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Review article

A catalog of *SCN1A* variants

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Abstract

Over the past 10 years mutations in voltage-gated sodium channels (Na_vs) have become closely associated with inheritable forms of epilepsy. One isoform in particular, $Na_v1.1$ (gene symbol *SCN1A*), appears to be a *superculprit*, registering with more than 330 mutations to date. The associated phenotypes range from benign febrile seizures to extremely serious conditions, such as Dravet's syndrome (SMEI). Despite the wealth of information, mutational analyses are cumbersome, owing to inconsistencies among the $Na_v1.1$ sequences to which different research groups refer. Splicing variability is the core problem: $Na_v1.1$ co-exists in three isoforms, two of them lack 11 or 28 amino acids compared to full-length $Na_v.1.1$. This review establishes a standardized nomenclature for $Na_v1.1$ variants so as to provide a platform from which future mutation analyses can be started without need for up-front data normalization. An online resource – *SCN1A infobase* – is introduced.

Keywords: *SCN1A*; $Na_v1.1$; Na^+ channel; Epilepsy; SMEI; GEFS+; Seizure

1. Introduction

Voltage-gated sodium channels (Na_v) are predestined to play a role in disorders of excitability. Equipped with a sophisticated membrane-potential sensing mechanism, these channels respond to minute voltage reductions by opening their gates and allowing Na^+ to rush into the cells. The resulting depolarization pushes the cell into a positive feedback loop: more Na_v channels open up, and an action-potential is triggered, all within milliseconds. It should come as no surprise that Na_v channel dysfunction creates excitatory havoc. Indeed, abnormal Na_v channel function goes hand-in-hand with various pathologies of heart, muscle, and brain. Cardiac arrhythmias, for example, frequently originate from $Na_v1.5$ defects, as is the case in Brugada syndrome or in type III long QT syndrome [1,2]. Skeletal muscle disorders, on the other hand, may arise from dysfunction of $Na_v1.4$, paramyotonia congenita or hyperkalemic periodic paralysis being only two examples [3], and pain perception appears to be heavily influenced by $Na_v1.9$ [4].

Over the past 10 years, a new branch of these so-called Na_v channelopathies has emerged. In these conditions, neurons spontaneously enter periods of simultaneous firing that interfere or fully prevent normal brain function: patients suffer from recurrent seizures. Essentially all bigger ion-channel groups have been implicated in some way in an epileptic disorder, and one may speculate that a large proportion of the idiopathic epilepsies are indeed, what I propose, *channelepsies* (a contraction of the English word *channel* and the Greek noun *lepsis*, meaning *seizure*, or *to take hold of*, similar to *epilepsy*). Voltage-gated sodium channels have gained special interest in the epilepsy field, owing to an unusually close connection with febrile seizures. One isoform in particular, $Na_v1.1$ (gene symbol *SCN1A*), appears to be an epilepsy *superculprit* as a continuing wave of publications produces an ever-expanding array of variants with phenotypes ranging from benign to extremely severe. Despite a wealth of information on

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the different mutations in *SCN1A*, there is presently no platform that would allow for an all-encompassing genotype–phenotype analysis, because a comprehensive catalog or review that brings together all published information is not available. A further complication is the lack of uniform mutation nomenclature, with different groups reporting their findings in reference to different $Na_v1.1$ splice variants. There are also some mutation reports with ambiguities in themselves, leaving it uncertain as to what part of the given information is correct. In all, no less than 63 of the *SCN1A* variants collected here could be interpreted in more ways than one (Table 5 and Online Table 1). The purpose of this review is to compile an up-to-date, standardized mutation database that will facilitate future work with $Na_v1.1$ mutations. To provide the proper context for further discussion, I will introduce some Na_v channel basics to lead into specific characteristics for $Na_v1.1$.

Table 1
Differences in amino acid coding between mutually exclusive exons 5N and 5A

ORF position	Exon			Topology
	5A (adult)		5N (neonatal)	
201	Tyr (Y)	⇨	Phe (F)	D1/S3
207	Asp (D)	⇨	Asn (N)	D1/S3-S4ex
211	Val (V)	⇨	Phe (F)	D1/S3-S4ex

Taken from Copley et al. [41].
Topology abbreviations as described in Table 2.

2. Na_v channel structure and function

Voltage-gated sodium channels set themselves apart with very large α subunit peptide chains in the order of 2000 amino acids. Hydrophobicity plotting predicts 24 transmembrane regions, with the N-terminus and the C-terminus directed toward the cell's interior. Closer sequence examination reveals the 4×6 architecture typical for these channels, organized in four homologous domains (D1–D4) that comprise six transmembrane regions each (S1–S6 left to right, Fig. 1A).

Functionally, Na_v channels are responsible for action-potential initiation. Slight changes in the cytosolic membrane-potential are registered by a channel-internal sensing mechanism involving positively charged residues in the S4 transmembrane regions. A depolarization exerts an electromotive force, pushing the S4 basic residues toward the outside, which in turn invokes conformational rearrangements of the *activation* gate that render

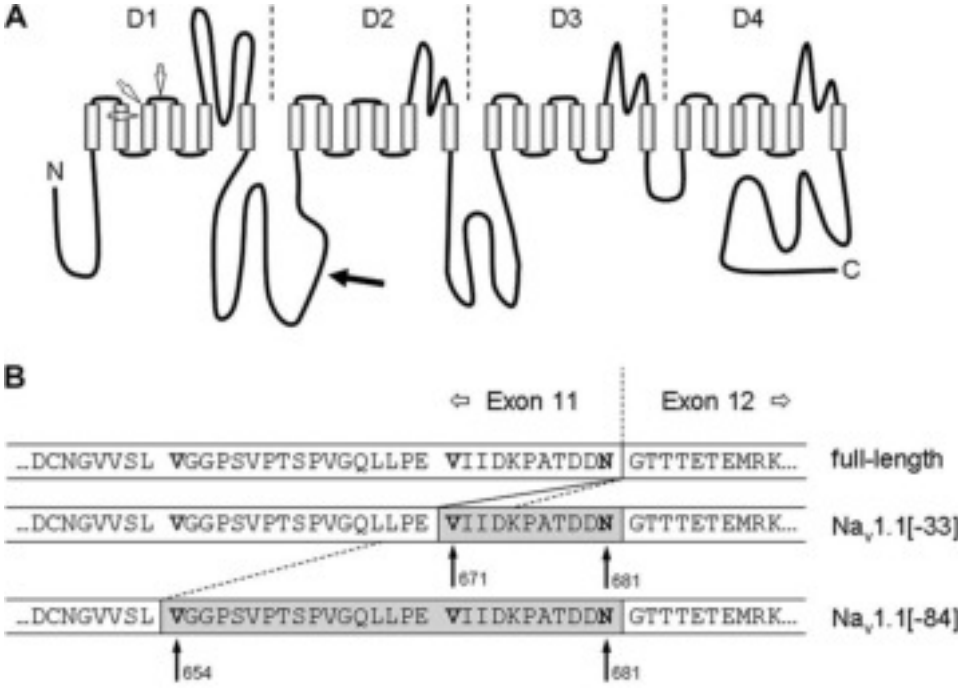

Fig. 1. Variable splicing of $Na_v1.1$. (A) Predicted membrane topology of $Na_v1.1$ with the 4×6 organization typical for voltage-gated sodium channels, namely four homologous domains (D1–D4) comprising six transmembrane regions each (S1–S6, from left to right). Amino- and carboxy termini end on the intracellular side. Arrows denote where differential splicing creates sequence variability in the final protein. Solid arrow: point where splice variants lack either 11 or 28 amino acids compared to full-length $Na_v1.1$. Open arrows: amino acid differences owing to alternate encoding via exon 5N or 5A [41] as outlined in Table 1. (B) Alignment of the full-length $Na_v1.1$ protein sequence with that of $Na_v1.1[-33]$ and $Na_v1.1[-84]$ at the exon 11/12 splice junction. Alternative endings of exon 11 create two shorter variants which omit residues 671–681 or 654–681. The isoform nomenclature refers to the nucleic acid level: compared to full-length $Na_v1.1$ cDNA, the shorter isoforms miss 33 or 84 base pairs. Biochemical and electrophysiological analysis suggest a functional importance of the spliced fragments (personal observation).

the ion-pore temporarily conducting. Within milliseconds, the pore is closed by an *inactivation* gate – the intracellular linker between D3 and D4 – which swings in front of the internal mouth of the pore. This so-called *fast inactivation* is unconditional and not dependent on voltage – a physiological necessity as sustained influx of Na^+ would otherwise continually depolarize (i.e., excite) the cell, effectively preventing it from repolarizing and coming to rest. Any alteration of the finely tuned kinetics that determine the gating of these channels can have decisive impact on cellular excitability. Depending on the spatial and temporal expression pattern of the Na_v channel both, gain- and loss-of-function, are a possible and plausible cause for an excitatory imbalance.

Often overseen is that the α subunits do not act independently. In fact, Na_v channel function is heavily regulated by "auxiliary" β subunits (gene symbols *SCN1B* through *SCN4B*) that determine the subcellular location of the Na_v channel complex [5,6] and modulate the current *per se* [7]. The size of the β subunits makes it easy to underestimate their importance: they are much smaller, spanning the cytoplasmic membrane only once, with the exception of a comparatively big and functionally important extracellular loop [8]. Early Na_v research showed that multiple β subunits bind to one α subunit [9,10].

3. The Na_v channel family and epilepsy

Five different Na_v channel isoforms exist in the nervous system: $Na_v1.1$, $Na_v1.2$ $Na_v1.3$, $Na_v1.6$, $Na_v1.7$ [11]. In the context of epilepsy, $Na_v1.7$ is of lesser importance as its expression is essentially limited to peripheral neurons [12,13]; all other isoforms are found in the brain. Not surprising, association with epilepsy is common [14–17]. Similar data exist for the β subunits, and two of them, β_1 and β_2, have already been implicated in epilepsy [18–20]. However, the main focus of the research community remains with the α subunits, although some rightfully point out that lack of α–β interaction or β dysfunction in itself may play a role in seizure generation [21,22]. Indeed, Na_v channels only entered the epilepsy scene when β_1 (*SCN1B*) was initially found to be mutated in patients with febrile seizures [23].

4. $Na_v1.1$. channelepsies and other neurological phenotypes

Within the family of voltage-gated sodium channels, the most researched contender in terms of epilepsy association is $Na_v1.1$. After the β_1 subunit, it was the second Na_v channel component to be linked to central hyperexcitability [14]. Two amino acid exchanges, T875M and R1648H, made their carriers susceptible to generalized epilepsy with febrile seizures plus or GEFS+ (OMIM 604233), whose existence as a separate entity only shortly before had been recognized, owing in part to an extremely diverse phenotype [24,25]. Patients present symptoms similar to classical febrile seizures, with the difference that the condition continues beyond age 5 in an extended spectrum that may also include afebrile seizures.

Soon after the publication of the *SCN1A*-GEFS+ linkage, Claes and colleagues tied *SCN1A* mutations to a second, devastating type of epilepsy [26]. Dravet's syndrome or severe myoclonic epilepsy in infancy – SMEI (OMIM 607208) is a crippling intractable encephalopathy that begins early in life, commonly within the first 12 months. Affected children develop normally up to their first seizure (usually a prolonged, fever-induced unilateral or generalized clonus), with their development beginning to deteriorate soon thereafter. Myoclonias follow, in some cases accompanied by absence seizures, or less frequently, complex partial seizures. Convulsion-induced status epilepticus is common. The prognosis for children suffering from SMEI is somber, since many cases are entirely resistant to pharmacological intervention. Secondary neuronal damage leads to retardation and psychomotor decline; 1 in 5 children dies [27,28]. The clinical picture of SMEI is not clear-cut: patients may present all but one critical diagnostic criterion, which has prompted a re-categorization within the SMEI spectrum for the subgroup of *borderline SMEI* or SMEB [29,30]. Within the SMEB pool further classifications may be warranted, as patients commonly share similarities with regards to the missing components [31]. There is also an ongoing debate about yet another separate phenotype designated as *intractable childhood epilepsy with generalized tonic–clonic seizures* or ICEGTC, although the criteria appear to be largely reminiscent of SMEB [32,33]. In rare cases, researchers have found *SCN1A* mutations in patients with cryptogenic focal or generalized epilepsy [31,34], West syndrome [35], and Lennox–Gastaut syndrome [31]. Genetic abnormalities in *SCN1A* have also been reported in non-epileptic conditions, such as migraine and autism [36–38].

5. *SCN1A* genomic organization and splicing variability

$Na_v1.1$ is encoded by *SCN1A*, an 81-kb gene on the long arm of chromosome 2. Situated at position 2q24.3, *SCN1A* is part of a cluster of voltage-gated sodium channel genes that is home to *SCN2A, SCN3A, SCN7A*, as well as *SCN9A*, which encode $Na_v1.2$, $Na_v1.3$, Na_x, and $Na_v1.7$, respectively [39]. Organized into 26 exons, the $Na_v1.1$ open-reading frame blueprints the instructions for a protein incorporating between 1976 and 2009 amino acids. The variance in length stems from alternative splice junctions at the end of exon 11 that produce a full-length isoform or two shortened versions thereof [40], from hereon referred to as $Na_v1.1[-33]$ and $Na_v1.1[-84]$ based on the number of

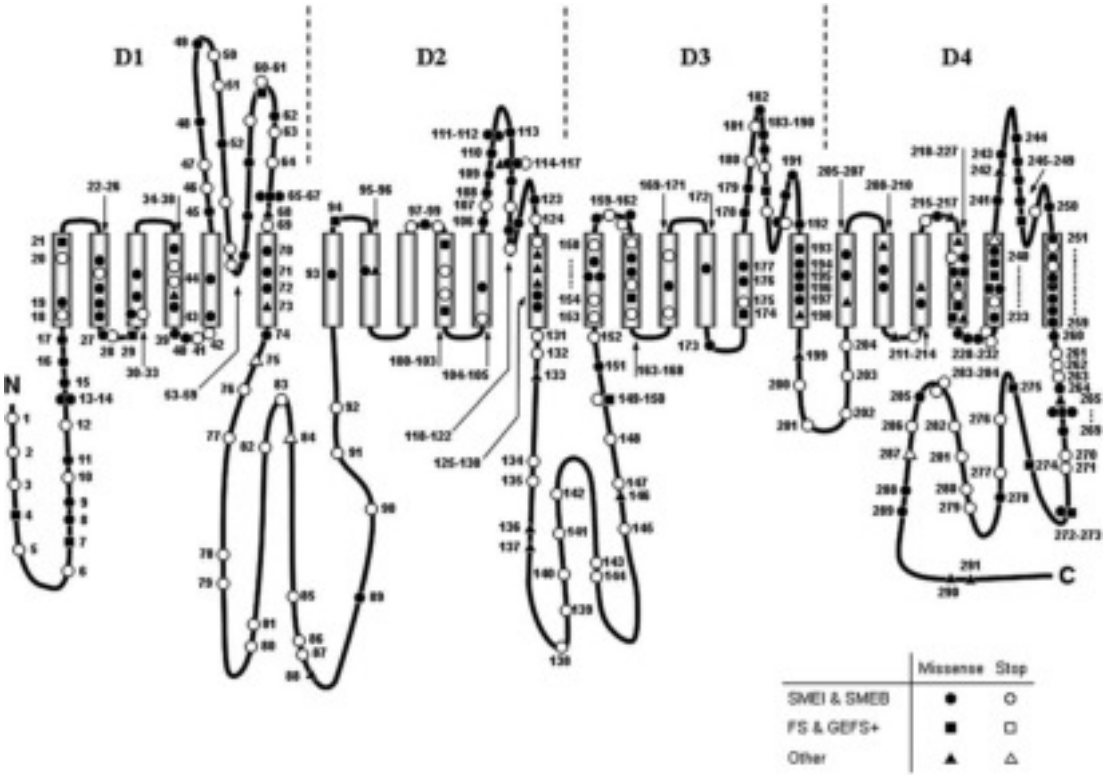

Fig. 2. Mutation map for $Na_v1.1$. Two dimensional rendering of the $Na_v1.1$ protein with all currently reported exonic mutations at their approximate location. Topology based on Escayg and colleagues [14]. For the sake of clarity, SMEI and SMEB phenotypes (e.g., SMEB-O, SMEB-M, aSMEI, etc.) were combined and drawn as circles on the basis of their phenotypic similarity. Benign febrile epilepsy types, GEFS+ and FS, are depicted as squares. Mutations causing epilepsy or neurological disorders not falling into the previous two categories are shown as triangles. The numbering of the mutations corresponds to Table 2. Open symbols highlight mutations that generate non-sense truncated $Na_v1.1$.

base pairs deleted (Fig. 1B). This splicing variability is the cause for the inconsistencies in mutation reports across different research groups, as some are referring to full-length $Na_v1.1$, while others reference $Na_v1.1[-33]$, which is approximately 15 times more abundant in the brain (personal observation). References to $Na_v1.1[-84]$, other than the original report, do not exist at this time (see Fig. 1).

A second site of *SCN1A* RNA processing variability was identified by Copley, who discovered two mutually exclusive exons, 5N and 5A, that give rise to a post-natal and an adulthood isoform of $Na_v1.1$ [41]. While unique at the nucleic acid level (71% identity), the amino-residue coding of these two alternative exons is nearly identical, differing only in three positions (90% identity, Table 1). A similar situation may exist in exon 8 in analogy to murine $Na_v1.6$ [42]; the required genomic sequence analyses have not been conducted at this time. In the following, I will refer to full-length $Na_v1.1$ that incorporates adult exon 5A coding unless indicated otherwise.

6. Mutation data collection

Genetic data were collected from published material as referenced. This includes original journal reports listed in the Public Library of Medicine (National Institute for Biotechnology Information, NCBI at http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed), as well as information gathered from published abstracts. In some cases, unpublished variants were included that were mentioned in personal communications. Several exonic single-nucleotide polymorphisms (SNPs) were taken from the NCBI Entrez Gene web site, GeneID 6323 (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6323). Not included were conservative base pair polymorphisms with no effect on amino acid coding. The possible shortcoming of the latter limitation is discussed in more detail below.

7. Nomenclature standardization

Allelic variations are named according to the full-length, 2009-residue sequence of human $Na_v1.1$ (UniProt Accession No. P35498, http://www.pir.uniprot.org). Mutations referring to shorter isoforms were accordingly adjusted (e.g., formerly: R701X; now: R712X). All exonic alterations are described using a non-standard but self-explanatory method that avoids redundancies (e.g., c.240A>C vs. A240C) and ambiguities (c.333insC *vs.* 333[C]334ins) of more traditional descriptions (http://www.hgvs.org/mutnomen/). In all

Table 2
Exonic mutations of the voltage-gated sodium channel $Na_v1.1$-epilepsies and other neurological disorders

No.	AA level	NA level	Exon	Topology	Phenotype	Reference
1	Q3X	C7T	1	N-terminus	SMEI	[68]
2	F14fsX91	[T]41del	1	N-terminus	SMEI	[31]
3	E20X	G58T	1	N-terminus	SMEI	[69]
4	R28C	C82T	1	N-terminus	GEFS+	A. George, unpublished data
5	P37fsX91	[C]111del	1	N-terminus	SMEI	[35]
6	Y65X	T195A	1	N-terminus	SMEI	[70]
7	S74P	T220C	1	N-terminus	FS	[52]
8	E78D	G234T	1	N-terminus	SMEI	[47]
9	D79H	G235C	1	N-terminus	SMEB-O	[31]
10	Y83X	C249G	1	N-terminus	SMEI	[47]
11	Y84C	A251G	1	N-terminus	SMEI	[31]
12	N94X	[TT]277-278del	2	N-terminus	SMEI	[45]
13	R101W	C301T	2	N-terminus	SMEI	[31]
14	R101Q	G302A	2	N-terminus	SMEB	[30]
15	S103G	A307G	2	N-terminus	SMEI	[33]
16	T112I	C335T	2	N-terminus	SMEI	[33]
17	R118S	G354C	2	N-terminus	SMEI	[70]
18	S128X	C383A	2	D1/S1	SMEI	[47]
19	[L]129del	[ATT]387-389del	3	D1/S1	SMEI	[45]
20	V143fsX148	[GT]429-430del	3	D1/S1	SMEI	[30]
21	M145T	T434C	3	D1/S1	FS	[71]
22	T162P	A484C	4	D1/S2	SMEI	[45]
23	Y165X	T495A	4	D1/S2	SMEI	[47]
24	T166fsX170	495[GTGAATC]496ins	4	D1/S2	SMEI	[31]
25	I171K	T512A	4	D1/S2	SMEB-SW	[31]
26	A175T	G523A	4	D1/S2	SMEB-O	[31]
27	G177E	G530A	4	D1/S2-S3in	SMEI	[47]
28	G177fsX180	[G]530del	4	D1/S2-S3in	SMEI	[33]
29	D188V	A563T	4	D1/S2-S3in	GEFS+	[72]
30	W190R	T568C	4	D1/S3	SMEI	[73]
31	W190X	G570A	4	D1/S3	SMEI	[52]
32	D194N	G580A	4	D1/S3	SMEI	[45]
33	T199R	C596G	4	D1/S3	SMEB-SW	[31]
34	T217K	C650A	5	D1/S4	SMEI	[45]
35	S219fsX275	[AG]657-658del	5	D1/S4	SMEI	[26]
36	R222X	C664T	5	D1/S4	SMEI	[26]
37	T226M	C677T	5	D1/S4	CGE	[31]
38	I227S	T680G	5	D1/S4	SMEI	[47]
39	A239T	G715A	6	D1/S4-S5in	SMEB-SW	[31]
40	V244L	G730T or G730C	6	D1/S4-S5in	SMEI	[74]
41	V244fsX275	[GT]731-732 del	6	D1/S4-S5in	SMEI	[52]
42	K246X	A736T	6	D1/S4-S5in	SMEI	[74]
43	I252N	T755A	6	D1/S5	SMEI	[69]
44	G265W	G793T	6	D1/S5	SMEI	[33]
45	W280R	T838C	6	P1	SMEI	[47]
46	A285fsX290	[CTTC]854-857del	6	P1	SMEI	[47]
47	E289X	G865T	6	P1	SMEI	[47]
48	T297I	C890T	6	P1	SMEI	[47]
49	R322I	G965T	6	P1	SMEI	[52]
50	Y323X	T969A	7	P1	SMEI	[45]
51	L331fsX339	992[T]993ins	7	P1	SMEI	[45]
52	G343E	G1028A	7	P1	aSMEI	[33]
53	G348X	G1042T	8	P1	SMEI	[45]
54	M350fsX355	[AT]1048-1049del	8	P1	SMEI	[31]
55	V352fsX355	[TG]1055-1056del	8	P1	SMEI	[31]
56	R356G	A1066G	8	P1	SMEB	[52]
57	P358T	C1072A	8	P1	SMEB	[52]
58	D366E	T1098A	8	P1	SMEI	[70]
59	S374fsX378	[C]1121del	8	P1	SMEI	[47]
60	R377X	C1129T	8	P1	SMEI	[45]
61	R377Q	G1130A	8	P1	GEFS+	[70]
62	F383L	C1149G	8	P1	SMEI	[45]

Table 2 (*continued*)

No.	AA level	NA level	Exon	Topology	Phenotype	Reference
63	W384X	G1152A	8	P1	SMEB	[75]
64	Q389X	C1165T	8	P1	SMEI	[47]
65	R393S	C1177A	9	P1	SMEI	[45]
66	R393C	C1177T	9	P1	SMEI	[45]
67	R393H	G1178A	9	P1	SMEI	[68]
68	A395P	G1183C	9	P1	CGE	[31]
69	Y399X	C1197A	9	P1	SMEI	[31]
70	[M]400del	[ATG]1198-120del	9	D1/S6	SMEI	[69]
71	F403L	T1207C	9	D1/S6	SMEI	[75]
72	Y413N	T1237A	9	D1/S6	SMEI	[75]
73	V422E	T1265A	9	D1/S6	CGE	[31]
74	Y426N	T1276A	9	L1	SMEI	[47]
75	L433fsX449	1299[C]1300ins	9	L1	MAE	[60]
76	E435X	G1303T	9	L1	SMEI	[30]
77	I448X	[ATTGAACAGCT] 1342-1352del	9	L1	SMEI	[35]
78	R501fsX543	[G]1502del	10	L1	SMEI	[76]
79	R542X	C1624T	10	L1	SMEI	[45]
80	K547fsX570	1640[A]1641ins	10	L1	SMEI	[76]
81	K547fsX569	[AA]1639-1640del	10	L1	SMEI	[31]
82	F563fsX622	[C]1687del	11	L1	SMEI	[31]
83	R568X	C1702T	11	L1	SMEI	[76]
84	F575fsX622	[T]1724del	11	L1	CFE	[31]
85	S607fsX622	[C]1820del	11	L1	SMEI	[76]
86	R613X	C1837T	11	L1	SMEI	[45]
87	S620fsX624	1857[GCAAC]1858ins	11	L1	SMEB	[52]
88	S626G	A1876G	11	L1	CGE	[31]
89	D674G	A2021G	11	L1	SMEI	[31]
90	P707fsX715	2118[AA]2119ins	12	L1	SMEI	[76]
91	R712X	C2134T	12	L1	SMEI	[77]
92	Q732fsX749	2196[CACCCGT]2197ins	13	L1	SMEI	[33]
93	L783P	T2348C	13	L1	SMEI	[31]
94	Y790C	A2369G	13	D2/S1-S2ex	GEFS+, PS	[78]
95	T808S	A2422T	14	D2/S2	ICEGTC	[33]
96	T808R	C2435G	14	D2/S2	SMEI	[45]
97	G854fs876X	[G]2561del	14	D2/S3-S4ex	SMEI	[79]
98	E853K	G2536A	14	D2/S3-S4ex	SMEI	[45]
99	G854fsX876	[A]2562del	14	D2/S3-S4ex	SMEI	[31]
100	R859C	C2575T	14	D2/S4	GEFS+	[80]
101	R865X	C2593T	15	D2/S4	SMEI	[81]
102	A870fsX874	[GCAAAAT]2608-2614del	15	D2/S4	SMEI	[52]
103	T875M	C2624T	15	D2/S4	GEFS+	[14]
104	L893X	T2678A	15	D2/S5	SMEI	[45]
105	F902C	T2705G	15	D2/S5	SMEI	[76]
106	R931C	C2791T	15	P2	SMEI	[76]
107	W932X	G2796A	15	P2	SMEI	[68]
108	M934I	G2802C or G2802A	15	P2	SMEB	[30]
109	H939Q	C2817G	15	P2	SMEI	[68]
110	L942P	T2825C	15	P2	SMEI	[45]
111	V944A	T2831C	15	P2	SMEB	[30]
112	V944E	T2831A	15	P2	SMEI	[31]
113	F945L	T2833C	15	P2	SMEI	[31]
114	R946C	C2836T	15	P2	SMEB	[30]
115	R946H	G2837A	15	P2	SMEB	[30]
116	R946S	C2836A	15	P2	SIGEI	[60]
117	R946fsX953	[C]2835del	15	P2	SMEI	[33]
118	G950E	G2849A	15	P2	SMEI	[31]
119	W952X	G2855A	15	P2	SMEI	[33]
120	W957L	G2870T	15	P2	SMEI	[52]
121	D958fsX973	[C]2874del	15	P2	SMEI	[77]
122	C959R	T2875C	15	P2	SMEI	[68]
123	M960V	A2878G	15	P2	SMEI	[33]
124	Q965X	C2893T	15	P2	SMEI	[31]

(*continued on next page*)

Table 2 (*continued*)

No.	AA level	NA level	Exon	Topology	Phenotype	Reference
125	T970fsX972	[CATG]2916-2919del	15	D2/S6	SMEI	[45]
126	M973V	A2917G	15	D2/S6	CGE	[31]
127	G979R	G2935A	15	D2/S6	ICEGTC	[33]
128	V983A	T2948C	16	D2/S6	ICEGTC	[33]
129	N985I	A2954T	16	D2/S6	SMEI	[33]
130	L986F	C2956T	16	D2/S6	SMEI	[26]
131	A1002fsX1009	[C]3006del	16	L2	SMEI	[76]
132	E1008X	G3022T	16	L2	SMEB-SW	[31]
133	N1011I	A3032T	16	L2	ICEGTC	[33]
134	K1027X	A3079T	16	L2	SMEI	[76]
135	E1032fsX1045	[A]3096del	16	L2	SMEI	[31]
136	I1034T	T3101C	16	L2	FA	[36]
137	F1038L	C3114 G or A	16	L2	FA	[36]
138	K1058fs1078X	[AAGA]3173-3176del	16	L2	SMEI	[45]
139	H1065fsX1073	[TA]3195-3196del	16	L2	SMEI	[47]
140	K1077fsX1079	[A]3231del	16	L2	SMEB	[75]
141	T1082fsX1086	[C]3245del	16	L2	SMEI	[76]
142	E1099X	G3295T	16	L2	SMEI	[45]
143	S1100fsX1107	3299[AA]3300ins	16	L2	SMEI	[26]
144	P1116fsX1119	[C]3347del	16	L2	SMEI	[52]
145	G1154fsX1163	[T]3462del	17	L2	SMEI	[31]
146	T1174S	C3521G	17	L2	FHM	[37]
147	L1175fsX1182	[TT]3524-3525del	17	L2	SMEI	[30]
148	Q1187fsX1215	[AA]3561-3562del	18	L2	SMEI	[31]
149	W1204X	G3611A	18	L2	SMEI	[82]
150	W1204R	T3610C	18	L2	GEFS+	[83]
151	L1207P	T3620C	18	L2	SMEI	[70]
152	R1213X	C3637T	18	L2	SMEI	[33]
153	I1214X	[TA]3641-3642del	18	D3/S1	SMEI	[47]
154	V1215X	3642[TA]3643ins	18	D3/S1	SMEI	[47]
155	S1231R	T3693A	18	D3/S1	SMEI	[33]
156	S1231T	G3692C	18	D3/S1	SMEI	[84]
157	G1233R	G3697C	18	D3/S1	SMEI	[47]
158	L1235fsX1244	[G]3705del, 3704 [20-bp]3705ins	18	D3/S1	SMEI	[45]
159	E1238D	A3714C	19	D3/S1-S2ex	SMEI	[75]
160	I1242fsX1270	3726[AT]3727ins	19	D3/S1-S2ex	SMEI	[52]
161	R1245Q	G3734A	19	D3/S1-S2ex	SMEI	[45]
162	R1245X	C3733T	19	D3/S1-S2ex	SMEI	[47]
163	V1257fsX1269	[T]3774del	19	D3/S2	SMEI	[70]
164	F1263L	C3789G	19	D3/S2	aSMEI	[33]
165	L1265P	T3794C	19	D3/S2	SMEI	[76]
166	L1269fsX1292	[A]3774del	19	D3/S2	SMEI	[70]
167	K1270T	A3809C	19	D3/S2	GEFS+	[85]
168	W1271X	G3812A	19	D3/S2	SMEI	[76]
169	W1284X	G3852A	19	D3/S3	SMEI	[33]
170	[F]1289del	[CTT]3867-3869del	19	D3/S3	SMEI	[76]
171	D1293fsX1299	[A]3878del	19	D3/S3	SMEI	[52]
172	A1326P	G3976C	20	D3/S4	SMEI	[35]
173	V1335M	G4003A	21	D3/S4-S5in	SMEI	[70]
174	V1353L	G4057C	21	D3/S5	GEFS+	[72]
175	C1354fsX1359	[T]4062del	21	D3/S5	SMEI	[75]
176	L1355P	T4064C	21	D3/S5	SMEB	[30]
177	W1358S	G4073C	21	D3/S5	SMEI	[70]
178	V1390M	G4168A	21	P3	SMEI	[76]
179	C1396G	T4186G	21	P3	SMEB	[75]
180	R1407X	C4219T	21	P3	SMEI	[77]
181	W1408X	G4223A	21	P3	SMEI	[33]
182	N1414Y	A4240T	21	P3	SMEI	[52]
183	Y1422C	A4265G	21	P3	SMEI	[45]
184	L1426R	T4277G	21	P3	SMEI	[45]
185	Q1427X	C4279T	21	P3	SMEB-SW	[31]
186	V1428A	C4283T	21	P3	GEFS+	[86]

Table 2 (*continued*)

No.	AA level	NA level	Exon	Topology	Phenotype	Reference
187	A1429fsX1443	[CCACA]4286-4290del, [ATGTCC]ins	22	P3	SMEI	[76]
188	W1434R	T4300C	22	P3	SMEI	[76]
189	W1434X	G4301A	22	P3	SMEI	[70]
190	A1441P	G4321C	22	P3	SMEI	[31]
191	Q1450R	A4349G	23	P3	SMEI	[76]
192	P1451L	C4352T	23	P3	SMEI	[45]
193	L1461I	C4381A	23	D3/S6	SMEI	[47]
194	Y1462C	A4385G	23	D3/S6	SMEI	[70]
195	F1463S	T4388C	23	D3/S6	SMEI	[47]
196	G1470W	G4408T	23	D3/S6	SMEI	[52]
197	L1475S	T4424C	23	D3/S6	SMEI	[45]
198	G1480V	G4439T	23	D3/S6	MAE	[31]
199	Q1489K	C4465A	23	L3	FHM	[38]
200	G1495fsX1500	[G]4484del	24	L3	SMEI	[45]
201	N1509fsX1511	[A]4526del	24	L3	SMEI	[75]
202	S1516X	C4546T	24	L3	SMEI	[77]
203	K1517fsX1536	4589[A]4590ins	24	L3	SMEI	[52]
204	R1525X	C4573T	24	L3	SMEI	[84]
205	F1543S	T4628C	25	D4/S1	CFE	[31]
206	I1545V	A4633G	25	D4/S1	SMEI	[31]
207	[M]1559del	[ATG]4675-46774del	25	D4/S1	SMEI	[30]
208	R1575C	C4723T	25	D4/S2	RE	[61]
209	[F]1584del	[TTT]4750-4752del	25	D4/S2	SMEB	[30]
210	C1588R	T4762C	25	D4/S2	SMEI	[52]
211	R1596C	C4786T	25	D4/S2-S3in	CFE	[31]
212	Y1598X	T4794A	25	D4/S2-S3in	SMEI	[31]
213	D1608Y	G4822T	25	D4/S3	SMEI	[52]
214	V1611F	G4831T	25	D4/S3	ICEGTC	[33]
215	Y1628X	T4884A	26	D4/S3-S4ex	SMEI	[47]
216	V1630M	G4888A	26	D4/S3-S4ex	SMEI	[52]
217	P1632S	C4894T	26	D4/S3-S4ex	ICEGTC	[33]
218	R1636Q	G4907A	26	D4/S4	LGS	[31]
219	R1645X	C4933T	26	D4/S4	SMEI	[30]
220	R1645Q	G4934A	26	D4/S4	SMEI	[75]
221	R1648C	C4942T	26	D4/S4	SMEI	[76]
222	R1648H	G4943A	26	D4/S4	GEFS+	[14]
223	L1649Q	T4946A	26	D4/S4	FHM	[62]
224	I1650fsX1672	4949-4950insT	26	D4/S4	SMEB-M	[31]
225	I1656M	C4968G	26	D4/S4	GEFS+	[72]
226	R1657C	C4969T	26	D4/S4	GEFS+	[44]
227	R1657H	G4970A	26	D4/S4	CFE	[31]
228	T1658R	C4973G	26	D4/S4-S5in	SMEB	[31]
229	F1661S	T4982C	26	D4/S4-S5in	SMEI	[68]
230	P1668A	C5002G	26	D4/S4-S5in	SMEI	[47]
231	F1671fsX1678	[TGTT]5008-5011del	26	D4/S4-S5in	SMEI	[45]
232	F1671fsX1678	[GTTT]5010-5013del	26	D4/S4-S5in	SMEI	[26]
233	G1674R	G5020C	26	D4/S5	SMEI	[76]
234	V1680fsX1715	5040[AA]5041ins	26	D4/S5	SMEI	[45]
235	A1685D	C5054A	26	D4/S5	SMEI	[33]
236	A1685V	C5054T	26	D4/S5	GEFS+	[86]
237	F1687S	T5060C	26	D4/S5	GEFS+	[52]
238	F1692S	T5075C	26	D4/S5	SMEI	[30]
239	Y1694C	A5081G	26	D4/S5	SMEI	[30]
240	V1695fsX1714X	[G]5083del	26	D4/S5	CGE	[34]
241	F1707V	T5119G	26	P4	SMEI	[31]
242	T1709I	C5126T	26	P4	ICEGTC	[33]
243	S1713N	G5138A	26	P4	SMEI/FS	[87]
244	M1714R	T5141G	26	P4	SMEI	[45]
245	C1716R	T5146C	26	P4	SMEB	[52]
246	T1721R	C5162G	26	P4	SMEI	[31]
247	W1726R	T5176C	26	P4	SMEI	[31]
248	D1742E	C5226A or G	26	P4	GEFS+	[88]
249	L1747fsX1779	5240[AA]5241ins	26	P4	SMEI	[89]

(*continued on next page*)

Table 2 (*continued*)

No.	AA level	NA level	Exon	Topology	Phenotype	Reference
250	G1749E	G5246A	26	P4	SMEI	[68]
251	G1762E	G5285A	26	D4/S6	SMEI	[45]
252	F1765fsX1794	5292[T]5293ins	26	D4/S6	SMEI	[33]
253	[F]1766del	[TTT]5296-5298del	26	D4/S6	SMEB	[30]
254	F1765fsX1777	[TTTT]5295del	26	D4/S6	SMEI	[52]
255	Y1781C	A5342G	26	D4/S6	SMEI	[30]
256	S1773F	C5318T	26	D4/S6	SMEI	[45]
257	M1780T	T5339C	26	D4/S6	SMEI	[47]
258	A1783T	G4347A	26	D4/S6	SMEI	[31]
259	A1783V	C5348T	26	D4/S6	SMEI	[52]
260	E1787K	G5359A	26	C-terminus	SMEI	[52]
261	N1788fsX1796	5363[TGACTTT]5364ins	26	C-terminus	SMEI	[35]
262	F1789fsX1793	[CA]5367-5368del	26	C-terminus	SMEI	[52]
263	F1805X	[TT]5414-5415del	26	C-terminus	SMEI	[47]
264	[MFYE]1807-1810del	[ATGTTCTATGAG] 5419-5430del	26	C-terminus	SMEI	[33]
265	F1808L	T5422C	26	C-terminus	ICEGTC	[33]
266	W1812G	T5434G	26	C-terminus	SMEI	[33]
267	W1812X	G5436A	26	C-terminus	SMEI	[31]
268	W1812C, [EFK]1813-1815del	[GGAGAAGTT] 5436-5444del	26	C-terminus	SMEI	[47]
269	F1831S	T5492C	26	C-terminus	SMEI	[33]
270	N1845fsX1856	[CAAA]5531-5534del	26	C-terminus	SMEI	[45]
271	K1846fsX1856	[AAAC]5536-5539del	26	C-terminus	SMEI	[26]
272	M1852R	T5555G	26	C-terminus	SMEI	[78]
273	M1852T	T5555C	26	C-terminus	GEFS+	[78]
274	V1857L	G5569C	26	C-terminus	GEFS+	[90]
275	D1866Y	G5596T	26	C-terminus	GEFS+	[21]
276	R1874fsX1941	[CGGGTTCT]5620del	26	C-terminus	SMEI	[52]
277	G1880fsX1881	[AGAGAT]5640-5645del, [CTAGAGTA]ins	26	C-terminus	SMEI	[76]
278	E1881D	G5643T or G5643C	26	C-terminus	SMEI	[35]
279	R1886X	C5656T	26	C-terminus	SMEI	[45]
280	L1885fsX1910	[G]5657del	26	C-terminus	SMEI	[45]
281	M1889fsX1910	[G]5668del	26	C-terminus	SMEI	[47]
282	R1892X	C5674T	26	C-terminus	SMEI	[77]
283	Q1904X	C5710T	26	C-terminus	SMEI	[31]
284	Q1904fsX1945	5712[ATCA]5723ins	26	C-terminus	SMEI	[77]
285	T1909I	C5726T	26	C-terminus	SMEI	[76]
286	R1912X	C5734T	26	C-terminus	SMEI	[30]
287	Q1914fsX1943	[AA]5741-5742del	26	C-terminus	ICEGTC	[31]
288	I1922T	T5765C	26	C-terminus	SMEI	[31]
289	R1928G	C5782G	26	C-terminus	SMEI	[70]
290	I1955T	T5864C	26	C-terminus	FA	[36]
291	E1957G	A5870G	26	C-terminus	IS	[35]

The nomenclature of the amino acid changes uses the single-letter amino acid code with the original residue at the beginning, followed by the open reading frame position and the residue present in the mutant. Exon–intron boundaries were deduced from rat *Scn1a* using NCBI's Basic Local Alignment Tool (BLAST, http://blast.ncbi.nlm.nih.gov/Blast.cgi).

An effort was made to reference the first, original report of the mutation. Topological data are taken from the secondary structure suggested by Escayg and colleagues [14]. Non-standard denominations: X – termination codon, del – deletion of residue/base, P37fsX91 (example) – frameshift with proline 37 being the last wild-type residue, followed by non-sense residues until ORF position 91, where the protein is prematurely terminated, AA: amino acid, D1/S2 (example): domain 1/transmembrane region 2 (topology code indexes "*in*" and "*ex*" denote internal and external loop, respectively), NA: nucleic acid.

Phenotype abbreviations are explained in Table 6.

cases, the position numbers are given along with the altered bases and amino acid residues to minimize misunderstandings and to facilitate identification of possible remaining errors (e.g., 3696Gdel ins22 = L1235fsX1243 was changed into [G]3705del, 3704[20-bp]3705ins = L1235fsX1244 as this seemed to be the closest possible solution with little chance of misinterpretation). Similar nomenclature changes were introduced for intronic changes to step away from conventional, somewhat cryptic abbreviations (e.g., c.88+1G>C referring to the +1 intron position following coding base 88). In the context of this manuscript, a more user-friendly approach was adopted that borrows from another common, but also cryptic and rigid

description (e.g., IVS4+1G>A, standing for *intervening sequence 4* position +1 G–A exchange). The newer nomenclature replaces intron descriptor but keeps the traditional plus or minus sign denoting the intronic 5′ beginning or 3′-ending, respectively, which allows for more flexibility, in particular with genetic alterations affecting more than a single base pair (e.g., Int4(+)G2A, [AA]6-7del). The membrane topology used throughout this review is identical to that suggested by Escayg and co-workers [14]. All sequence analyses were done with Clone Manager 9 Professional Edition software (Scientific & Educational Software, Cary, NC).

8. Nature of the mutations

A total of 331 *SCN1A* mutations were recorded (Fig. 2 and Tables 2–5). The large majority of these were exonic (86.1%). Only 29 (8.6%) intronic mutations are known at this time, and genomic deletions affecting parts of *SCN1A* or ablating the gene in its entirety, constitute merely a fraction of the mutation pool, counting in with 18 reports so far (5.3%). This distribution may in part be attributed to the methodology of the original mutation analyses, namely the use of exon-flanking sequencing primers. At a gene size of 81 kb, this is an economical compromise commonly justified by a traditional bias of exons being the only parent to the protein, owing to their responsibility of encoding the amino acid sequence. This view is now changing, as it becomes evermore apparent that intronic gene regulation and post-transcriptional alteration (e.g., variable splicing) has tremendous potential for functional diversification. In this context, one may speculate that the present, small fraction of epilepsy-associated *SCN1A* mutations not falling into the exonic category will increase in the future. Taking it further, it may well be that simple exonic sequencing of candidate genes generally has the potential to seriously underestimate a gene's involvement in an inheritable condition.

Almost all $Na_v1.1$ mutations (92.3%) are spatially confined, affecting 1 to 6 base pairs. Approximately half (48.5%) give rise to isolated, non-terminating amino acid changes. Close to one fifth (18.9%) result in a frameshift, either by deletion or insertion. A somewhat smaller number (16.6%) causes premature termination of protein synthesis by introducing a rogue stop codon.

Table 3
Intronic epilepsy-associated mutations of the voltage-gated sodium channel $Na_v1.1$

No.	Mutation	Phenotype	Other	Reference
1	Int1(−)G1A	SMEI		[31]
2	Int1(−)C3A	SMEI		[52]
3	Int1(+)G5A	SMEI		[45]
4	Int2(+)T3G	SMEI		[45]
5	Int2(−)G20C	SMEB	Unclear: splice junction lies between base pairs-383/384 not 385/386, initial report as "c.385-20G>C" on poster	[34]
6	Int3(−)T13A	SMEI		[31]
7	Int4(+)C1T	SMEI		[45]
8	Int4(+)G1A	SMEI	Mosaic mutation in Marini et al. (2006), Epilepsia 47:1737	[33]
9	Int5(+)G1C	SMEI		[45]
10	Int6(−)A2C	SMEI		[91]
11	Int7(+)G1T	SMEI		[31]
12	Int8(+)G1A	SMEI		[70]
13	Int8(+)C2T	SMEI	Milder phenotype	[92]
14	Int10(+)G1T	SMEI		[45]
15	Int10(+)T2C	SMEI		[31]
16	Int10(−)G1C	SMEI		[31]
17	Int14(+)T2A	SMEB-SW		[31]
18	Int14(+)A3T	SMEI		[31]
19	Int15(+)G1T	CGE		[31]
20	Int16(−)G1A	SMEI		[52]
21	Int18(+)G1T	SMEI		[47]
22	Int18(−)G1A	SMEI	Either Int18(+)G1A (in text) or Int18(−)G1A (in table)	[35]
23	Int18(+)G5C	SIGEI		[60]
24	Int22(−)G1T	SMEI		[47]
25	Int22(−)T14G	SMEI		[35]
26	Int22(+)G1A	SMEI		[26]
27	Int24(+)A2G	SMEI		[45]
28	Int25(−)T14G	SMEI		[31]
29	Int25(−)G1C	SMEI		[45]

Nomenclature example: Int3(−)G2A: intron 3,3′ end, second to last base pair before the splice junction, G to A exchange.
Use of a plus (+) or minus (−) symbol indicates the position within the intron (5′ or 3′ end, respectively).
Phenotype abbreviations are identical to what is used in Table 6.

Table 4
Genomic alterations of the voltage-gated sodium channel $Na_v1.1$ associated with epilepsy

No.	Extent	Effect	Phenotype	Reference
1	6499 bp deletion	Intron 20 (partial), exon 21, intron 21 (partial)	SMEI	[48]
2	n/a	Exon 21–26	SMEI	[48]
3	5 Mb deletion	*SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, *SCN9A* & several other genes	SMEI	[51]
4	4 Mb deletion	*SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, *SCN9A* & several other genes	SMEI	[51]
5	4.5 Mb deletion	*SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, *SCN9A* & several other genes	SMEI	[51]
6	Balanced chr. 2q>5q translocation	Breakpoint within *SCN1A*	SMEI	[49]
7	0.6 Mb deletion	Part of *SCN1A*, all of *SCN7A*, *SCN9A*	SMEI	[46]
8	4.7 Mb deletion	*SCN1A*, *SCN7A*, *SCN9A* + dozens other genes	SMEI	[46]
9	3.1 Mb deletion	*SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, *SCN9A* & several other genes	SMEI	[46]
10	n/a	Deletion of exons 12–14	SMEI	[52]
11	n/a	Deletion of *SCN1A*	SMEI	[52]
12	0.26 Mb deletion	Deletion of exons 8–26	SMEI	[50]
13	0.16 Mb deletion	Deletion of exons 20–26	SMEI	[50]
14	0.16 Mb deletion	Deletion of exons 17–26	SMEI	[50]
15	0.75 Mb deletion	*SCN1A*, *SCN7A*, *SCN9A* & one adjacent gene (FLJ11457)	SMEI	[50]
16	1.14 Mb deletion	*SCN1A*, *SCN7A*, *SCN9A* & two adjacent genes	SMEI	[50]
17	1.55 Mb deletion	*SCN1A*, *SCN7A*, *SCN9A* & several other genes	SMEI	[50]
18	1.28 Mb deletion	*SCN1A*, *SCN7A*, *SCN9A* & several other genes	SMEI	[50]

Abbreviations are identical to what is used in Table 6.

Taking presumed altered splicing into account, in other words exonic or intronic nucleic acid changes within 5 base pairs of the splice junction (0.9% and 7.7%, respectively), 45.3% of all *SCN1A* mutations produce non-sense products. This number excludes the effect of exonic and intronic base pair changes distant (>5 bp) to splice junctions. Given the latter restriction, can we assume that the calculated 45.3% for non-sense products is consistent with the *in vivo* number or is this an underestimate? Can one equate spatial distance (in this case >5 bp) to a splice junction with low likelihood of splicing interference? At this time, it is uncertain how the processing of *SCN1A* precursor mRNA is regulated, where the splicing regulatory sites are, and which enhancing or silencing factors participate. It is possible, however, to examine $Na_v1.1$ mRNA indirectly by looking at a mutant's current density. Since macroscopic current is the product of the single-channel conductance, the channel's unitary current, and the number of channels in the cytosolic membrane, low- (or no-) current expressing $Na_v1.1$ mutants without any defects in the former two parameters must have a reduced cell surface presence. This possibility has been discussed before [43], and researched in the laboratory with the hypothesis that the current density reduction or lack of expression commonly associated with mutant $Na_v1.1$ [40,44] is the result of aberrant protein sequences, misfolding, and ultimately endoplasmic retention. Not addressed so far, is whether seemingly moderate or simple genetic variations impact splicing. Do such changes contribute to the already large pool of truncation mutations? It would be interesting to establish whether this possibility constitutes a reality. Lack of $Na_v1.1$ expression as a cause for Dravet's syndrome (as opposed to milder phenotypes resulting from $Na_v1.1$ *dys*function) has been debated in the past, and the here-presented analysis shows that all truncated $Na_v1.1$ protein leads to severe epilepsy (ICEGTC, SMEB, or SMEI; two cases of CGE). Abnormal splicing regulation represents a possible, so-far unexplored and intriguing solution to the phenotypic dilemma: Is it possible that mutants with comparatively unremarkable electrophysiology (K1270T, personal observation) are in fact victims of aberrant splicing that renders a critical percentage of the produced protein non-functional? If true, wild-type-level $Na_v1.1$ current stemming from an SMEI mutant would then be an methodological artifact, since heterologous expression bypasses RNA processing by using artificial $Na_v1.1$ open reading frame inserts.

Another possible basis for loss-of-function is the alteration of functionally important sites, be it directly via glycosylation or phosphorylation, or, indirectly, through interaction with secondary partner proteins. As for phosphorylation – there is no scarcity of computer applications that are capable of identifying protein sequence residues that meet the consensual criteria for post-translational alteration. Whether or not the suggested sites can indeed be modified may only be established experimentally, by mass spectrometry for example. Personal communication with researchers employing both methods has prompted me not to use the former, as the prediction power of virtual analyses can digress greatly from hard experimental evidence. Unfortunately, there are no experimental phosphorylation data available on $Na_v1.1$ currently, nor is there any such information on closely related $Na_v1.1$ isoforms that would allow for estimates based on homology. Fortunately, mass spectrometric experimentation address-

Table 5
Statistics (Mutation Data)

	N	
Mutation location		
Exonic	291	(86.1%)
Intronic	29	(8.6%)
Genomic	18	(5.3%)
Total	338	
Mutation type		
Single-amino acid substitutions (SUB)	164	(48.5%)
Frameshifts (FrS)	64	(18.9%)
Premature stop codons (PSC)	56	(16.6%)
Intronic mutations <5 bp from splice site (INT < 5)	26	(7.7%)
Intronic mutations >5 bp from splice site (INT > 5)	3	(0.9%)
Genomic deletions (gDEL)	11	(5.3%)
In-frame deletions (DEL)	7	(2.1%)
SUBs <5 bp from splice site (SUB < 5)	4	(1.2%)
Truncations (subtotal for FrS, PSCs, INT > 5s, INT < 5s, and SUB < 5s)	150	(45.3%)
Adjustments & Corrections		
Mutations not referring to full-length $Na_v1.1$, incorrect mutation data, or ambiguous reports	63	(19.6%)

Percentages in the "*Mutation type*" and "*Adjustments & Corrections*" categories were based on $N = 338$, which is the total number of mutations recorded in this review.
Note that single-amino acid substitutions within 5 bp of the splice junction must be subtracted when the total is calculated, as they are tallied under "SUB" already.

ing phosphorylation of a close $Na_v1.1$ paralog is presently underway.

9. GEFS+ and SMEI... polygenic disorders?

Owing to the strong links between SMEI/GEFS+ and mutations in *SCN1A*, it has become common practice in the clinic to perform candidate genetic screenings. This approach has been remarkably successful in some studies, where virtually all [26] or the majority of the subjects presented with some form of *SCN1A* alteration [31,45]. However, in a subgroup of patients, *SCN1A* appears to be intact [30,46], which may have one of two possible explanations: (1) SMEI and other *SCN1A*-associated phenotypes are polygenic disorders, where $Na_v1.1$ dysfunction is etiologically contributing but not required; or (2) the finding that *SCN1A* is not mutated is a methodological limitation. The discussion of SMEI and GEFS+ as polygenic conditions is not new [45,47], but experimental data supporting or opposing them as such is difficult to obtain. What would be required is evidence demonstrating integrity of the full *SCN1A* gene and all of its control elements. At present this is not only impractical – *SCN1A* encompasses more than 81 kb – but also impossible as the *SCN1A* regulatory regions are not defined. Conceivably, SMEI studies failing to find mutations fall victim to analytical approaches. Genomic alterations extending beyond short insertions, deletions, or point mutations commonly produce negatives in analyses where exonic sequencing is employed. One copy of *SCN1A* missing as a result of a genomic deletion, for example, cannot be detected in that fashion. This problem has been addressed in a number of studies with partial success. Several groups have identified microchromosomal deletions ablating one or several *SCN1A* exons [48,49]. In six cases, the chromosomal defects extend beyond *SCN1A* into adjacent genes that include *SCN2A*, *SCN3A*, *SCN7A*, and *SCN9A* [46,50–52]. The common denominator in all is the genetic abnormality in *SCN1A*. It is also true, however, that the interpretability of these data regarding an association between SMEI/GEFS+ and *SCN1A* is challenging at best due to the extent of the chromosomal aberrations. The deletion of various other genes, paralogous Na_v channels included, may produce in itself distinct pathologies [15,17,53]. On the other hand, since none of the other genes has been linked to SMEI at this time, haploinsufficiency of $Na_v1.1$ remains the most probable cause for the encountered pathologies.

Finally, it should be reiterated that many studies finding mutations in *SCN1A* did so using a candidate screening approach without providing actual genetic linkage data, which makes the reported association plausible, but also possibly circumstantial. The sheer number of studies finding problems in *SCN1A* speaks against the latter possibility, as does the work that did indeed genetically map *SCN1A* as a febrile seizure locus [54–56]. However, GEFS+ has also been linked to mutations in the GABA receptor γ_2 subunit [57,58] and the Na_v channel β_1 subunit. The single-gene scenario for GEFS+ is thus already ruled out, but it remains to be seen what combination of factors determines the clinical outcome [59]. Genetic modification via other Na_v channel paralogs, $Na_v1.6$ for example, is now being discussed [16].

10. Phenotype prevalence

Severe myoclonic epilepsy in infancy is by far the most common (71.6%) phenotype encountered (Table 6). If atypical SMEI variations are included (e.g., SMEB and subtypes, ICEGTC, etc.), almost 9 out of 10 individuals (86.1%) with *SCN1A* mutations are afflicted with this debilitating disorder. Second most common, but rare, are febrile seizures and related syndromes (6.7%). The remaining associated epileptic conditions comprise cryptogenic focal and cryptogenic generalized epilepsy (together 3%) as well as infrequent occurrences of myoclonic astatic epilepsy [31,60], severe idiopathic

Table 6
Statistics (Phenotype Data)

	N	
SMEI & derivatives		
SMEI (severe myoclonic epilepsy in infancy, Dravet's syndrome)	257	(71.6%)
SMEB (SMEI-borderland)	17	(4.7%)
SMEB-M (SMEB without myoclonus)	3	(0.8%)
SMEB-SW (SMEB without generalized spike-wave)	11	(3.1%)
SMEB-O (SMEB lacking more than one typical SMEI characteristic)	10	(2.8%)
ICEGTC (intractable childhood epilepsy with generalized tonic–clonic seizures)	9	(2.5%)
aSMEI (atypical SMEI)	2	(0.6%)
Subtotal	309	(86.1%)
GEFS+ & derivatives		
GEFS+ (generalized epilepsy with febrile seizures, plus)	21	(5.8%)
FS (febrile seizures)	3	(0.8%)
Subtotal	24	(6.7%)
Other epileptic disorders		
CGE (cryptogenic generalized epilepsy)	7	(1.9%)
CFE (cryptogenic focal epilepsy)	4	(1.1%)
MAE (myoclonic astatic epilepsy, Doose syndrome)	3	(0.8%)
SIGEI (severe idiopathic generalized epilepsy of infancy)	2	(0.6%)
RE (Rasmussen's encephalitis)	1	(0.3%)
IS (infantile spasms, West syndrome)	1	(0.3%)
LGS (Lennox–Gastaut syndrome)	1	(0.3%)
Subtotal	19	(5.3%)
Non-epileptic disorders		
FA (familial autism)	3	(0.8%)
FHM (familial hemiplegic migraine)	3	(0.8%)
PS (Panayiotopoulos syndrome)	1	(0.3%)
Subtotal	7	(1.9%)

Percentages were based on $N = 359$, which is the total patient number.
Some variants are listed with more than one phenotype owing to differing diagnoses between publications.

generalized epilepsy of infancy [60], West syndrome [35], Lennox–Gastaut syndrome [31], and Rasmussen encephalitis [61]. Combined, the latter account for eight cases or 2.3%. There are also rare reports of *SCN1A* defects in patients suffering from other neurological disorders, such as familial autism in three cases [36], familial hemiplegic migraine in three cases [37,38,62], and Panayiotopoulos syndrome in one case [63].

11. Data representation

It is uncertain whether the numbers and specifications of the published *SCN1A* variants are a good representation of naturally occurring genetic changes. Many of the mutations were identified after it had been discovered that *SCN1A* abnormality can lead to SMEI. This of course creates bias and one cannot say whether the mutation and phenotype percentages calculated in this review approach reality. As discussed above, the extensive genomic analysis required to grasp the full scope of possible *SCN1A* mutations poses a considerable challenge at this time. Advances in sequencing technology and more information on *SCN1A* gene regulation may adjust the here-quoted mutation percentages, in particular with respect to intronic changes. Something similar may become necessary with respect to *SCN1A*-associated phenotypes. Patients with SMEI, GEFS+, or similar presentations are now genetically scrutinized for *SCN1A* alterations. This, again, may produce a skewing of the data, distracting from *SCN1A* associations with other neurological disorders, autism and migraine being only the first two examples. Also not taken into account is how genetic changes in *SCN1A* may predispose prenatal or infantile lethality; not an unlikely scenario considering the severe phenotype of *Scn1a* knockout mice [64].

12. Genotype–phenotype correlation

Throughout the writing of this article, I made several attempts to identify patterns in the pool of *SCN1A* mutations. There is no scarcity of data with a total of some 330+ genetic alterations, but a truthful correlation between the reported phenotypes and genotypes is exceedingly difficult to establish. One of the challenges

to reconcile is the seeming paradox of SMEI-associated mutations producing loss-of-function at one time [44,65], but gain-of-function at another [66]. Several researchers have tried to address this issue [67], and the consensus from these studies is that coding alterations presumed to severely interfere with the protein's function, be it by truncation or rearrangement of functionally important regions, exhibit a high likelihood of clinically severe syndromes. Albeit, structurally significant changes are not always predictive of severe epilepsy. Several cases exist where one mutation causes controllable seizures in one generation that regress to pharmacoresistance in the next. The relationship between the clinical picture and the position of the mutation within the protein is similarly complex. Biochemically comparable changes in adjacent residues can produce markedly different effects. Of course, intricate structural information may readily explain the diverging clinical outcomes. In theory, mutations of adjacent hydrophobic residues may well differentially affect the channel's functionality, depending on the three dimensional placement of the residue within the protein. A residue lining the pore or stretching its charged sidearm toward the selectivity filter, for example, has likely larger impact on the channel's performance than its neighboring residue, which is a third α-helix turn averted. More informative analyses will be possible once the $Na_v1.1$ crystal structure becomes available.

13. Summary

The purpose of this review was to provide a compilation of all *SCN1A* mutations currently found. Having done so, it is understood that the listings and calculations will be updated in the future. To provide a continued platform that is in keeping with the latest data, a web site has been set up where all information can be accessed and downloaded (http://web.scn1a.info). At this time, I deliberately refrain from scoring mutational weights or correlating the biochemical impact of the amino acid alteration with the phenotype. Without structural information on $Na_v1.1$ that is significantly more detailed, I feel that such analyses are premature.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.braindev.2008.07.011.

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