30 aa)** Makita et al., 1996				90.1%
C-ter	FGF12/13	**(1784–1864) EPL—LGE (81 aa)** Liu et al., 2003 Wang et al., 2011	E1784K E1784K E1784K S1787N D1790G 1795insD 1795insD Y1795C L1825P R1826H Q1832E, V1861I D1840G	BrS LQT3 L/B LQT3 LQT3 L/B LQT3 L/B LQT3 LQT3 BrS LQT3	Priori et al., 2002 Splawski et al., 2000 Makita et al., 2008 Splawski et al., 2000 An et al., 1998 Bezzina et al., 1999 van Langen et al., 2003 Rivolta et al., 2001 Makita et al., 2002 Ackerman et al., 2001 Kapplinger et al., 2010 Benhorin et al., 1998	Equivalent sequence: (1610–1690) EPL—LGD (81 aa)				95.1%
C-ter	Calmodulin	**(1908–1919) IQ-motif IQRAFRRHLLQR (12aa)** Tan et al., 2002 Young and Caldwell, 2005	Q1909R R1913H	LQT3 LQT3	Tester et al., 2005 Napolitano et al., 2005	**(1734–1745) IQRAYRRHLLQR (12aa)** Young and Caldwell, 2005				100.0%

(Continued)

TABLE 3 | Continued

Region	Nav1.4/1.5 interacting proteins	Nav1.5				Nav1.4				% aa sequence similarity
		Binding sites	Mutations	Pathologies	References	Binding sites	Mutations	Pathologies	References	
	Nedd4-2	**(1974-1980) PY-motif PPSYDSV (7 aa)**			van Bemmelen et al., 2004	No homology				No homology
	Syntrophin	**(2014–2016) SIV (3 aa)**			Ou et al., 2003	**(1834–1836) SLV (3 aa)**			Gee et al., 1998	100.0%
	PTPH1	**(2014–2016) SIV (3 aa)**			Jespersen et al., 2006	Equivalent sequence: (1834–1836) SLV (3 aa)				100.0%
	SAP97	**(2014–2016) SIV (3 aa)**			Petitprez et al., 2011	Equivalent sequence: (1834–1836) SLV (3 aa)				100.0%

*For each channel the identified binding site **(in bold)** and the equivalent sequence on the channel counterpart are presented. The % amino acid sequence similarities between Nav1.5 (NCBI Reference Sequence NP_932173.1) and Nav1.4 (NP_000325.4) channels were estimated using the following website: http://www.ch.embnet.org/software/LALIGN_form.html. Nav1.4 interaction with ankyrin is only suggested by chimeric constructs, it remains to be studied with full length proteins (Lemaillet et al., 2003). It is noticeable that Nedd4-2 consensus binding site "PPSYD(E in Nav1.8)S(R in Nav1.1)" is present in all human Nav channels except Nav1.4. Single amino acid mutations identified in human disease in each binding site are reported. DI to DIV, domains I to IV; DI(S5-S6) and DIV(S5-S6), extracellular connecting loops between S5 and S6 intramembrane segments in domains I and IV; ID, intracellular interdomains; N-ter and C-ter, N- and C-terminus ends; BrS, Brugada Syndrome; AF, Atrial Fibrillation; LQT3, Type 3 long QT syndrome; L/B, Overlap of LQT3 and BrS; DCM, Dilated Cardiomyopathy; SCM, Sodium Channel Myotonia; SNEL, Sporadic Neonatal Episodic Laryngospasm; PC, Paramyotonia Congenita; SNDM, Severe neonatal Non-Dystrophic Myotonia.*



B

	N-ter	*DI*	*ID I-II*	*DII*	*ID II-III*	*DIII*	*ID III-IV*	*DIV*	*C-ter*
Nav1.4	1-127	128-450	451-574	575-802	803-1026	1027-1295	1296-1350	1351-1598	1599-1836
# of aa	127	323	124	228	224	269	55	248	238
Nav1.5	1-127	128-416	417-713	714-939	940-1200	1201-1470	1471-1525	1526-1772	1773-2016
# of aa	127	289	297	226	261	270	55	247	244

FIGURE 1 | (A) Schematic representation of the localization of the binding sites of associated/regulatory proteins identified for Nav1.4 (blue), Nav1.5 (pink), or both (purple). Nav1.4 interaction with ankyrin is only suggested by chimeric constructs, it remains to be studied with full length proteins (Lemaillet et al., 2003). DI to DIV, domains I to IV; ID, intracellular interdomains; N-ter and C-ter, N-and C-terminus ends. **(B)** Table presenting the amino-acid (aa) numbering and length of specific regions and domains in Nav1.4 and Nav1.5 proteins. It is noticeable that Nav1.4 IDI-II total amino-acid length is shorter than Nav1.5 IDI-II.

patch-clamp in heterologous expression systems, mutated Nav1.5 channels are showing different types of loss of function, such as a decrease in current density, a positive shift in the activation curve, a negative shift in the inactivation curve, or a loss of regulation by PKA (Tarradas et al., 2013; Zeng et al., 2013; Aiba et al., 2014). Mutations in *SCN5A* have also been found in patients presenting with LQT syndrome (named LQTS3 when *SCN5A* is mutated). As opposed to BrS, mutated channels in LQTS3 patients show a gain a function, mainly through an increase in a persistent Na^+ current (cf. Part Clinical Description of the Main Nav1.4 and Nav1.5 Related Pathologies). As a result, **BrS** mutations are associated to membrane **hypo-excitability**, whereas **LQTS3** mutations are associated to prolonged action potential, referred here as membrane **hyper-activity**.

In the skeletal muscle, a similar binary classification is observable among the 70 mutations identified so far, that are nearly exclusively missense or rarely in-frame deletions/insertions. **NDM** are linked to membrane **hyper-excitability**, often due to defective inactivation and hence **a gain of function** of Nav1.4 channel activity (Clarke et al., 2011). On the contrary, **hypoPP** is linked to membrane **hypo-excitability**, and is often due to the apparition of an aberrant current through the gating pore that can be a proton or a monovalent cation current (Sokolov et al., 2007). This so-called "omega" current (or gating pore current) causes paradoxical depolarization of myofibers in low K^+, which inactivates Nav1.4 and renders myofibers non excitable. Seemingly paradoxical, **hyperPP** is associated with **gain of function of Nav1.4** (as observed for myotonia) but loss of function on skeletal muscles (paralysis). As for myotonia, defective inactivation of Nav1.4 is often observed and favors membrane depolarization. The paradox is resolved if we consider that wild type Nav1.4 channels will be more inactivated due to a slightly more depolarized membrane, thus causing a loss of sarcolemmal excitability and myofiber paralysis (Cannon, 2015). The development of myotonia or hyperPP may depend on the degree of membrane excitability. This has been suggested for instance when in the same family, females carrying the M1370V mutation develop only a myotonia (PC) whereas males are presenting with both myotonia and hyperPP (Okuda et al., 2001).

Nav1.4 and Nav1.5 are similar. If we consider the aligned region between Nav1.5 and Nav1.4, which represents 95% of Nav1.4 sequence, 67% of the amino-acids are identical. Knowing that, one can wonder whether mutations have been identified at equivalent positions in both channels, and whether, in this case, the new amino-acid is the same, such as Q270K in both Nav1.4 and Nav1.5 or V445M in Nav1.4 and V411M in Nav1.5 (V445 is aligned with V411). It is possible to use an online

TABLE 4 | List of equivalent amino acids found to be similarly mutated in patients with cardiac (Nav1.5) or skeletal (Nav1.4) pathologies.

Region	Nav1.4	Pathology	References	Nav1.5	Pathology	References
Domain I S4	R222Q	Myotonia	Durran et al., 2011	R222Q	MEPPC	Laurent et al., 2012
Domain I S5	Q270K	PC	Carle et al., 2009	Q270K	LQT3	Kapplinger et al., 2010; Calloe et al., 2011
Domain I S6	N440K	Normo Hyper PP	Lehmann-Horn et al., 2011; Lossin et al., 2012	N406K	LQT3	Kato et al., 2014
Domain I S6	V445M	SCM	Takahashi and Cannon, 1999	V411M	LQT3	Horne et al., 2011
Domain II S4	R675Q	Normo, Hyper or Hypo PP?	Vicart et al., 2004; Wu et al., 2014	R814Q	BrS/ CM-AF	Frigo et al., 2007
Interdomain II-III	S804N	SCM	Fournier et al., 2006	S941N	LQT3/de novo SIDS	Schwartz et al., 2000
Interdomain III-IV	G1306E	SCM SNEL	Mitrovic et al., 1995; Fleischhauer et al., 1998	G1481E	LQT3	Kapplinger et al., 2009
Domain IV S6	V1589M	Overlap PC-SCM	Heine et al., 1993; Mitrovic et al., 1994; Hayward et al., 1999	V1763M	LQT3	Chang et al., 2004; Ma et al., 2013

Same amino acid substitutions occurring in both channels lead to consistent pathologies (in green) regarding membrane excitability. PC, Paramyotonia Congenita; MEPPC, Multifocal Ectopic Purkinje-related Premature Contraction; LQT3, Type 3 Long QT syndrome; SIDS, Sudden Infant death syndrome; Hypo, Normo, Hyper PP, Hypo, Normo, Hyper-kalemic Periodic Paralysis; SCM, Sodium channel Myotonia; BrS, Brugada Syndrome; CM, Cardiomyopathy; AF, Atrial Fibrillation; SNEL, Sporadic Neonatal Episodic Laryngospasm.

TABLE 5 | List of equivalent amino acids found to be differently mutated in patients with cardiac (for Nav1.5) or neuromuscular (for Nav1.4) pathologies.

Region	Nav1.4 mutation	Pathology	References	Nav1.5 mutation	Pathology	References
IS4	R222W	Hypo PP	Matthews et al., 2009	R222Q	MEPPC	Laurent et al., 2012
IS4	R225W	SCM	Lee et al., 2009	R225P	LQT3	Beckermann et al., 2014
IS6	N440K	Normo Hyper PP	Lehmann-Horn et al., 2011; Lossin et al., 2012	N406S	BrS	Itoh et al., 2005b
IIS4	R669H	Hypo PP	Struyk et al., 2000; Kuzmenkin et al., 2002	R808P	BrS	Kapplinger et al., 2010
III inter S4-S5	V1149L	HyperPP with myotonia	Yoshinaga et al., 2015	V1323G	BrS	Kapplinger et al., 2010
IIIS6	V1293I	SCM	Koch et al., 1995; Green et al., 1998	V1468F	BrS	Kapplinger et al., 2010
IVS4	R1448H	PC	Ptácek et al., 1992; Chahine et al., 1994; Mohammadi et al., 2003; Holzherr et al., 2014	R1623Q	LQT3	Kambouris et al., 1998; Makita et al., 1998
IVS4	R1448C	PC	Ptácek et al., 1992; Chahine et al., 1994; Featherstone et al., 1998	R1623Q	LQT3	Kambouris et al., 1998; Makita et al., 1998
IVS4	R1448P	PC	Featherstone et al., 1998	R1623Q	LQT3	Kambouris et al., 1998; Makita et al., 1998
IVS4	R1448S	PC (mild)	Bendahhou et al., 1999	R1623Q	LQT3	Kambouris et al., 1998; Makita et al., 1998
IVS4	R1451C	Hypo PP	Arzel-Hézode et al., 2009	R1626P	LQT3	Ruan et al., 2007
IVS6	M1592V	Normo Hyper PP	Rojas et al., 1991; Cannon and Strittmatter, 1993; Hayward et al., 1999; Rojas et al., 1999	M1766L	LQT3	Valdivia et al., 2002; Ye et al., 2003

Divergent amino-acid substitutions occurring in the two channels lead either to consistent (in green) or inconsistent (in red) pathologies regarding membrane excitability. Hypo, Normo, Hyper PP, Hypo, Normo, Hyper-kalemic Periodic Paralysis; MEPPC, Multifocal Ectopic Purkinje-related Premature Contraction; SCM, Sodium channel Myotonia; PC, Paramyotonia Congenita; LQT3, Type 3 Long QT syndrome; BrS, Brugada Syndrome.

compilation that has been proposed using a paralog annotation approach in order to retrieve homologous or nearly homologous variants in both genes (Ware et al., 2012; Walsh et al., 2014). If the same mutations of homologous residues exist, do they give rise to similar dysfunction on both channels? If yes, we can expect that both mutations give rise to the same change in membrane excitability. For instance, if a Nav1.5 mutation leads to hyper-activity of cardiac cells (LQTS3), the corresponding mutation in Nav1.4 may also give rise to a hyper-excitability phenotype of the skeletal muscle cells such as HyperPP, PC, or SCM. **Tables 4**, **5** present **all the corresponding amino acids found to be mutated** in patients with cardiac (Nav1.5) or neuromuscular (Nav1.4) pathologies. **Table 4** and **Figure 2A** list the mutations for which the amino acid substitutions are the same, and **Table 5** and **Figure 2B** those for which they are divergent.

When looking at **Table 4** and **Figure 2A**, it is striking to observe that all paralog mutations give rise to clearly consistent

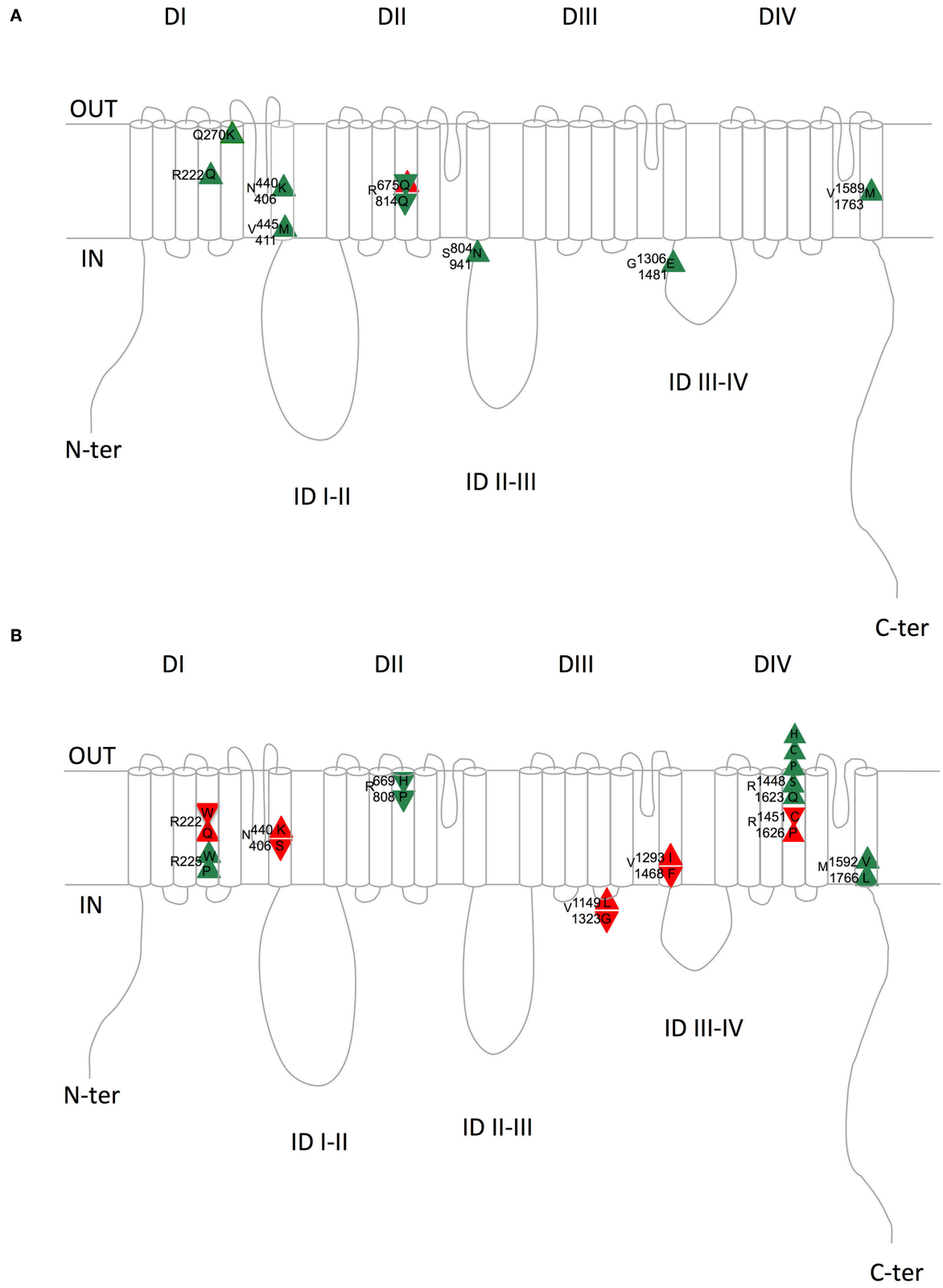


FIGURE 2 | Schematic representation of the equivalent Nav1.4/Nav1.5 amino acids with similar (A) or divergent (B) mutations in patients with skeletal (Nav1.4) or cardiac (Nav1.5) pathologies. Upward triangles indicate a gain of function on membrane excitability and downward triangles a loss of function on membrane excitability. Green and red triangles indicate consistent and inconsistent effects on Nav1.4 and Nav1.5 regarding membrane excitability, respectively. Upper amino acid number/letter, Nav1.4; Lower amino acid number/letter, Nav1.5. DI to DIV, domains I to IV; ID, intracellular interdomains; N-ter and C-ter, N-and C-terminus ends.

TABLE 6 | Variations of biophysical parameters compared to wild type channels for five equivalent mutations identified in Nav1.4 and Nav1.5 that have been studied extensively in patch clamp.

Subunit	Mutation	Pathologies	Cell model	ΔV0.5 act (mV)	ΔV0.5 fast inac (mV)	Mutant/WT Fast inact tau *	Mutant/WT i persistent	References
Nav1.4	I141V	SCM	HEK	−10	0	77% at −10 mV	?	Petitprez et al., 2008; Amarouch et al., 2014
Nav1.5	I141V	ExPVC	HEK	−8	0	86%	?	Amarouch et al., 2014; Swan et al., 2014
Nav1.4	Q270K	PC	HEK	1.3	12.5	168% at −25 mV	200%	Carle et al., 2009
Nav1.5	Q270K	LQT3 conduc	CHO	5.8	9.9	260% at −25 mV	338%	Calloe et al., 2011
Nav1.4	N440K	Normo Hyper PP	HEK	0	7.1	100%	800%	Lossin et al., 2012
Nav1.5	N406K	LQT3	CHO	8.6	0	217%	550%	Kato et al., 2014
Nav1.4	V445M	Myotonia	HEK	−4.1	−4.9	?	1400%	Takahashi and Cannon, 1999
Nav1.5	V411M	LQT3	HEK	−8.1	−7.9	75%	176%	Horne et al., 2011
Nav1.4	V1589M	overlap PC-SCM	HEK	0	5.4	100%	362%	Mitrovic et al., 1994
Nav1.5	V1763M	LQT3	hiPSC-CMs	0	16.8	?	486%	Ma et al., 2013

*Recording were all done at room temperature (except for Nav1.4 N440K: not indicated). *Fast inactivation tau is measured at −30 mV except when indicated. Green, consistent effect; red, inconsistent effect; SCM, Sodium Channel Myotonia; ExPVC, exercise-induced polymorphic ventricular premature complexes; PC, Paramyotonia Congenita; LQT3, Type 3 Long QT syndrome; Normo, Hyper PP, Normo, Hyper-kalemic Periodic Paralysis; Conduc, conduction disease; hiPSC-CMs, cardiomyocytes generated from human induced pluripotent cells; ?, means not determined.*

functional effects, except one which is at first unclear, as detailed below. Indeed, all Nav1.4 mutations linked to membrane hyper-excitability (PC, SCM, and HyperPP) correspond to Nav1.5 mutations linked to membrane hyper-activity (LQTS3), except R675Q (R814Q in Nav1.5). The comparison between Nav1.4 R675Q and Nav1.5 R814Q is not obvious because the pathology induced by Nav1.4 R675Q mutation is difficult to classify as Normo/Hyper PP or Hypo PP (Vicart et al., 2004). Indeed, patients experienced normal as well as decreased potassium levels concomitant to attacks. The rat ortholog of human Nav1.4 R675Q generates an omega current activated by depolarization when expressed in *Xenopus* oocytes (Sokolov et al., 2008) (cf. above). The omega current represents less than 1% of the peak pore current but it remains constant after slow inactivation of the pore current and requires high hyperpolarizations to deactivate. Therefore, it is suspected that this current, carried by Na^+ and K^+ ions, maintained during trains of action potentials and with a residual non-deactivated activity at resting potential could lead to sodium accumulation and a decrease in membrane excitability. It will be interesting to test whether the corresponding mutation in Nav1.5 is also responsible for an omega current. Moreover, the R675Q Nav1.4 mutation gives rise to a hyperpolarizing shift of the inactivation curve and a slower recovery from inactivation when expressed in HEK293 cells. (Vicart et al., 2004; Wu et al., 2014). Altogether, these observations suggested us to rank it as a hypo-excitability causing mutation, consistent with the BrS phenotype (loss of function) induced by the homologous Nav1.5 mutation R814Q.

Table 4 and **Figure 2A** summarize the (dys-)functional homology between the equivalent mutant in Nav1.4 and Nav1.5. On the contrary, **Table 5** and **Figure 2B** show that divergent amino acid substitution at the equivalent position leads to some inconsistencies (in red, 5/12). This suggests that the nature of the amino acid substitution is determinant for the direction of the functional net effect (loss or gain of function).

At last, we focused on five equivalent mutations that have been studied extensively in patch-clamp in both Nav1.4 and Nav1.5. **Table 6** shows changes in each biophysical parameter for these mutations. When looking at the direction of the functional effects (gain or loss of function), we observe two major points. First, a strikingly similar functional effect of the same mutations in both channels. Second, all the gain of function mutations leading to hyper-activity/excitability provoke an increase in the persistent current, when measured, suggesting that this mechanism plays a major role in the pathogenesis of Nav channelopathies.

Recently, an omega current has been observed in Nav1.5 mutant channels identified in patients presenting with arrhythmic DCM or MEPPC (Gosselin-Badaroudine et al., 2012b; Moreau et al., 2015b). This omega current, due to mutations of arginine in the S4 of domain I, is similar to the one observed in Nav1.4 (Sokolov et al., 2007; Struyk et al., 2008; Francis et al., 2011; Gosselin-Badaroudine et al., 2012a; Groome et al., 2014). This further strengthens the functional similarity between Nav1.4 and Nav1.5 in pathophysiological situations. A common feature of MEPPC, is an increase in window current provoked by the Nav1.5 R225W, R222Q, and R225P mutations, increasing cardiac excitability of the fascicular-Purkinje system (Laurent et al., 2012; Mann et al., 2012). Another common feature of two of these mutations: R222Q and R225W is the presence of an omega current. This Nav1.5 omega current may be responsible for the peculiar cardiac phenotype (Moreau et al., 2015a), similar to the omega current of Nav1.4 being responsible for the hypoPP phenotype, through sodium accumulation and a decrease in membrane excitability (Sokolov et al., 2008). Indeed, most of the *SCN5A* mutations linked to DCM are located in the voltage sensor domain (VSD) as pointed by McNair

et al. (2011). However, in some cases DCM may be secondary to arrhythmias and window current increase. For instance, preventing arrhythmias by quinidine improved the ventricular function (ejection fraction) in patients with the Nav1.5 R222Q mutation, *via* a decrease in the window sodium current (Laurent et al., 2012). The use of specific inhibitor of the alpha pore and the omega (or gating pore) current would allow to test for the respective role of the altered gating (activation, inactivation) and the omega current on the development of the pathology. Noteworthy, the various localization of the Nav1.4 mutations giving rise to omega current (in domains I, II, and III) strongly suggests that similar mutations in Nav1.5 will be identified in domain II and III in addition to the ones already identified in domain I (Moreau et al., 2015b).

To conclude, given the sequence similarity between Nav1.4 and Nav1.5, any characteristics described for one channel subunit may shed light on the properties of the counterpart channel subunit, such as the presence of specific protein partners, or the effects of a specific amino acid substitution. One can argue that the effect of a mutation on Nav1.4 is difficult to compare with Nav1.5 since the different molecular and cellular environment may drastically modify the effect of the mutation. Nevertheless, we noticed that the same mutation lead to comparable effect regarding membrane hypo or hyper-excitability (**Table 4** and **Figure 2A**). This suggests that the cellular environment is usually not able to invert the effect of a mutation from gain to loss of function phenotypes and reciprocally. Such comparison between Nav1.4 and Nav1.5 will probably draw more and more interest, to address the challenge of interpreting and understanding pathogenicity of rare *SCN4A* or *SCN5A* variants revealed by next-generation sequencing studies (Arnold et al., 2015; Bergareche et al., 2015; Coll et al., 2015).

AUTHOR CONTRIBUTIONS

Parts were written by: Part I : DS, YP, VF (Nav1.4), FC (Nav1.5). Part II: SN (Nav1.4), GT (Nav1.5). Part III: FL, CM. Part IV: DS (Nav1.4), JB, OM, IB, GL (Nav1.5). DS and GL initiated the project. IB, FC, JB, YP critically read the entire Manuscript. GL supervised the Ms.

FUNDING

This work was supported by INSERM, CNRS, the Fondation d'entreprise Génavie, the Fondation pour la Recherche Médicale (PLP20141031304), the Association Française contre les Myopathies - Téléthon (16495), the 7th European Community Framework Programme (PIOF-GA-2011-298280, PIRG06-GA-2009-256397, HEALTH-F2-2009-241526), the ANR (ANR-12-BSV1-0013-01), Investissements d'avenir (ANR-10-IAIHU-06), and Nantes and Sorbonne universities, UPMC-Paris 06.

REFERENCES

Abriel, H. (2010). Cardiac sodium channel Na(v)1.5 and interacting proteins: physiology and pathophysiology. *J. Mol. Cell. Cardiol.* 48, 2–11. doi: 10.1016/j.yjmcc.2009.08.025

Ackerman, M. J., Priori, S. G., Willems, S., Berul, C., Brugada, R., Calkins, H., et al. (2011). 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* 8, 1308–1339. doi: 10.1016/j.hrthm.2011.05.020

Ackerman, M. J., Siu, B. L., Sturner, W. Q., Tester, D. J., Valdivia, C. R., Makielski, J. C., et al. (2001). Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. *JAMA* 286, 2264–2269. doi: 10.1001/jama.286.18.2264

Aiba, T., Farinelli, F., Kostecki, G., Hesketh, G. G., Edwards, D., Biswas, S., et al. (2014). A mutation causing Brugada syndrome identifies a mechanism for altered autonomic and oxidant regulation of cardiac sodium currents. *Circ. Cardiovasc. Genet.* 7, 249–256. doi: 10.1161/CIRCGENETICS.113.000480

Allouis, M., Le Bouffant, F., Wilders, R., Péroz, D., Schott, J. J., Noireaud, J., et al. (2006). 14-3-3 is a regulator of the cardiac voltage-gated sodium channel Nav1.5. *Circ. Res.* 98, 1538–1546. doi: 10.1161/01.RES.0000229244.97497.2c

Amarouch, M. Y., Kasimova, M. A., Tarek, M., and Abriel, H. (2014). Functional interaction between S1 and S4 segments in voltage-gated sodium channels revealed by human channelopathies. *Channels (Austin.)* 8, 414–420. doi: 10.4161/19336950.2014.958922

Amin, A. S. (2014). SCN5A-related dilated cardiomyopathy: what do we know? *Heart Rhythm* 11, 1454–1455. doi: 10.1016/j.hrthm.2014.05.031

Amin, A. S., Pinto, Y. M., and Wilde, A. A. (2013). Long QT syndrome: beyond the causal mutation. *J. Physiol.* 591, 4125–4139. doi: 10.1113/jphysiol.2013.254920

An, R. H., Wang, X. L., Kerem, B., Benhorin, J., Medina, A., Goldmit, M., et al. (1998). Novel LQT-3 mutation affects Na+ channel activity through interactions between alpha- and beta1-subunits. *Circ. Res.* 83, 141–146. doi: 10.1161/01.RES.83.2.141

Antzelevitch, C., Brugada, P., Borggrefe, M., Brugada, J., Brugada, R., Corrado, D., et al. (2005). Brugada syndrome: report of the second consensus conference. *Heart Rhythm* 2, 429–440. doi: 10.1016/j.hrthm.2005.01.005

Antzelevitch, C., Pollevick, G. D., Cordeiro, J. M., Casis, O., Sanguinetti, M. C., Aizawa, Y., et al. (2007). Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 115, 442–449. doi: 10.1161/CIRCULATIONAHA.106.668392

Antzelevitch, C., and Yan, G. X. (2015). J-wave syndromes: brugada and early repolarization syndromes. *Heart Rhythm* 12, 1852–1866. doi: 10.1016/j.hrthm.2015.04.014

Arnold, W. D., Feldman, D. H., Ramirez, S., He, L., Kassar, D., Quick, A., et al. (2015). Defective fast inactivation recovery of Nav 1.4 in congenital myasthenic syndrome. *Ann. Neurol.* 77, 840–850. doi: 10.1002/ana.24389

Arzel-Hézode, M., McGoey, S., Sternberg, D., Vicart, S., Eymard, B., and Fontaine, B. (2009). Glucocorticoids may trigger attacks in several types of periodic paralysis. *Neuromuscul. Disord.* 19, 217–219. doi: 10.1016/j.nmd.2008.12.008

Ashpole, N. M., Herren, A. W., Ginsburg, K. S., Brogan, J. D., Johnson, D. E., Cummins, T. R., et al. (2012). Ca2+/calmodulin-dependent protein kinase II (CaMKII) regulates cardiac sodium channel NaV1.5 gating by multiple phosphorylation sites. *J. Biol. Chem.* 287, 19856–19869. doi: 10.1074/jbc.M111.322537

Awad, S. S., Lightowlers, R. N., Young, C., Chrzanowska-Lightowlers, Z. M., Lomo, T., and Slater, C. R. (2001). Sodium channel mRNAs at the neuromuscular junction: distinct patterns of accumulation and effects of muscle activity. *J. Neurosci.* 21, 8456–8463.

Bai, C. X., Kurokawa, J., Tamagawa, M., Nakaya, H., and Furukawa, T. (2005). Nontranscriptional regulation of cardiac repolarization currents by testosterone. *Circulation* 112, 1701–1710. doi: 10.1161/CIRCULATIONAHA.104.523217

Balasuriya, D., Stewart, A. P., Crottès, D., Borgese, F., Soriani, O., and Edwardson, J. M. (2012). The sigma-1 receptor binds to the Nav1.5 voltage-gated Na+ channel with 4-fold symmetry. *J. Biol. Chem*. 287, 37021–37029. doi: 10.1074/jbc.M112.382077

Beckermann, T. M., McLeod, K., Murday, V., Potet, F., and George, A. L. Jr. (2014). Novel SCN5A mutation in amiodarone-responsive multifocal ventricular ectopy-associated cardiomyopathy. *Heart Rhythm* 11, 1446–1453. doi: 10.1016/j.hrthm.2014.04.042

Bendahhou, S., Cummins, T. R., Griggs, R. C., Fu, Y. H., and Ptácek, L. J. (2001). Sodium channel inactivation defects are associated with acetazolamide-exacerbated hypokalemic periodic paralysis. *Ann. Neurol*. 50, 417–420. doi: 10.1002/ana.1144

Bendahhou, S., Cummins, T. R., Kwiecinski, H., Waxman, S. G., and Ptácek, L. J. (1999). Characterization of a new sodium channel mutation at arginine 1448 associated with moderate Paramyotonia congenita in humans. *J. Physiol.* 518(Pt 2), 337–344. doi: 10.1111/j.1469-7793.1999.0337p.x

Benhorin, J., Goldmit, M., MacCluer, J. W., Blangero, J., Goffen, R., Leibovitch, A., et al. (1998). Identification of a new SCN5A mutation, D1840G, associated with the long QT syndrome. Mutations in brief no. 153. Online. *Hum. Mutat*. 12, 72.

Bergareche, A., Bednarz, M., Sánchez, E., Krebs, C. E., Ruiz-Martinez, J., De La Riva, P., et al. (2015). SCN4A pore mutation pathogenetically contributes to autosomal dominant essential tremor and may increase susceptibility to epilepsy. *Hum. Mol. Genet*. 24, 7111–7120. doi: 10.1093/hmg/ddv410

Béziau, D. M., Barc, J., O'Hara, T., Le, G. L., Amarouch, M. Y., Solnon, A., et al. (2014). Complex Brugada syndrome inheritance in a family harbouring compound SCN5A and CACNA1C mutations. *Basic Res. Cardiol*. 109, 446. doi: 10.1007/s00395-014-0446-5

Bezzina, C., Veldkamp, M. W., van Den Berg, M. P., Postma, A. V., Rook, M. B., Viersma, J. W., et al. (1999). A single Na(+) channel mutation causing both long-QT and Brugada syndromes. *Circ. Res*. 85, 1206–1213. doi: 10.1161/01.RES.85.12.1206

Bezzina, C. R., Barc, J., Mizusawa, Y., Remme, C. A., Gourraud, J. B., Simonet, F., et al. (2013). Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nat. Genet*. 45, 1044–1049. doi: 10.1038/ng.2712

Bezzina, C. R., Rook, M. B., Groenewegen, W. A., Herfst, L. J., van der Wal, A. C., Lam, J., et al. (2003). Compound heterozygosity for mutations (W156X and R225W) in SCN5A associated with severe cardiac conduction disturbances and degenerative changes in the conduction system. *Circ. Res*. 92, 159–168. doi: 10.1161/01.RES.0000052672.97759.36

Bissay, V., Van Malderen, S. C., Keymolen, K., Lissens, W., Peeters, U., Daneels, D., et al. (2015). SCN4A variants and Brugada syndrome: phenotypic and genotypic overlap between cardiac and skeletal muscle sodium channelopathies. *Eur. J. Hum. Genet*. doi: 10.1038/ejhg.2015.125. [Epub ahead of print].

Blair, E. R., Hoffman, H. E., and Bishop, A. C. (2006). Engineering non-natural inhibitor sensitivity in protein tyrosine phosphatase H1. *Bioorg. Med. Chem*. 14, 464–471. doi: 10.1016/j.bmc.2005.08.025

Bouhours, M., Sternberg, D., Davoine, C. S., Ferrer, X., Willer, J. C., Fontaine, B., et al. (2004). Functional characterization and cold sensitivity of T1313A, a new mutation of the skeletal muscle sodium channel causing paramyotonia congenita in humans. *J. Physiol.* 554, 635–647. doi: 10.1113/jphysiol.2003.053082

Brugada, P., and Brugada, J. (1992). 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*. 20, 1391–1396. doi: 10.1016/0735-1097(92)90253-J

Bulman, D. E., Scoggan, K. A., van Oene, M. D., Nicolle, M. W., Hahn, A. F., Tollar, L. L., et al. (1999). A novel sodium channel mutation in a family with hypokalemic periodic paralysis. *Neurology* 53, 1932–1936. doi: 10.1212/WNL.53.9.1932

Burashnikov, E., Pfeiffer, R., Barajas-Martinez, H., Delpón, E., Hu, D., Desai, M., et al. (2010). Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm* 7, 1872–1882. doi: 10.1016/j.hrthm.2010.08.026

Calloe, K., Schmitt, N., Grubb, S., Pfeiffer, R., David, J. P., Kanter, R., et al. (2011). Multiple arrhythmic syndromes in a newborn, owing to a novel mutation in SCN5A. *Can. J. Physiol. Pharmacol*. 89, 723–736. doi: 10.1139/y11-070

Cannon, S. C. (2015). Channelopathies of skeletal muscle excitability. *Compr. Physiol.* 5, 761–790. doi: 10.1002/cphy.c140062

Cannon, S. C., and Strittmatter, S. M. (1993). Functional expression of sodium channel mutations identified in families with periodic paralysis. *Neuron* 10, 317–326. doi: 10.1016/0896-6273(93)90321-H

Carle, T., Fournier, E., Sternberg, D., Fontaine, B., and Tabti, N. (2009). Cold-induced disruption of Na+ channel slow inactivation underlies paralysis in highly thermosensitive paramyotonia. *J. Physiol.* 587, 1705–1714. doi: 10.1113/jphysiol.2008.165787

Carle, T., Lhuillier, L., Luce, S., Sternberg, D., Devuyst, O., Fontaine, B., et al. (2006). Gating defects of a novel Na+ channel mutant causing hypokalemic periodic paralysis. *Biochem. Biophys. Res. Commun*. 348, 653–661. doi: 10.1016/j.bbrc.2006.07.101

Chahine, M., George, A. L. Jr., Zhou, M., Ji, S., Sun, W., Barchi, R. L., et al. (1994). Sodium channel mutations in paramyotonia congenita uncouple inactivation from activation. *Neuron* 12, 281–294. doi: 10.1016/0896-6273(94)90271-2

Chang, C. C., Acharfi, S., Wu, M. H., Chiang, F. T., Wang, J. K., Sung, T. C., et al. (2004). A novel SCN5A mutation manifests as a malignant form of long QT syndrome with perinatal onset of tachycardia/bradycardia. *Cardiovasc. Res*. 64, 268–278. doi: 10.1016/j.cardiores.2004.07.007

Clarke, C., Howard, R., Rossor, M., Shorvon, S. D. (2011). *Neurology: A Queen Square Textbook*. Hoboken, NJ: Wiley Blackwell Publishing Ltd.

Chatin, B., Colombier, P., Gamblin, A. L., Allouis, M., and Le Bouffant, F. (2014). Dynamitin affects cell-surface expression of voltage-gated sodium channel Nav1.5. *Biochem. J*. 463, 339–349. doi: 10.1042/BJ20140604

Coll, M., Allegue, C., Partemi, S., Mates, J., Del, O. B., Campuzano, O., et al. (2015). Genetic investigation of sudden unexpected death in epilepsy cohort by panel target resequencing. *Int. J. Legal Med*. doi: 10.1007/s00414-015-1269-0. [Epub ahead of print].

Crotti, L., Marcou, C. A., Tester, D. J., Castelletti, S., Giudicessi, J. R., Torchio, M., et al. (2012). Spectrum and prevalence of mutations involving BrS1- through BrS12-susceptibility genes in a cohort of unrelated patients referred for Brugada syndrome genetic testing: implications for genetic testing. *J. Am. Coll. Cardiol*. 60, 1410–1418. doi: 10.1016/j.jacc.2012.04.037

Darbar, D., Kannankeril, P. J., Donahue, B. S., Kucera, G., Stubblefield, T., Haines, J. L., et al. (2008). Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. *Circulation* 117, 1927–1935. doi: 10.1161/CIRCULATIONAHA.107.757955

Delpón, E., Cordeiro, J. M., Nunez, L., Thomsen, P. E., Guerchicoff, A., Pollevick, G. D., et al. (2008). Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circ. Arrhythm. Electrophysiol*. 1, 209–218. doi: 10.1161/CIRCEP.107.748103

Deschênes, I., Baroudi, G., Berthet, M., Barde, I., Chalvidan, T., Denjoy, I., et al. (2000). Electrophysiological characterization of SCN5A mutations causing long QT (E1784K) and Brugada (R1512W and R1432G) syndromes. *Cardiovasc. Res*. 46, 55–65. doi: 10.1016/S0008-6363(00)00006-7

Durran, S. C., Matthews, E., Raja Rayan, D. L., Sud, R., Polke, J., Haworth, A., et al. (2011). "Genetic heterogeneity and mechanisms of phenotypic variability in human skeletal muscle channelopathies," in *UK Neuromuscular Translational Research Conference 2011* (London).

Featherstone, D. E., Fujimoto, E., and Ruben, P. C. (1998). A defect in skeletal muscle sodium channel deactivation exacerbates hyperexcitability in human paramyotonia congenita. *J. Physiol.* 506(Pt 3), 627–638. doi: 10.1111/j.1469-7793.1998.627bv.x

Fleischhauer, R., Mitrovic, N., Deymeer, F., Lehmann-Horn, F., and Lerche, H. (1998). Effects of temperature and mexiletine on the F1473S Na+ channel mutation causing paramyotonia congenita. *Pflugers Arch.* 436, 757–765. doi: 10.1007/s004240050699

Foley, K. S., and Young, P. W. (2014). The non-muscle functions of actinins: an update. *Biochem. J*. 459, 1–13. doi: 10.1042/BJ20131511

Fournier, E., Arzel, M., Sternberg, D., Vicart, S., Laforet, P., Eymard, B., et al. (2004). Electromyography guides toward subgroups of mutations in muscle channelopathies. *Ann. Neurol*. 56, 650–661. doi: 10.1002/ana.20241

Fournier, E., Viala, K., Gervais, H., Sternberg, D., Arzel-Hézode, M., Laforet, P., et al. (2006). Cold extends electromyography distinction between ion channel mutations causing myotonia. *Ann. Neurol*. 60, 356–365. doi: 10.1002/ana.20905

Francis, D. G., Rybalchenko, V., Struyk, A., and Cannon, S. C. (2011). Leaky sodium channels from voltage sensor mutations in periodic paralysis, but

not paramyotonia. *Neurology* 76, 1635–1641. doi: 10.1212/WNL.0b013e318219fb57

Frigo, G., Rampazzo, A., Bauce, B., Pilichou, K., Beffagna, G., Danieli, G. A., et al. (2007). Homozygous SCN5A mutation in Brugada syndrome with monomorphic ventricular tachycardia and structural heart abnormalities. *Europace* 9, 391–397. doi: 10.1093/europace/eum053

Frustaci, A., Priori, S. G., Pieroni, M., Chimenti, C., Napolitano, C., Rivolta, I., et al. (2005). Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. *Circulation* 112, 3680–3687. doi: 10.1161/CIRCULATIONAHA.105.520999

Fukudome, T., Izumoto, H., Goto, H., Matsuo, H., Yoshimura, T., Sakoda, S., et al. (2003). Paramyotonia congenita due to a *de novo* mutation: a case report. *Muscle Nerve* 28, 232–235. doi: 10.1002/mus.10396

Gaborit, N., Varro, A., Le, B. S., Szuts, V., Escande, D., Nattel, S., et al. (2010). Gender-related differences in ion-channel and transporter subunit expression in non-diseased human hearts. *J. Mol. Cell Cardiol.* 49, 639–646. doi: 10.1016/j.yjmcc.2010.06.005

Gao, G., and Dudley, S. C. Jr. (2013). RBM25/LUC7L3 function in cardiac sodium channel splicing regulation of human heart failure. *Trends Cardiovasc. Med.* 23, 5–8. doi: 10.1016/j.tcm.2012.08.003

Gao, G., Xie, A., Huang, S. C., Zhou, A., Zhang, J., Herman, A. M., et al. (2011). Role of RBM25/LUC7L3 in abnormal cardiac sodium channel splicing regulation in human heart failure. *Circulation* 124, 1124–1131. doi: 10.1161/CIRCULATIONAHA.111.044495

Gay, S., Dupuis, D., Faivre, L., Masurel-Paulet, A., Labenne, M., Colombani, M., et al. (2008). Severe neonatal non-dystrophic myotonia secondary to a novel mutation of the voltage-gated sodium channel (SCN4A) gene. *Am. J. Med. Genet. A* 146A, 380–383. doi: 10.1002/ajmg.a.32141

Ge, J., Sun, A., Paajanen, V., Wang, S., Su, C., Yang, Z., et al. (2008). Molecular and clinical characterization of a novel SCN5A mutation associated with atrioventricular block and dilated cardiomyopathy. *Circ. Arrhythm. Electrophysiol.* 1, 83–92. doi: 10.1161/CIRCEP.107.750752

Gee, S. H., Madhavan, R., Levinson, S. R., Caldwell, J. H., Sealock, R., and Froehner, S. C. (1998). Interaction of muscle and brain sodium channels with multiple members of the syntrophin family of dystrophin-associated proteins. *J. Neurosci.* 18, 128–137.

Gellens, M. E., George, A. L. Jr., Chen, L. Q., Chahine, M., Horn, R., Barchi, R. L., et al. (1992). Primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel. *Proc. Natl. Acad. Sci. U.S.A.* 89, 554–558. doi: 10.1073/pnas.89.2.554

George, A. L. Jr. (2005). Inherited disorders of voltage-gated sodium channels. *J. Clin. Invest.* 115, 1990–1999. doi: 10.1172/JCI25505

George, A. L. Jr., Knittle, T. J., and Tamkun, M. M. (1992a). Molecular cloning of an atypical voltage-gated sodium channel expressed in human heart and uterus: evidence for a distinct gene family. *Proc. Natl. Acad. Sci. U.S.A.* 89, 4893–4897.

George, A. L. Jr., Komisarof, J., Kallen, R. G., and Barchi, R. L. (1992b). Primary structure of the adult human skeletal muscle voltage-dependent sodium channel. *Ann. Neurol.* 31, 131–137.

Giudicessi, J. R., and Ackerman, M. J. (2013). Genotype- and phenotype-guided management of congenital long QT syndrome. *Curr. Probl. Cardiol.* 38, 417–455. doi: 10.1016/j.cpcardiol.2013.08.001

Giudicessi, J. R., Ye, D., Tester, D. J., Crotti, L., Mugione, A., Nesterenko, V. V., et al. (2011). Transient outward current (I(to)) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. *Heart Rhythm* 8, 1024–1032. doi: 10.1016/j.hrthm.2011.02.021

Gosselin-Badaroudine, P., Delemotte, L., Moreau, A., Klein, M. L., and Chahine, M. (2012a). Gating pore currents and the resting state of Nav1.4 voltage sensor domains. *Proc. Natl. Acad. Sci. U.S.A.* 109, 19250–19255. doi: 10.1073/pnas.1217990109

Gosselin-Badaroudine, P., Keller, D. I., Huang, H., Pouliot, V., Chatelier, A., Osswald, S., et al. (2012b). A proton leak current through the cardiac sodium channel is linked to mixed arrhythmia and the dilated cardiomyopathy phenotype. *PLoS ONE.* 7:e38331. doi: 10.1371/journal.pone.0038331

Green, D. S., George, A. L. Jr., and Cannon, S. C. (1998). Human sodium channel gating defects caused by missense mutations in S6 segments associated with myotonia: S804F and V1293I. *J. Physiol.* 510(Pt 3), 685–694. doi: 10.1111/j.1469-7793.1998.685bj.x

Groome, J. R., Jurkat-Rott, K., and Lehmann-Horn, F. (2014). Domain III S4 in closed-state fast inactivation: insights from a periodic paralysis mutation. *Channels (Austin.)* 8, 467–471. doi: 10.4161/19336950.2014.958924

Hayward, L. J., Brown, R. H. Jr., and Cannon, S. C. (1996). Inactivation defects caused by myotonia-associated mutations in the sodium channel III-IV linker. *J. Gen. Physiol.* 107, 559–576. doi: 10.1085/jgp.107.5.559

Hayward, L. J., Sandoval, G. M., and Cannon, S. C. (1999). Defective slow inactivation of sodium channels contributes to familial periodic paralysis. *Neurology* 52, 1447–1453. doi: 10.1212/WNL.52.7.1447

Hebert, S. L., Simmons, C., Thompson, A. L., Zorc, C. S., Blalock, E. M., and Kraner, S. D. (2007). Basic helix-loop-helix factors recruit nuclear factor I to enhance expression of the NaV 1.4 Na+ channel gene. *Biochim. Biophys. Acta* 1769, 649–658. doi: 10.1016/j.bbaexp.2007.08.004

Heine, R., Pika, U., and Lehmann-Horn, F. (1993). A novel SCN4A mutation causing myotonia aggravated by cold and potassium. *Hum. Mol. Genet.* 2, 1349–1353. doi: 10.1093/hmg/2.9.1349

Hershberger, R. E., Hedges, D. J., and Morales, A. (2013). Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat. Rev. Cardiol.* 10, 531–547. doi: 10.1038/nrcardio.2013.105

Holzherr, B., Lehmann-Horn, F., Kuzmenkina, E., Fan, C., and Jurkat-Rott, K. (2014). A gating model for wildtype and R1448H Nav1.4 channels in paramyotonia. *Acta Myol.* 33, 22–33.

Horga, A., Raja Rayan, D. L., Matthews, E., Sud, R., Fialho, D., Durran, S. C., et al. (2013). Prevalence study of genetically defined skeletal muscle channelopathies in England. *Neurology* 80, 1472–1475. doi: 10.1212/WNL.0b013e31828cf8d0

Horne, A. J., Eldstrom, J., Sanatani, S., and Fedida, D. (2011). A novel mechanism for LQT3 with 2:1 block: a pore-lining mutation in Nav1.5 significantly affects voltage-dependence of activation. *Heart Rhythm* 8, 770–777. doi: 10.1016/j.hrthm.2010.12.041

Iaizzo, P. A., Quasthoff, S., and Lehmann-Horn, F. (1995). Differential diagnosis of periodic paralysis aided by *in vitro* myography. *Neuromuscul. Disord.* 5, 115–124. doi: 10.1016/0960-8966(94)00036-9

Itoh, H., Shimizu, M., Mabuchi, H., and Imoto, K. (2005a). Clinical and electrophysiological characteristics of Brugada syndrome caused by a missense mutation in the S5-pore site of SCN5A. *J. Cardiovasc. Electrophysiol.* 16, 378–383. doi: 10.1046/j.1540-8167.2005.40606.x

Itoh, H., Shimizu, M., Takata, S., Mabuchi, H., and Imoto, K. (2005b). A novel missense mutation in the SCN5A gene associated with Brugada syndrome bidirectionally affecting blocking actions of antiarrhythmic drugs. *J. Cardiovasc. Electrophysiol.* 16, 486–493. doi: 10.1111/j.1540-8167.2005.40711.x

Jespersen, T., Gavillet, B., van Bemmelen, M. X., Cordonier, S., Thomas, M. A., Staub, O., et al. (2006). Cardiac sodium channel Na(v)1.5 interacts with and is regulated by the protein tyrosine phosphatase PTPH1. *Biochem. Biophys. Res. Commun.* 348, 1455–1462. doi: 10.1016/j.bbrc.2006.08.014

Jurkat-Rott, K., Holzherr, B., Fauler, M., and Lehmann-Horn, F. (2010). Sodium channelopathies of skeletal muscle result from gain or loss of function. *Pflugers Arch.* 460, 239–248. doi: 10.1007/s00424-010-0814-4

Jurkat-Rott, K., Mitrovic, N., Hang, C., Kouzmekine, A., Iaizzo, P., Herzog, J., et al. (2000). Voltage-sensor sodium channel mutations cause hypokalemic periodic paralysis type 2 by enhanced inactivation and reduced current. *Proc. Natl. Acad. Sci. U.S.A.* 97, 9549–9554. doi: 10.1073/pnas.97.17.9549

Kallen, R. G., Sheng, Z. H., Yang, J., Chen, L. Q., Rogart, R. B., and Barchi, R. L. (1990). Primary structure and expression of a sodium channel characteristic of denervated and immature rat skeletal muscle. *Neuron* 4, 233–242. doi: 10.1016/0896-6273(90)90098-Z

Kambouris, N. G., Nuss, H. B., Johns, D. C., Tomaselli, G. F., Marban, E., and Balser, J. R. (1998). Phenotypic characterization of a novel long-QT syndrome mutation (R1623Q) in the cardiac sodium channel. *Circulation* 97, 640–644. doi: 10.1161/01.CIR.97.7.640

Kapplinger, J. D., Tester, D. J., Alders, M., Benito, B., Berthet, M., Brugada, J., et al. (2010). An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm* 7, 33–46. doi: 10.1016/j.hrthm.2009.09.069

Kapplinger, J. D., Tester, D. J., Salisbury, B. A., Carr, J. L., Harris-Kerr, C., Pollevick, G. D., et al. (2009). Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION long QT syndrome genetic test. *Heart Rhythm* 6, 1297–1303. doi: 10.1016/j.hrthm.2009.05.021

Kato, K., Makiyama, T., Wu, J., Ding, W. G., Kimura, H., Naiki, N., et al. (2014). Cardiac channelopathies associated with infantile fatal ventricular arrhythmias: from the cradle to the bench. *J. Cardiovasc. Electrophysiol.* 25, 66–73. doi: 10.1111/jce.12270

Ke, Q., Luo, B., Qi, M., Du, Y., and Wu, W. (2013). Gender differences in penetrance and phenotype in hypokalemic periodic paralysis. *Muscle Nerve* 47, 41–45. doi: 10.1002/mus.23460

Keller, D. I., Acharfi, S., Delacrétaz, E., Benammar, N., Rotter, M., Pfammatter, J. P., et al. (2003). A novel mutation in SCN5A, delQKP 1507-1509, causing long QT syndrome: role of Q1507 residue in sodium channel inactivation. *J. Mol. Cell. Cardiol.* 35, 1513–1521. doi: 10.1016/j.yjmcc.2003.08.007

Keller, D. I., Rougier, J. S., Kucera, J. P., Benammar, N., Fressart, V., Guicheney, P., et al. (2005). Brugada syndrome and fever: genetic and molecular characterization of patients carrying SCN5A mutations. *Cardiovasc. Res.* 67, 510–519. doi: 10.1016/j.cardiores.2005.03.024

Koch, M. C., Baumbach, K., George, A. L., and Ricker, K. (1995). Paramyotonia congenita without paralysis on exposure to cold: a novel mutation in the SCN4A gene (Val1293Ile). *Neuroreport* 6, 2001–2004. doi: 10.1097/00001756-199510010-00012

Kraner, S. D., Rich, M. M., Kallen, R. G., and Barchi, R. L. (1998). Two E-boxes are the focal point of muscle-specific skeletal muscle type 1 Na+ channel gene expression. *J. Biol. Chem.* 273, 11327–11334. doi: 10.1074/jbc.273.18.11327

Kraner, S. D., Rich, M. M., Sholl, M. A., Zhou, H., Zorc, C. S., Kallen, R. G., et al. (1999). Interaction between the skeletal muscle type 1 Na+ channel promoter E-box and an upstream repressor element. Release of repression by myogenin. *J. Biol. Chem.* 274, 8129–8136. doi: 10.1074/jbc.274.12.8129

Kuzmenkin, A., Muncan, V., Jurkat-Rott, K., Hang, C., Lerche, H., Lehmann-Horn, F., et al. (2002). Enhanced inactivation and pH sensitivity of Na(+) channel mutations causing hypokalaemic periodic paralysis type II. *Brain* 125, 835–843. doi: 10.1093/brain/awf071

Kyndt, F., Probst, V., Potet, F., Demolombe, S., Chevallier, J. C., Baro, I., et al. (2001). Novel SCN5A mutation leading either to isolated cardiac conduction defect or Brugada syndrome in a large French family. *Circulation* 104, 3081–3086. doi: 10.1161/hc5001.100834

Laurent, G., Saal, S., Amarouch, M. Y., Béziau, D. M., Marsman, R. F., Faivre, L., et al. (2012). Multifocal ectopic Purkinje-related premature contractions: a new SCN5A-related cardiac channelopathy. *J. Am. Coll. Cardiol.* 60, 144–156. doi: 10.1016/j.jacc.2012.02.052

Lee, S. C., Kim, H. S., Park, Y. E., Choi, Y. C., Park, K. H., and Kim, D. S. (2009). Clinical diversity of SCN4A-mutation-associated skeletal muscle sodium channelopathy. *J. Clin. Neurol.* 5, 186–191. doi: 10.3988/jcn.2009.5.4.186

Lehmann-Horn, F., Orth, M., Kuhn, M., and Jurkat-Rott, K. (2011). A novel N440K sodium channel mutation causes myotonia with exercise-induced weakness–exclusion of CLCN1 exon deletion/duplication by MLPA. *Acta Myol.* 30, 133–137.

Lemaillet, G., Walker, B., and Lambert, S. (2003). Identification of a conserved ankyrin-binding motif in the family of sodium channel alpha subunits. *J. Biol. Chem.* 278, 27333–27339. doi: 10.1074/jbc.M303327200

Lerche, H., Heine, R., Pika, U., George, A. L. Jr., Mitrovic, N., Browatzki, M., et al. (1993). Human sodium channel myotonia: slowed channel inactivation due to substitutions for a glycine within the III-IV linker. *J. Physiol.* 470, 13–22. doi: 10.1113/jphysiol.1993.sp019843

Lion-Francois, L., Mignot, C., Vicart, S., Manel, V., Sternberg, D., Landrieu, P., et al. (2010). Severe neonatal episodic laryngospasm due to de novo SCN4A mutations: a new treatable disorder. *Neurology* 75, 641–645. doi: 10.1212/WNL.0b013e3181ed9e96

Liu, C. J., Dib-Hajj, S. D., Renganathan, M., Cummins, T. R., and Waxman, S. G. (2003). Modulation of the cardiac sodium channel Nav1.5 by fibroblast growth factor homologous factor 1B. *J. Biol. Chem.* 278, 1029–1036. doi: 10.1074/jbc.M207074200

Lossin, C., Nam, T. S., Shahangian, S., Rogawski, M. A., Choi, S. Y., Kim, M. K., et al. (2012). Altered fast and slow inactivation of the N440K Nav1.4 mutant in a periodic paralysis syndrome. *Neurology* 79, 1033–1040. doi: 10.1212/WNL.0b013e3182684683

Ma, D., Wei, H., Zhao, Y., Lu, J., Li, G., Sahib, N. B., et al. (2013). Modeling type 3 long QT syndrome with cardiomyocytes derived from patient-specific induced pluripotent stem cells. *Int. J. Cardiol.* 168, 5277–5286. doi: 10.1016/j.ijcard.2013.08.015

Makielski, J. C., Ye, B., Valdivia, C. R., Pagel, M. D., Pu, J., Tester, D. J., et al. (2003). A ubiquitous splice variant and a common polymorphism affect heterologous expression of recombinant human SCN5A heart sodium channels. *Circ. Res.* 93, 821–828. doi: 10.1161/01.RES.0000096652.14509.96

Makita, N., Behr, E., Shimizu, W., Horie, M., Sunami, A., Crotti, L., et al. (2008). The E1784K mutation in SCN5A is associated with mixed clinical phenotype of type 3 long QT syndrome. *J. Clin. Invest.* 118, 2219–2229. doi: 10.1172/jci34057

Makita, N., Bennett, P. B., and George, A. L. Jr. (1996). Molecular determinants of beta 1 subunit-induced gating modulation in voltage-dependent Na+ channels. *J. Neurosci.* 16, 7117–7127.

Makita, N., Horie, M., Nakamura, T., Ai, T., Sasaki, K., Yokoi, H., et al. (2002). Drug-induced long-QT syndrome associated with a subclinical SCN5A mutation. *Circulation* 106, 1269–1274. doi: 10.1161/01.CIR.0000027139.42087.B6

Makita, N., Shirai, N., Nagashima, M., Matsuoka, R., Yamada, Y., Tohse, N., et al. (1998). A de novo missense mutation of human cardiac Na+ channel exhibiting novel molecular mechanisms of long QT syndrome. *FEBS Lett.* 423, 5–9. doi: 10.1016/S0014-5793(98)00033-7

Makiyama, T., Akao, M., Tsuji, K., Doi, T., Ohno, S., Takenaka, K., et al. (2005). High risk for bradyarrhythmic complications in patients with Brugada syndrome caused by SCN5A gene mutations. *J. Am. Coll. Cardiol.* 46, 2100–2106. doi: 10.1016/j.jacc.2005.08.043

Mann, S. A., Castro, M. L., Ohanian, M., Guo, G., Zodgekar, P., Sheu, A., et al. (2012). R222Q SCN5A mutation is associated with reversible ventricular ectopy and dilated cardiomyopathy. *J. Am. Coll. Cardiol.* 60, 1566–1573. doi: 10.1016/j.jacc.2012.05.050

Marfatia, K. A., Harreman, M. T., Fanara, P., Vertino, P. M., and Corbett, A. H. (2001). Identification and characterization of the human MOG1 gene. *Gene* 266, 45–56. doi: 10.1016/S0378-1119(01)00364-X

Matthews, E., Labrum, R., Sweeney, M. G., Sud, R., Haworth, A., Chinnery, P. F., et al. (2009). Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. *Neurology* 72, 1544–1547. doi: 10.1212/01.wnl.0000342387.65477.46

McClatchey, A. I., McKenna-Yasek, D., Cros, D., Worthen, H. G., Kuncl, R. W., DeSilva, S. M., et al. (1992a). Novel mutations in families with unusual and variable disorders of the skeletal muscle sodium channel. *Nat. Genet.* 2, 148–152.

McClatchey, A. I., Van den Bergh, P., Pericak-Vance, M. A., Raskind, W., Verellen, C., McKenna-Yasek, D., et al. (1992b). Temperature-sensitive mutations in the III-IV cytoplasmic loop region of the skeletal muscle sodium channel gene in paramyotonia congenita. *Cell* 68, 769–774.

McNair, W. P., Sinagra, G., Taylor, M. R., Di, L. A., Ferguson, D. A., Salcedo, E. E., et al. (2011). SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. *J. Am. Coll. Cardiol.* 57, 2160–2168. doi: 10.1016/j.jacc.2010.09.084

Méjat, A., Ravel-Chapuis, A., Vandromme, M., and Schaeffer, L. (2003). Synapse-specific gene expression at the neuromuscular junction. *Ann. N.Y. Acad. Sci.* 998, 53–65. doi: 10.1196/annals.1254.008

Mitrovic, N., George, A. L. Jr., Heine, R., Wagner, S., Pika, U., Hartlaub, U., et al. (1994). K(+)-aggravated myotonia: destabilization of the inactivated state of the human muscle Na+ channel by the V1589M mutation. *J. Physiol.* 478(Pt 3), 395–402. doi: 10.1113/jphysiol.1994.sp020260

Mitrovic, N., George, A. L. Jr., Lerche, H., Wagner, S., Fahlke, C., and Lehmann-Horn, F. (1995). Different effects on gating of three myotonia-causing mutations in the inactivation gate of the human muscle sodium channel. *J. Physiol.* 487(Pt 1), 107–114.

Mohammadi, B., Mitrovic, N., Lehmann-Horn, F., Dengler, R., and Bufler, J. (2003). Mechanisms of cold sensitivity of paramyotonia congenita mutation R1448H and overlap syndrome mutation M1360V. *J. Physiol.* 547, 691–698. doi: 10.1113/jphysiol.2002.033928

Mohler, P. J., Rivolta, I., Napolitano, C., LeMaillet, G., Lambert, S., Priori, S. G., et al. (2004). Nav1.5 E1053K mutation causing Brugada syndrome blocks binding to ankyrin-G and expression of Nav1.5 on the surface of cardiomyocytes. *Proc. Natl. Acad. Sci. U.S.A.* 101, 17533–17538. doi: 10.1073/pnas.0403711101

Moreau, A., Gosselin-Badaroudine, P., and Chahine, M. (2015a). Gating pore currents, a new pathological mechanism underlying cardiac arrhythmias

associated with dilated cardiomyopathy. *Channels (Austin.)* 9, 139–144. doi: 10.1080/19336950.2015.1031937

Moreau, A., Gosselin-Badaroudine, P., Delemotte, L., Klein, M. L., and Chahine, M. (2015b). Gating pore currents are defects in common with two Nav1.5 mutations in patients with mixed arrhythmias and dilated cardiomyopathy. *J. Gen. Physiol.* 145, 93–106. doi: 10.1085/jgp.201411304

Moss, A. J. (2002). T-wave patterns associated with the hereditary long QT syndrome. *Card. Electrophysiol. Rev.* 6, 311–315. doi: 10.1023/A:1016301730302

Nair, K., Pekhletski, R., Harris, L., Care, M., Morel, C., Farid, T., et al. (2012). Escape capture bigeminy: phenotypic marker of cardiac sodium channel voltage sensor mutation R222Q. *Heart Rhythm* 9, 1681–1688. doi: 10.1016/j.hrthm.2012.06.029

Napolitano, C., Priori, S. G., Schwartz, P. J., Bloise, R., Ronchetti, E., Nastoli, J., et al. (2005). Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA* 294, 2975–2980. doi: 10.1001/jama.294.23.2975

Nicole, S., and Fontaine, B. (2015). Skeletal muscle sodium channelopathies. *Curr. Opin. Neurol.* 28, 508–514. doi: 10.1097/wco.0000000000000238

Nielsen, M. W., Holst, A. G., Olesen, S. P., and Olesen, M. S. (2013). The genetic component of Brugada syndrome. *Front. Physiol.* 4:179. doi: 10.3389/fphys.2013.00179

Niimura, H., Matsunaga, A., Kumagai, K., Ohwaki, K., Ogawa, M., Noguchi, H., et al. (2004). Genetic analysis of Brugada syndrome in Western Japan: two novel mutations. *Circ. J.* 68, 740–746. doi: 10.1253/circj.68.740

Okuda, S., Kanda, F., Nishimoto, K., Sasaki, R., and Chihara, K. (2001). Hyperkalemic periodic paralysis and paramyotonia congenita—a novel sodium channel mutation. *J. Neurol.* 248, 1003–1004. doi: 10.1007/s004150170059

Ou, Y., Strege, P., Miller, S. M., Makielski, J., Ackerman, M., Gibbons, S. J., et al. (2003). Syntrophin gamma 2 regulates SCN5A gating by a PDZ domain-mediated interaction. *J. Biol. Chem.* 278, 1915–1923. doi: 10.1074/jbc.M209938200

Péréon, Y., Lande, G., Demolombe, S., Nguyen The Tich, S., Sternberg, D., Le, M. H., et al. (2003). Paramyotonia congenita with an SCN4A mutation affecting cardiac repolarization. *Neurology* 60, 340–342. doi: 10.1212/01.WNL.0000042093.96309.5A

Petitprez, S., Tiab, L., Chen, L., Kappeler, L., Rösler, K. M., Schorderet, D., et al. (2008). A novel dominant mutation of the Nav1.4 alpha-subunit domain I leading to sodium channel myotonia. *Neurology* 71, 1669–1675. doi: 10.1212/01.wnl.0000335168.86248.55

Petitprez, S., Zmoos, A. F., Ogrodnik, J., Balse, E., Raad, N., El-Haou, S., et al. (2011). SAP97 and dystrophin macromolecular complexes determine two pools of cardiac sodium channels Nav1.5 in cardiomyocytes. *Circ. Res.* 108, 294–304. doi: 10.1161/CIRCRESAHA.110.228312

Pfahnl, A. E., Viswanathan, P. C., Weiss, R., Shang, L. L., Sanyal, S., Shusterman, V., et al. (2007). A sodium channel pore mutation causing Brugada syndrome. *Heart Rhythm* 4, 46–53. doi: 10.1016/j.hrthm.2006.09.031

Plassart, E., Reboul, J., Rime, C. S., Recan, D., Millasseau, P., Eymard, B., et al. (1994). Mutations in the muscle sodium channel gene (SCN4A) in 13 French families with hyperkalemic periodic paralysis and paramyotonia congenita: phenotype to genotype correlations and demonstration of the predominance of two mutations. *Eur. J. Hum. Genet.* 2, 110–124.

Potet, F., Chagot, B., Anghelescu, M., Viswanathan, P. C., Stepanovic, S. Z., Kupershmidt, S., et al. (2009). Functional Interactions between distinct sodium channel cytoplasmic domains through the action of calmodulin. *J. Biol. Chem.* 284, 8846–8854. doi: 10.1074/jbc.M806871200

Priori, S. G., Napolitano, C., and Schwartz, P. J. (1999). Low penetrance in the long-QT syndrome: clinical impact. *Circulation* 99, 529–533. doi: 10.1161/01.CIR.99.4.529

Priori, S. G., Napolitano, C., Gasparini, M., Pappone, C., Della, B. P., Giordano, U., et al. (2002). Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation* 105, 1342–1347. doi: 10.1161/hc1102.105288

Priori, S. G., Schwartz, P. J., Napolitano, C., Bloise, R., Ronchetti, E., Grillo, M., et al. (2003). Risk stratification in the long-QT syndrome. *N. Engl. J. Med.* 348, 1866–1874. doi: 10.1056/NEJMoa022147

Probst, V., Wilde, A. A., Barc, J., Sacher, F., Babuty, D., Mabo, P., et al. (2009). SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome. *Circ. Cardiovasc. Genet.* 2, 552–557. doi: 10.1161/CIRCGENETICS.109.853374

Ptácek, L. J., George, A. L. Jr., Barchi, R. L., Griggs, R. C., Riggs, J. E., Robertson, M., et al. (1992). Mutations in an S4 segment of the adult skeletal muscle sodium channel cause paramyotonia congenita. *Neuron* 8, 891–897. doi: 10.1016/0896-6273(92)90203-P

Ptácek, L. J., George, A. L. Jr., Griggs, R. C., Tawil, R., Kallen, R. G., Barchi, R. L., et al. (1991). Identification of a mutation in the gene causing hyperkalemic periodic paralysis. *Cell* 67, 1021–1027. doi: 10.1016/0092-8674(91)90374-8

Raja Rayan, D. L., and Hanna, M. G. (2010). Skeletal muscle channelopathies: nondystrophic myotonias and periodic paralysis. *Curr. Opin. Neurol.* 23, 466–476. doi: 10.1097/WCO.0b013e32833cc97e

Remme, C. A., Wilde, A. A., and Bezzina, C. R. (2008). Cardiac sodium channel overlap syndromes: different faces of SCN5A mutations. *Trends Cardiovasc. Med.* 18, 78–87. doi: 10.1016/j.tcm.2008.01.002

Ricker, K., Moxley, R. T. III, Heine, R., and Lehmann-Horn, F. (1994). Myotonia fluctuans. A third type of muscle sodium channel disease. *Arch Neurol.* 51, 1095–1102. doi: 10.1001/archneur.1994.00540230033009

Rivolta, I., Abriel, H., Tateyama, M., Liu, H., Memmi, M., Vardas, P., et al. (2001). Inherited Brugada and long QT-3 syndrome mutations of a single residue of the cardiac sodium channel confer distinct channel and clinical phenotypes. *J. Biol. Chem.* 276, 30623–30630. doi: 10.1074/jbc.M104471200

Rojas, C. V., Neely, A., Velasco-Loyden, G., Palma, V., and Kukuljan, M. (1999). Hyperkalemic periodic paralysis M1592V mutation modifies activation in human skeletal muscle Na+ channel. *Am. J. Physiol.* 276, C259–C266.

Rojas, C. V., Wang, J. Z., Schwartz, L. S., Hoffman, E. P., Powell, B. R., and Brown, R. H. Jr. (1991). A Met-to-Val mutation in the skeletal muscle Na+ channel alpha-subunit in hyperkalaemic periodic paralysis. *Nature* 354, 387–389. doi: 10.1038/354387a0

Rook, M. B., Evers, M. M., Vos, M. A., and Bierhuizen, M. F. (2012). Biology of cardiac sodium channel Nav1.5 expression. *Cardiovasc. Res.* 93, 12–23. doi: 10.1093/cvr/cvr252

Rosenfeld, J., Sloan-Brown, K., and George, A. L. Jr. (1997). A novel muscle sodium channel mutation causes painful congenital myotonia. *Ann. Neurol.* 42, 811–814. doi: 10.1002/ana.410420520

Rossenbacker, T., Carroll, S. J., Liu, H., Kuipéri, C., de Ravel, T. J., Devriendt, K., et al. (2004). Novel pore mutation in SCN5A manifests as a spectrum of phenotypes ranging from atrial flutter, conduction disease, and Brugada syndrome to sudden cardiac death. *Heart Rhythm* 1, 610–615. doi: 10.1016/j.hrthm.2004.07.001

Rougier, J. S., van Bemmelen, M. X., Bruce, M. C., Jespersen, T., Gavillet, B., Apothéloz, F., et al. (2005). Molecular determinants of voltage-gated sodium channel regulation by the Nedd4/Nedd4-like proteins. *Am. J. Physiol. Cell Physiol.* 288, C692–C701. doi: 10.1152/ajpcell.00460.2004

Ruan, Y., Liu, N., Bloise, R., Napolitano, C., and Priori, S. G. (2007). Gating properties of SCN5A mutations and the response to mexiletine in long-QT syndrome type 3 patients. *Circulation* 116, 1137–1144. doi: 10.1161/CIRCULATIONAHA.107.707877

Rüdel, R., Ricker, K., and Lehmann-Horn, F. (1993). Genotype-phenotype correlations in human skeletal muscle sodium channel diseases. *Arch Neurol.* 50, 1241–1248. doi: 10.1001/archneur.1993.00540110113011

Schwartz, P. J., Priori, S. G., Dumaine, R., Napolitano, C., Antzelevitch, C., Stramba-Badiale, M., et al. (2000). A molecular link between the sudden infant death syndrome and the long-QT syndrome. *N. Engl. J. Med.* 343, 262–267. doi: 10.1056/NEJM200007273430405

Schwartz, P. J., Stramba-Badiale, M., Crotti, L., Pedrazzini, M., Besana, A., Bosi, G., et al. (2009). Prevalence of the congenital long-QT syndrome. *Circulation* 120, 1761–1767. doi: 10.1161/CIRCULATIONAHA.109.863209

Shang, L. L., and Dudley, S. C. Jr. (2005). Tandem promoters and developmentally regulated 5′- and 3′-mRNA untranslated regions of the mouse Scn5a cardiac sodium channel. *J. Biol. Chem.* 280, 933–940. doi: 10.1074/jbc.M409977200

Shang, L. L., Pfahnl, A. E., Sanyal, S., Jiao, Z., Allen, J., Banach, K., et al. (2007). Human heart failure is associated with abnormal C-terminal splicing variants in the cardiac sodium channel. *Circ. Res.* 101, 1146–1154. doi: 10.1161/CIRCRESAHA.107.152918

Smits, J. P., Eckardt, L., Probst, V., Bezzina, C. R., Schott, J. J., Remme, C. A., et al. (2002). Genotype-phenotype relationship in Brugada syndrome:

electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. *J. Am. Coll. Cardiol.* 40, 350–356. doi: 10.1016/S0735-1097(02)01962-9

Smits, J. P., Veldkamp, M. W., Bezzina, C. R., Bhuiyan, Z. A., Wedekind, H., Schulze-Bahr, E., et al. (2005). Substitution of a conserved alanine in the domain IIIS4-S5 linker of the cardiac sodium channel causes long QT syndrome. *Cardiovasc. Res.* 67, 459–466. doi: 10.1016/j.cardiores.2005.01.017

Sokolov, S., Scheuer, T., and Catterall, W. A. (2007). Gating pore current in an inherited ion channelopathy. *Nature* 446, 76–78. doi: 10.1038/nature05598

Sokolov, S., Scheuer, T., and Catterall, W. A. (2008). Depolarization-activated gating pore current conducted by mutant sodium channels in potassium-sensitive normokalemic periodic paralysis. *Proc. Natl. Acad. Sci. U.S.A.* 105, 19980–19985. doi: 10.1073/pnas.0810562105

Splawski, I., Shen, J., Timothy, K. W., Lehmann, M. H., Priori, S., Robinson, J. L., et al. (2000). Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation* 102, 1178–1185. doi: 10.1161/01.CIR.102.10.1178

Sternberg, D., Maisonobe, T., Jurkat-Rott, K., Nicole, S., Launay, E., Chauveau, D., et al. (2001). Hypokalaemic periodic paralysis type 2 caused by mutations at codon 672 in the muscle sodium channel gene SCN4A. *Brain* 124, 1091–1099. doi: 10.1093/brain/124.6.1091

Stocksley, M. A., Awad, S. S., Young, C., Lightowlers, R. N., Brenner, H. R., and Slater, C. R. (2005). Accumulation of Nav1 mRNAs at differentiating postsynaptic sites in rat soleus muscles. *Mol. Cell Neurosci.* 28, 694–702. doi: 10.1016/j.mcn.2004.11.015

Struyk, A. F., Markin, V. S., Francis, D., and Cannon, S. C. (2008). Gating pore currents in DIIS4 mutations of NaV1.4 associated with periodic paralysis: saturation of ion flux and implications for disease pathogenesis. *J. Gen. Physiol.* 132, 447–464. doi: 10.1085/jgp.200809967

Struyk, A. F., Scoggan, K. A., Bulman, D. E., and Cannon, S. C. (2000). The human skeletal muscle Na channel mutation R669H associated with hypokalemic periodic paralysis enhances slow inactivation. *J. Neurosci.* 20, 8610–8617.

Sugiura, Y., Makita, N., Li, L., Noble, P. J., Kimura, J., Kumagai, Y., et al. (2003). Cold induces shifts of voltage dependence in mutant SCN4A, causing hypokalemic periodic paralysis. *Neurology* 61, 914–918. doi: 10.1212/01.WNL.0000086820.54065.A0

Swan, H., Amarouch, M. Y., Leinonen, J., Marjamaa, A., Kucera, J. P., Laitinen-Forsblom, P. J., et al. (2014). Gain-of-function mutation of the SCN5A gene causes exercise-induced polymorphic ventricular arrhythmias. *Circ. Cardiovasc. Genet.* 7, 771–781. doi: 10.1161/CIRCGENETICS.114.000703

Takahashi, M. P., and Cannon, S. C. (1999). Enhanced slow inactivation by V445M: a sodium channel mutation associated with myotonia. *Biophys. J.* 76, 861–868. doi: 10.1016/S0006-3495(99)77249-8

Takehara, N., Makita, N., Kawabe, J., Sato, N., Kawamura, Y., Kitabatake, A., et al. (2004). A cardiac sodium channel mutation identified in Brugada syndrome associated with atrial standstill. *J. Intern. Med.* 255, 137–142. doi: 10.1046/j.0954-6820.2003.01247.x

Tan, H. L., Kupershmidt, S., Zhang, R., Stepanovic, S., Roden, D. M., Wilde, A. A., et al. (2002). A calcium sensor in the sodium channel modulates cardiac excitability. *Nature* 415, 442–447. doi: 10.1038/415442a

Tanabe, S., Hata, T., and Hiraoka, M. (1999). Effects of estrogen on action potential and membrane currents in guinea pig ventricular myocytes. *Am. J. Physiol.* 277, H826–H833.

Tarradas, A., Selga, E., Beltran-Alvarez, P., Pérez-Serra, A., Riuro, H., Pico, F., et al. (2013). A novel missense mutation, I890T, in the pore region of cardiac sodium channel causes Brugada syndrome. *PLoS ONE* 8:e53220. doi: 10.1371/journal.pone.0053220

Tester, D. J., Will, M. L., Haglund, C. M., and Ackerman, M. J. (2005). Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. *Heart Rhythm* 2, 507–517. doi: 10.1016/j.hrthm.2005.01.020

Tian, L., Zhu, J. F., and Yang, J. G. (2007). [Gene (SCN5A) mutation analysis of a Chinese family with Brugada syndrome]. *Zhonghua Xin. Xue. Guan. Bing. Za Zhi.* 35, 1122–1125.

Trimmer, J. S., Cooperman, S. S., Tomiko, S. A., Zhou, J. Y., Crean, S. M., Boyle, M. B., et al. (1989). Primary structure and functional expression of a mammalian skeletal muscle sodium channel. *Neuron* 3, 33–49. doi: 10.1016/0896-6273(89)90113-X

Trip, J., Drost, G., Ginjaar, H. B., Nieman, F. H., van der Kooi, A. J., de Visser, M., et al. (2009). Redefining the clinical phenotypes of non-dystrophic myotonic syndromes. *J. Neurol. Neurosurg. Psychiatry* 80, 647–652. doi: 10.1136/jnnp.2008.162396

Tsujino, A., Maertens, C., Ohno, K., Shen, X. M., Fukuda, T., Harper, C. M., et al. (2003). Myasthenic syndrome caused by mutation of the SCN4A sodium channel. *Proc. Natl. Acad. Sci. U.S.A.* 100, 7377–7382. doi: 10.1073/pnas.1230273100

Valdivia, C. R., Ackerman, M. J., Tester, D. J., Wada, T., McCormack, J., Ye, B., et al. (2002). A novel SCN5A arrhythmia mutation, M1766L, with expression defect rescued by mexiletine. *Cardiovasc. Res.* 55, 279–289. doi: 10.1016/S0008-6363(02)00445-5

van Bemmelen, M. X., Rougier, J. S., Gavillet, B., Apothéloz, F., Daidie, D., Tateyama, M., et al. (2004). Cardiac voltage-gated sodium channel Nav1.5 is regulated by Nedd4-2 mediated ubiquitination. *Circ. Res.* 95, 284–291. doi: 10.1161/01.RES.0000136816.05109.89

van den Boogaard, M., Smemo, S., Burnicka-Turek, O., Arnolds, D. E., van de Werken, H. J., Klous, P., et al. (2014). A common genetic variant within SCN10A modulates cardiac SCN5A expression. *J. Clin. Invest.* 124, 1844–1852. doi: 10.1172/JCI73140

van Langen, I. M., Birnie, E., Alders, M., Jongbloed, R. J., Le, M. H., and Wilde, A. A. (2003). The use of genotype-phenotype correlations in mutation analysis for the long QT syndrome. *J. Med. Genet.* 40, 141–145. doi: 10.1136/jmg.40.2.141

Vatta, M., Dumaine, R., Antzelevitch, C., Brugada, R., Li, H., Bowles, N. E., et al. (2002). Novel mutations in domain I of SCN5A cause Brugada syndrome. *Mol. Genet. Metab.* 75, 317–324. doi: 10.1016/S1096-7192(02)00006-9

Veerman, C. C., Wilde, A. A., and Lodder, E. M. (2015). The cardiac sodium channel gene SCN5A and its gene product NaV1.5: Role in physiology and pathophysiology. *Gene* 573, 177–187. doi: 10.1016/j.gene.2015.08.062

Viadero, M. T., Rubín, E., Amigo, T., and González-Lamuño, D. (2011). Three generations of hereditary long-QT syndrome with complete penetrance caused by the p.G316E KCNQ1 mutation. *Pediatr. Cardiol.* 32, 102–104. doi: 10.1007/s00246-010-9821-7

Vicart, S., Sternberg, D., Fontaine, B., and Meola, G. (2005). Human skeletal muscle sodium channelopathies. *Neurol. Sci.* 26, 194–202. doi: 10.1007/s10072-005-0461-x

Vicart, S., Sternberg, D., Fournier, E., Ochsner, F., Laforet, P., Kuntzer, T., et al. (2004). New mutations of SCN4A cause a potassium-sensitive normokalemic periodic paralysis. *Neurology* 63, 2120–2127. doi: 10.1212/01.WNL.0000145768.09934.EC

Wahbi, K., Algalarrondo, V., Bécane, H. M., Fressart, V., Beldjord, C., Azibi, K., et al. (2013). Brugada syndrome and abnormal splicing of SCN5A in myotonic dystrophy type 1. *Arch. Cardiovasc. Dis.* 106, 635–643. doi: 10.1016/j.acvd.2013.08.003

Walsh, R., Peters, N. S., Cook, S. A., and Ware, J. S. (2014). Paralogue annotation identifies novel pathogenic variants in patients with Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. *J. Med. Genet.* 51, 35–44. doi: 10.1136/jmedgenet-2013-101917

Wang, C., Wang, C., Hoch, E. G., and Pitt, G. S. (2011). Identification of novel interaction sites that determine specificity between fibroblast growth factor homologous factors and voltage-gated sodium channels. *J. Biol. Chem.* 286, 24253–24263. doi: 10.1074/jbc.M111.245803

Wang, D. W., Desai, R. R., Crotti, L., Arnestad, M., Insolia, R., Pedrazzini, M., et al. (2007). Cardiac sodium channel dysfunction in sudden infant death syndrome. *Circulation* 115, 368–376. doi: 10.1161/CIRCULATIONAHA.106.646513

Wang, Q., Chen, S., Chen, Q., Wan, X., Shen, J., Hoeltge, G. A., et al. (2004). The common SCN5A mutation R1193Q causes LQTS-type electrophysiological alterations of the cardiac sodium channel. *J. Med. Genet.* 41, e66. doi: 10.1136/jmg.2003.013300

Wang, Q., Li, Z., Shen, J., and Keating, M. T. (1996). Genomic organization of the human SCN5A gene encoding the cardiac sodium channel. *Genomics* 34, 9–16. doi: 10.1006/geno.1996.0236

Wang, Q., Shen, J., Splawski, I., Atkinson, D., Li, Z., Robinson, J. L., et al. (1995). SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 80, 805–811. doi: 10.1016/0092-8674(95)90359-3

Ware, J. S., Walsh, R., Cunningham, F., Birney, E., and Cook, S. A. (2012). Paralogous annotation of disease-causing variants in long QT syndrome genes. *Hum. Mutat.* 33, 1188–1191. doi: 10.1002/humu.22114

Webb, J., and Cannon, S. C. (2008). Cold-induced defects of sodium channel gating in atypical periodic paralysis plus myotonia. *Neurology* 70, 755–761. doi: 10.1212/01.wnl.0000265397.70057.d8

Wu, L., Yong, S. L., Fan, C., Ni, Y., Yoo, S., Zhang, T., et al. (2008). Identification of a new co-factor, MOG1, required for the full function of cardiac sodium channel Nav 1.5. *J. Biol. Chem*. 283, 6968–6978. doi: 10.1074/jbc.M709721200

Wu, L., Zhang, B., Kang, Y., and Wu, W. (2014). Enhanced slow inactivation of the human skeletal muscle sodium channel causing normokalemic periodic paralysis. *Cell Mol. Neurobiol*. 34, 707–714. doi: 10.1007/s10571-014-0052-y

Wu, Q., and Krainer, A. R. (1999). AT-AC pre-mRNA splicing mechanisms and conservation of minor introns in voltage-gated ion channel genes. *Mol. Cell Biol*. 19, 3225–3236. doi: 10.1128/MCB.19.5.3225

Yang, N., Ji, S., Zhou, M., Ptácek, L. J., Barchi, R. L., Horn, R., et al. (1994). Sodium channel mutations in paramyotonia congenita exhibit similar biophysical phenotypes *in vitro*. *Proc. Natl. Acad. Sci. U.S.A.* 91, 12785–12789. doi: 10.1073/pnas.91.26.12785

Yang, P., Kupershmidt, S., and Roden, D. M. (2004). Cloning and initial characterization of the human cardiac sodium channel (SCN5A) promoter. *Cardiovasc. Res*. 61, 56–65. doi: 10.1016/j.cardiores.2003.09.030

Ye, B., Valdivia, C. R., Ackerman, M. J., and Makielski, J. C. (2003). A common human SCN5A polymorphism modifies expression of an arrhythmia causing mutation. *Physiol. Genomics* 12, 187–193. doi: 10.1152/physiolgenomics.00117.2002

Yi, S. D., Meng, S. R., Cui, Y. K., Chen, Z. M., and Peng, J. (2003). [PCR-based site-directed mutagenesis and recombinant expression plasmid construction of a SCN5A mutation (K317N) identified in a Chinese family with Brugada syndrome]. *Di Yi Jun Yi Da Xue Xue Bao* 23, 1139–1142.

Yoshinaga, H., Sakoda, S., Good, J. M., Takahashi, M. P., Kubota, T., Arikawa-Hirasawa, E., et al. (2012). A novel mutation in SCN4A causes severe myotonia and school-age-onset paralytic episodes. *J. Neurol. Sci*. 315, 15–19. doi: 10.1016/j.jns.2011.12.015

Yoshinaga, H., Sakoda, S., Shibata, T., Akiyama, T., Oka, M., Yuan, J. H., et al. (2015). Phenotypic variability in childhood of skeletal muscle sodium channelopathies. *Pediatr. Neurol*. 52, 504–508. doi: 10.1016/j.pediatrneurol.2015.01.014

Young, K. A., and Caldwell, J. H. (2005). Modulation of skeletal and cardiac voltage-gated sodium channels by calmodulin. *J. Physiol.* 565, 349–370. doi: 10.1113/jphysiol.2004.081422

Zeng, Z., Zhou, J., Hou, Y., Liang, X., Zhang, Z., Xu, X., et al. (2013). Electrophysiological characteristics of a SCN5A voltage sensors mutation R1629Q associated with Brugada syndrome. *PLoS ONE* 8:e78382. doi: 10.1371/journal.pone.0078382

Ziane, R., Huang, H., Moghadaszadeh, B., Beggs, A. H., Levesque, G., and Chahine, M. (2010). Cell membrane expression of cardiac sodium channel Na(v)1.5 is modulated by alpha-actinin-2 interaction. *Biochemistry* 49, 166–178. doi: 10.1021/bi901086v

Zicha, S., Moss, I., Allen, B., Varro, A., Papp, J., Dumaine, R., et al. (2003). Molecular basis of species-specific expression of repolarizing K+ currents in the heart. *Am. J. Physiol. Heart Circ. Physiol.* 285, H1641–H1649. doi: 10.1152/ajpheart.00346.2003

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.