Supplementary Material

Supplementary Methods

Functional classification of mutations:

For each mutation described we assessed the overall effect with respect to channel function in terms of net current flow during voltage steps. Channel function is not necessarily the same as overall effect on *cellular* function as elegantly shown recently in Liu et al., 2019,[1] where a gain in function for the channel, led to a paradoxical loss of function through depolarising block at the cellular level. As the vast majority of channels are characterised in non-excitable mammalian cell lines in voltage clamp only, we have used this baseline to allow comparisons between published studies. Assessing the net effect where a mutation can have multiple effects on channels, we have looked at different parameters in the following approach:

1. Peak currents: we first checked whether a mutation reduced or increased the peak current substantially. Where data allow (e.g. for FHM3 mutations in Cestele et al., 2013)[2] we have also asked whether these effects on peak current are dependent on expression system in a way that means they may not be physiologically relevant in the endogenous cells. If there are data suggesting the effects on peak current are dependent on system, we have noted this as 'mixed' in the first instance.

2. Voltage dependence of inactivation: as the channels must be able to activate in order to pass current, we have asked whether there were shifts in the voltage dependence of inactivation that suggest a substantial portion of channels would be stuck in inactivated states in resting cells at ~-70 or -80 mV. In a very few cases we have suggested that were a large shift in voltage dependence of inactivation would effectively make channels non-functional, we have indicated this is likely an overall LoF effect, even if the peak current is increased and voltage dependence of activation (see #3) was also shifted (we gave inactivation precedence as the channels would be unable to open in resting cells if inactivated at resting potentials).

3. Voltage dependence of activation: given functional channels (i.e. peak current is not lost) that are not stuck in inactivated states at rest (i.e. voltage dependence of inactivation not shifted so all channels are inactive at -80 mV), we asked how much stimulation is required to open channels – that is to say, is the voltage dependence of activation shifted significantly? Here a shift to more

negative voltage dependences of activation would be a gain of function, but again – only if there are sufficient currents, and a significant population of non-inactivated channels.

4. Persistent currents: These can be increased, sometimes even when peak currents are reduced. Increases in persistent currents are included as gain of function, unless peak currents or voltage dependence of inactivation are shifted so much that channels are unlikely to be open at all, in which case, given the profound effects of sodium leaks on cellular activity we have still called cases with large increases in persistent currents 'mixed'.

5. Gating pore currents: Few groups using neuronal channels have been able to interrogate whether in the cases of S4 arginines these include gating pore leak, we have not rigorously separated gating pore leaks (but see R853Q in SCN2A for one example where these currents have been seen in neuronal channels; Mason et al., 2019)[3]. Where gating pore leaks are described, these are a gain of function (and one that is highly likely to be pathogenic in any cell). Further technically challenging work on neuronal channels will be needed to confirm the conservation of these gating pore currents across channel subtypes.

6. There are many additional features that can come into play, and where the above 5 criteria do not give an overriding answer, we have looked at these. For example, many groups also look at recovery from inactivation, but in our survey, this was rarely changed enough to be the dominating feature of a channel's functional change. However, where there were large impacts on recovery from inactivation and these were in contrast to other effects on the channel, we have given the results as mixed.

In practice this functional hierarchy, albeit simplistic and incomplete, typically agrees with the author assessments of the channels, with rare exceptions. We emphasise that this functional assessment is from the perspective of the channel, not the cell or the organism (indeed as these are mutations associated with diseases, they would all be loss of function from the organism's perspective).

Additional studies, including dynamic clamp, expression in excitable cells and interrogating current clamp properties, modelling, and the golden standard of knock-in studies in mice, all will bring additional insights to the consequences of the mutations on the cells, networks and behaviours, but for the purposes of comparing the effects of mutations across different channels we have relied on the reductionist, most commonly used experimental approach. It remains to be

seen whether functional effects that alter, for example channel trafficking, are conserved in different types of sodium channels expressed in different cellular backgrounds. In addition, some effects, for example where the different threshold of activation of SCN9A has specific effects on cellular activity (in this case in DRG neurons, Dib-Hajj et al., 2012)[4] which are highly unlikely to be conserved in (for example) SCN4A in muscle cells. In these cases, the reductionist effect on voltage dependence of activation may be conserved, but the cellular effect divergent.

References

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Supplementary Table 1: *SCN* Functionally Characterized Variants

No.	Gene	Variant	Overall effect	Reference for function	Primary disease	Reference for phenotype	SCN1A Equivalent	gnomAD frequency	Conservation
1-128 Cytoplasmic segment									
1	*SCN5A*	G9V	STW	Glazer (2020)[1]	LQT3	Millat (2006)[2] Gutter (2013)[3]	G10V	-	NC
2	*SCN9A*	Q10R	GoF	Han (2009)[4]	IEM	Han (2009)[4]	D12R	1.29e-4	NC
3	*SCN2A*	D12N	LoF	Ben-Shalom (2017)[5]	ASD	Ben-Shalom (2017)[5]	D12N	-	NC
4	*SCN5A*	R18W	GoF	Gutter (2013)[3]	LQT3	Tester (2005)[6]	R19W	2.57e-4	NC
5	*SCN5A*	R27H	LoF	Gutter (2013)[3]	BrS	Priori (2002)[7]	R28H	2.36e-4	NC
6	*SCN5A*	E30G	STW	Kapplinger (2015)[8]	LQT3	Kapplinger (2015)[8]	E31G	-	NC
7	*SCN5A*	R43Q	STW	Lin (2008)[9]	LQT3	Lin (2008)[9]	K41Q	4.85e-5	NC
8	*SCN1A*	E78D	LoF	Kluckova (2020)[10]	EPI	Mancardi (2006)[11]	E78D	-	-
9	*SCN5A*	D84N	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	D81N	-	-
10	*SCN2A*	D82G	LoF	Ben-Shalom (2017)[5]	ASD	Ben-Shalom (2017)[5]	D81G	-	-
11	*SCN5A*	F93S	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	F90S	-	-
12	*SCN10A*	V94G	LoF	Jabbari (2015)[13]	AF	Jabbari (2015)[13]	V92G	-	-
13	*SCN4A*	R104H	LoF	Zaharieva (2016)[14]	CMS	Zaharieva (2016)[14]	R101H	4.01e-6	-
14	*SCN5A*	R104Q	LoF	Gutter (2013)[3]	BrS	Levy-Nissenbaum (2001)[15]	R101Q	-	-
15	*SCN5A*	R104W	LoF	Clatot (2012)[16]	BrS	Clatot (2012)[16]	R101W	4.01e-6	-
16	*SCN5A*	N109K	STW	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	S106K	4.01e-6	NC
17	*SCN5A*	R121W	LoF	Clatot (2012)[16] Glazer (2020)[1]	BrS	Kapplinger (2010)[12] Holst (2010)[17]	R118W	-	-
18	*SCN5A*	A124D	LoF	Moreau (2012)[18]	BrS	Moreau (2012)[18]	A121D	-	NC
19	*SCN5A*	V125L	GoF	Gutter (2013)[3]	LQT3	Kapplinger (2009)[19]	I122L	2.17e-4	NC

20	*SCN5A*	K126E	LoF	Gutter (2013)[3]	BrS	Gutter (2013)[3]	K123E	-	NC
129-147 S1 of D1									
21	*SCN5A*	L136P	LoF	Glazer (2020)[1]	BrS	Yokokawa (2007)[20] Yamagata (2017)[21]	L133P	-	NC
22	*SCN8A*	M139I	GoF	Zaman (2019)[22]	EPI	Zaman (2019)[22]	M135I	-	NC
23	*SCN4A*	I141V	GoF	Petitprez (2008)[23]	PMC	Petitprez (2008)[23]	I138V	-	NC
24	*SCN9A*	I136V	GoF	Cheng (2008)[24]	IEM	Lee (2007)[25]		-	NC
25	*SCN1A*	M145T	LoF	Mantegazza (2005)[26]	EPI	Mantegazza (2005)[26]	M145T	-	-
148-154 Extracellular									
155-175 S2 of D1									
26	*SCN5A*	E161K	LoF	Smits (2005a)[27]	BrS	Smits (2005a)[27]	E158K	4.15e-6	-
27	*SCN10A*	Y158D	GoF	Savio-Galimberti (2014)[28]	AF	Savio-Galimberti (2014)[28]	Y159D	2.58e-4	NC
28	*SCN5A*	K175N	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	K172N	-	-
29	*SCN5A*	A178G	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	A175G	-	-
176-189 Cytoplasmic									
30	*SCN1A*	G177A	LoF	Nissenkorn (2019)[29]	EPI	Nissenkorn (2019)[29]	G177A	-	-
31	*SCN1A*	G177E	LoF	Ohmori (2006)[30]	EPI	Ohmori (2006)[30]	G177E	-	-
32	*SCN5A*	T187I	LoF	Makiyama (2005)[31]	BrS	Makyama (2005)[31]	T184I	-	NC
33	*SCN2A*	R188W	Mixed	Sugawara (2001)[32]	EPI	Sugawara (2001)[32]	R187W	1.99e-5	-
190-207 S3 of D1									
34	*SCN4A*	M203K	LoF	Zaharieva (2016)[14]	CMS	Zaharieva (2016)[14]	F200K	7.99e-6	NC
35	*SCN2A*	V208E	GoF	Lauxmann (2018)[33]	EPI	Lauxmann (2018)[33] Lemke (2012)[34]	V207E	-	NC
208-213 Extracellular									

36	*SCN5A*	S216L	Mixed	Marangoni (2011)[35] Wang (2007)[36]	LQT3; BrS	Marangoni (2011)[35] Wang (2007)[36]	S213L	8.09e-5	NC
37	*SCN9A*	S211P	GoF	Estacion (2010)[37]	IEM	Estacion (2010)[37]	S213P	-	NC
214-230 S4 of D1									
38	*SCN11A*	R222H	GoF	Han (2017)[38]	PPN	Han (2017)[38] Okuda (2016)[39]	R216H	-	-
39	*SCN5A*	T220I	STW	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	T217I	7.14e-4	NC
40	*SCN9A*	F216S	GoF	Choi (2006)[40] Sheets (2007)[41]	IEM	Drenth (2005)[42] Kim (2013)[43]	F218S	-	-
41	*SCN8A*	R223G	LoF	De Kovel (2014)[44]	EPI	De Kovel (2014)[44]	R219G	-	-
42	*SCN5A*	V223L	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	V220L	-	-
43	*SCN4A*	R225W	LoF	Zaharieva (2016)[14]	CMS	Zaharieva (2016)[14]	R222W	-	-
44	*SCN5A*	R225W	LoF	Bezzina (2003)[45]	LQT3; BrS	Kapplinger (2009)[19] Kapplinger (2010)[12]		-	-
45	*SCN5A*	R225P	GoF	Beckermann (2014)[46]	LQT3	Beckermann (2014)[46]	R222P	-	-
46	*SCN5A*	A226V	LoF	Tan (2016)[47]	BrS	Tan (2016)[47]	A223V	-	-
47	*SCN1A*	T226M	Mixed	Berecki (2019)[48]	EPI	Sadleir (2017)[49]	T226M	-	NC
48	*SCN1A*	I227S	LoF	Ohmori (2006)[30]	EPI	Nabbout (2003)[50]	I227S	-	NC
49	*SCN5A*	V232I	STW	Barajaz-Martinez (2008)[51]	BrS	Barajaz-Martinez (2008)[51] Kapplinger (2010)[12] [compound missense with L1308F]	V229I	-	NC
50	*SCN9A*	I228M	GoF	Estacion (2011)[52]	SFN	Estacion (2011)[52] Faber (2012)[53]	I230M	8.58-e4	NC
231-249 Cytoplasmic									
51	*SCN2A*	T236S	GoF	Thompson (2020)[54]	EPI	Nakamura (2013)[55]	T235S	3.98e-6	NC
52	*SCN9A*	I234T	GoF	Ahn (2010)[56]	IEM	Ahn (2010)[56]	I236T	-	-
53	*SCN4A*	S246L	STW	Tsujino (2003)[57]	CMS	Tsujino (2003)[57]	S243L	-	NC
54	*SCN9A*	S241T	GoF	Lampert (2006)[58]	IEM	Lampert (2006)[58] Michiels (2005)[59]	S243T	-	-
55	*SCN10A*	S242T	GoF	Han (2018)[60]	PPN	Han (2018)[60]		1.91-e4	-

56	*SCN3A*	L247P	LoF	Lamar (2017)[61]	EPI	Lamar (2017)[61]	L247P	-	-
57	*SCN1A*	D249E	LoF	Kluckova (2020)[10]	EPI	Kluckova (2020)[10]	D249E	-	NC
250-269 S5 of D1									
58	*SCN1A*	S259R	LoF	Nissenkorn (2019)[29]	EPI	Nissenkorn (2019)[29]	S259R	-	-
59	*SCN2A*	A263V	GoF	Liao (2010a)[62]	EPI	Liao (2010a)[62] Schwarz (2016)[63]	A262V	-	-
60	*SCN1A*	L263V	GoF	Kahlig (2008)[64]	FHM	Kahlig (2008)[64]	L263V	-	-
61	*SCN8A*	G269R	LoF	Wengert (2019)[65]	NDD without epilepsy	Wengert (2019)[65]	G265R	-	-
62	*SCN4A*	Q270K	Mixed	Carle (2009)[66]	PMC	Carle (2009)[66]	Q267K	-	-
63	*SCN5A*	Q270K	Mixed	Calloe (2011)[67]	LQT3	Calloe (2011)[67]		-	-
270-367 Extracellular									
64	*SCN5A*	L276Q	LoF	Glazer (2020)[1]	BrS	Sommariva (2013)[68] Yamagata (2017)[21]	L273Q	-	-
65	*SCN5A*	R282H	LoF	Polezing (2006)[69]	BrS	Priori (2002)[7] Itoh (2005)[70]	Q279H	1.60e-5	NC
66	*SCN5A*	R282C	LoF	Glazer (2020)[1]	BrS	Andorin (2016)[71]	Q279C	-	NC
67	*SCN1A*	T297I	LoF	Binini (2017)[72]	EPI	Binini (2017)[72]	T297I	-	NC
68	*SCN5A*	L325R	LoF	Keller (2005)[73]	BrS	Keller (2005)[73]	L335R	-	NC
69	*SCN5A*	C335R	LoF	Glazer (2020)[1]	BrS	Van Malderen (2017)[74]	C345R	-	-
70	*SCN5A*	P336L	LoF	Cordeiro (2006)[75]	BrS	Cordeiro (2006)[75]	P346L	-	NC
71	*SCN3A*	K354Q	GoF	Estacion (2010)[76]	EPI	Holland (2008)[77]	K353Q	-	NC
72	*SCN5A*	E346D	Mixed	Glazer (2020)[1]	BrS	Probst (2006)[78]	R356D	-	NC
73	*SCN4A*	P382T	LoF	Zaharieva (2016)[14]	CMS	Zaharieva (2016)[14]	P358T	-	-
74	*SCN5A*	D349N	LoF	Glazer (2020)[1]	BrS	Savastano (2014)[79]	N359N	1.43e-5	NC
75	*SCN5A*	T353I	LoF	Pfahnl (2007)[80] Zhang (2015)[81] Glazer (2020)[1]	BrS	Pfahnl (2007)[80]	T363I	-	-

76	*SCN5A*	D356N	LoF	Makiyama (2005)[31]	BrS	Makiyama (2005)[31]	D366N	4.02e-6	-
368-392 Pore-forming									
77	*SCN5A*	R367C	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12] Amin (2011)[82]	R377C	1.07e-5	-
78	*SCN2A*	R379H	LoF	Ben-Shalom (2017)[5]	ASD	Ben-Shalom (2017)[5]	R377H	-	-
79	*SCN5A*	R367H	LoF	Hong (2004)[83]	BrS	Hong (2004)[83]		-	-
80	*SCN5A*	R367L	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	R377L	-	-
81	*SCN5A*	M369K	LoF	Glazer (2020)[1]	BrS	Probst (2006)[78] Probst (2007)[84] Andorin (2016)[71]	M379K	-	-
82	*SCN5A*	W374G	LoF	Nakajima (2021)[85]	BrS	Kapplinger (2010)[12] Nakajima (2021)[85]	W384G	-	-
83	*SCN5A*	R376H	LoF	Rossenbacker (2004)[86] Frustaci (2005)[87] Peters (2016)[88]	BrS	Rossenbacker (2004)[86] Frustaci (2005)[87]	N386H	8.08e-6	NC
84	*SCN8A*	N374K	GoF	Zaman (2019)[22]	EPI	Zaman (2019)[22]	N386K	-	NC
393-399 Extracellular									
85	*SCN1A*	R393H	LoF	Ohmori (2006)[30]	EPI	Claes (2003)[89]	R393H	-	-
86	*SCN5A*	G386R	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	G396R	-	-
400-420 S6 of D1									
87	*SCN11A*	I381T	GoF	Huang (2014)[90]	SFN	Huang (2014)[90]	V404T	7.96e-6	NC
88	*SCN5A*	V396L	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	V406L	-	NC
89	*SCN10A*	L388M	LoF	Gando (2020)[91]	SUD	Gando (2020)[91]	L414M	-	-
90	*SCN4A*	N440K	GoF	Lossin (2012)[92]	PMC; PAM	Lossin (2012)[92]	N416K	-	-
91	*SCN5A*	N406K	Mixed	Hu (2018)[93] Kato (2014)[94]	LQT3	Hu (2018)[93] Kato (2014)[94]		-	-
92	*SCN9A*	N395K	GoF	Sheets (2007)[41]	IEM	Drenth (2005)[42]		-	-
93	*SCN5A*	N406S	LoF	Itoh (2007)[95]	BrS	Itoh (2007)[95]	N416S	-	-
421-768 Cytoplasmic									

94	*SCN2A*	V423L	GoF	Wolff (2017)[96]	EPI	Wolff (2017)[96]	V421L	-	-
95	*SCN4A*	V445M	GoF	Wang (1999)[97] Huang (2020)[98]	PMC	Liu (2015)[99] Huang (2020)[98]	V421M	-	-
96	*SCN5A*	V411M	GoF	Horne (2011)[100] Zhou (2015)[101]	LQT3	Horne (2011)[100] Zhou (2015)[101]		-	-
97	*SCN9A*	V400M	GoF	Fischer (2009)[102]	IEM	Fischer (2009)[102]		-	-
98	*SCN1A*	Y426N	LoF	Ohmori (2006)[30]	EPI	Nabbout (2003)[50]	Y426N	-	-
99	*SCN5A*	R458C	GoF	Winkel (2015)[103]	LQT3	Winkel (2015)[103]	D481C	1.45e-4	NC
100	*SCN5A*	A551T	LoF	Chiang (2009)[104] Juang (2014)[105]	BrS	Chiang (2009)[104] Juang (2014)[105]	F598T	-	NC
101	*SCN5A*	H558R	STW	Ye (2003)[106] Tester (2010)[107] Veltmann (2016)[108]	LQT3; BrS	Ye (2003)[106] Veltmann (2016)[108] Juang (2014)[105]	R605R	0.22	NC
102	*SCN5A*	L567Q	LoF	Wan (2001)[109]	BrS	Priori (2000)[110]	H614Q	-	NC
103	*SCN5A*	R569W	GoF	Kapplinger (2015)[8]	LQT3	Kapplinger (2015)[8]	E616W	8.03e-6	NC
104	*SCN5A*	A572D	STW	Tester (2010)[107]	LQT3	Tester (2010)[107]	N619D	5.18e-3	NC
105	*SCN10A*	L554P	GoF	Faber (2012)[111]	PPN	Faber (2012)[111]	R630P	8.60e-5	NC
106	*SCN5A*	N592K	LoF	Juang (2014)[105]	BrS	Juang (2014)[105]	H642K	3.23e-5	NC
107	*SCN9A*	D623N	GoF	Ahn (2013)[112]	SFN	Faber (2012)[53]	D646N	-	-
108	*SCN5A*	L619F	GoF	Wehrens (2003)[113]	LQT3	Wehrens (2003)[113]	L668F	4.03e-5	NC
109	*SCN5A*	R620H	STW	Calloe (2013)[114] Glazer (2020)[1]	BrS	Calloe (2013)[114]	P669H	3.14e-5	NC
110	*SCN5A*	R689H	LoF	Hong (2012)[115]	BrS	Hong (2012)[115]	K740H	9.25e-5	NC
111	*SCN10A*	M650K	Mixed	Kist (2016)[116]	IEM	Kist (2016)[116]	Y753K	5.45e-4	NC
769-787 S1 of D2									
112	*SCN9A*	I739V	GoF	Han (2012)[117]	SFN	Faber (2012)[53] Han (2012)[117]	I774V	2.47e-3	-
113	*SCN2A*	T773I	GoF	Lauxmann (2018)[33]	EPI	Lauxmann (2018)[33]	T782I	-	-
114	*SCN8A*	T767I	GoF	Estacion (2014)[118] Pan (2020)[119]	EPI	Estacion (2014)[118]		-	-

115	*SCN5A*	M734V	LoF	Glazer (2020)[1]	BrS	Le Scouarnec (2015)[120]	M785V	-	NC
116	*SCN5A*	A735E	LoF	Glazer (2020)[1]	BrS	Priori (2002)[7] Nakajima (2011)[121]	A786E	-	-
117	*SCN5A*	A735T	LoF	Glazer (2020)[1]	BrS	García-Castro (2010)[122]	A786T	-	-
118	*SCN5A*	A735V	LoF	De la Roche (2019)[123]	BrS	De la Roche (2019)[123]	A786V	4.01e-6	-
788-798 Extracellular									
119	*SCN1A*	E788K	LoF	Kluckova (2020)[10]	EPI	Kluckova (2020)[10]	E788K	-	-
120	*SCN1A*	Y790C	LoF	Bechi (2015)[124]	EPI	Annesi (2003)[125]	Y790C	-	NC
121	*SCN5A*	E746K	LoF	Glazer (2020)[1]	BrS	Peters (2008)[126]	N797K	2.14e-5	NC
799-818 S2 of D2									
122	*SCN5A*	G752R	LoF	Glazer (2020)[1]	BrS	Smits (2002)[127] Probst (2006)[78] Probst (2009)[128] Hoogendijk (2010)[129]	G803R	4.03e-6	-
123	*SCN1A*	T808S	Mixed	Rhodes (2005)[130]	EPI	Fujiwara (2003)[131] [compound missense with N1011I]	T808S	-	-
819-832 Cytoplasmic									
124	*SCN5A*	D772N	Mixed	Glazer (2020)[1]	LQT3; BrS	Kapplinger (2009)[19] Kapplinger (2010)[12]	D823N	2.01e-5	-
125	*SCN5A*	P773S	STW	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	P824S	-	NC
833-852 S3 of D2									
126	*SCN5A*	D785N	LoF	Glazer (2020)[1]	BrS	Sayeed (2014)[132]	D836N	-	-
127	*SCN8A*	G822R	LoF	Wengert (2019)[65]	NDD without epilepsy	Wengert (2019)[65]	G837R	-	NC
853-854 Extracellular									
855-872 S4 of D2									
128	*SCN9A*	L823R	Mixed	Lampert (2009)[133]	IEM	Lampert (2009)[133]	L858R	-	-
129	*SCN10A*	R756W	LoF	Gando (2020)[91]	SUD	Gando (2020)[91]	R859W	5.68e-5	-
130	*SCN1A*	R859H	LoF	Volkers (2011)[134]	EPI	Volkers (2011)[134]	R859H	7.99e-6	-

131	*SCN4A*	R669H	LoF	Kuzmenkin (2002)[135]	HypoPP	Bulman (1999)[136]		8.05e-6	-
132	*SCN1A*	R859C	LoF	Bechi (2015)[124]	EPI	Depienne (2009)[137]	R859C	-	-
133	*SCN5A*	R808C	LoF	Glazer (2020)[1]	BrS	Kotta (2010)[138]		8.07e-6	-
134	*SCN9A*	F826Y	GoF	Wu (2017)[139]	IEM	Wu (2017)[139]	F861Y	-	-
135	*SCN4A*	R672G	LoF	Jurkatt-Rott (2000)[140] Kuzmenkin (2002)[135]	HypoPP	Jurkatt-Rott (2000)[140]	R862G	-	-
136	*SCN4A*	R672H	LoF	Jurkatt-Rott (2000)[140] Kuzmenkin (2002)[135]	HypoPP	Jurkatt-Rott (2000)[140]	R862H	1.21e-5	-
137	*SCN5A*	R811H	LoF	Calloe (2013)[114]	BrS	Calloe (2013)[114]		1.22e-5	-
138	*SCN2A*	R853Q	Mixed	Berecki (2018)[141] Mason (2019)[142]	EPI	Nakamura (2013)[55] Epi (2013)[143] Samanta (2015)[144] Kobayashi (2016)[145] Li (2016)[146] Wolff (2017)[96] Berecki (2018)[141]	R862Q	-	
139	*SCN3A*	L855P	GoF	Zaman (2020)[147]	Fetal Akinesia	Zaman (2020)[147]	L863P	-	NC
140	*SCN5A*	L812Q	LoF	Wang (2015)[148]	BrS	Wang (2015)[148]	L863Q	-	-
141	*SCN1A*	R865G	GoF	Volkers (2011)[134]	EPI	Volkers (2011)[134]	R865G	-	-
142	*SCN4A*	R675Q	Mixed	Wu (2014)[149]	NormoPP	Wu (2014)[149]	R865Q	8.19e-6	-
143	*SCN5A*	R814Q	Mixed	Glazer (2020)[1]	LQT3; BrS	Frigo (2007)[150] Sommariva (2013)[68] Itoh (2016)[151] Yamagata (2017)[21]		2.51e-5	-
144	*SCN5A*	K817E	LoF	Kinoshita (2016)[152]	BrS	Kinoshita (2016)[152]	K868E	-	-
873-888 Cytoplasmic									
145	*SCN1A*	T875M	LoF	Lossin (2002)[153]	EPI	Escayg (2000)[154]	T875M	-	-
146	*SCN3A*	I875T	GoF	Zaman (2018)[155] Zaman (2020)[147]	EPI/PMG	Zaman (2018)[155] Miyatake (2018)[156] Zaman (2020)[147]	I883T	-	-
147	*SCN9A*	I848T	GoF	Cummins (2004)[157] Namer (2015)[158] Thiele (2011)[159]	IEM	Yang (2004)[160] Drenth (2005)[42] Namer (2015)[158]		-	-
148	*SCN11A*	G699R	GoF	Han (2015)[161]	SFN	Han (2015)[161]	G888R	1.63e-4	-
889-907 S5 of D2									

149	*SCN5A*	L839P	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	L890P	-	-
150	*SCN9A*	G856D	GoF	Hoeijmakers (2012)[162]	IEM; SFN	Hoeijmakers (2012)[162]	G891D	-	-
151	*SCN9A*	G856R	GoF	Tanaka (2017)[163]	IEM	Tanaka (2017)[163]	G891R	-	-
152	*SCN9A*	L858F	GoF	Han (2006)[164] Han (2007)[165] Cregg (2014)[166]	IEM	Han (2006)[164] Drenth (2005)[42]	L893F	-	-
153	*SCN9A*	L858H	GoF	Cummins (2004)[157] Estacion (2010)[167] Thiele (2011)[159] Vasylyev (2014)[168]	IEM	Yang (2004)[160]	L893H	-	-
154	*SCN4A*	T704M	GoF	Bendahhou (1999)[169]	HyperPP; PMC	Huang (2019)[170]	T894M	-	-
155	*SCN9A*	A863P	GoF	Harty (2006)[171]	IEM	Harty (2006)[171]	A898P	-	NC
156	*SCN1A*	F902C	LoF	Rhodes (2004)[172]	EPI	Ohmori (2002)[173] - reported as F891C	F902C	-	-
157	*SCN5A*	F851L	LoF	Glazer (2020)[1]	BrS	Priori (2002)[7]	F902L	7.07e-6	-
158	*SCN9A*	V872G	GoF	Choi (2009)[174]	IEM	Choi (2009)[174]	V907G	-	-
908-936 Extracellular									
159	*SCN2A*	G899S	LoF	Wolff (2017)[96]	EPI	Wolff (2017)[96]	G908S	-	-
160	*SCN1A*	M909K	LoF	Kluckova (2020)[10]	EPI	Kluckova (2020)[10]	M909K	-	NC
161	*SCN9A*	Q875E	GoF	Stadler (2015)[175]	IEM	Skeik 2012[176]	Q910E	-	-
162	*SCN10A*	R814H	GoF	Savio-Galimberti (2014)[28]	AF	Savio-Galimberti (2014)[28]	K917H	3.08e-4	NC
163	*SCN2A*	K908E	GoF	Lauxmann (2018)[33]	EPI	Wolff (2017)[96] Lauxmann (2018)[33]	K917E	-	NC
164	*SCN9A*	R896Q	LoF	Cox (2010)[177]	CIP	Cox (2010)[177]	R931Q	1.06e-5	NC
165	*SCN5A*	W879R	LoF	Glazer (2020)[1]	BrS	Glazer (2020)[1]	W932R	-	-
937-957 Pore-forming									
166	*SCN1A*	H939Q	LoF	Ohmori (2006)[30]	EPI	Ohmori (2006)[30]	H939Q	-	-
167	*SCN5A*	I890T	LoF	Tarradas (2013)[178]	BrS	Tarradas (2013)[178]	I943T	-	NC
168	*SCN5A*	F892I	LoF	Glazer (2020)[1]	BrS	Savastano (2014)[179]	F945L	-	-

169	*SCN1A*	R946C	LoF	Volkers (2011)[134]	EPI	Volkers (2011)[134]	R946C	-	-
170	*SCN2A*	R937C	LoF	Ben-Shalom (2017)[5] Begemann (2019)[180]	ASD	Ben-Shalom (2017)[5] Begemann (2019)[180] Rauch (2012)[181]		-	-
171	*SCN1A*	R946H	LoF	Liao (2010b)[182] Volkers (2011)[134]	EPI	Liao (2010b)[182] Volkers (2011)[134]	R946H	-	-
172	*SCN2A*	R937H	LoF	Ben-Shalom (2017)[5]	ASD	Ben-Shalom (2017)[5]		-	-
173	*SCN5A*	E901K	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	E954K	-	-
174	*SCN1A*	M956T	LoF	Bechi (2015)[124]	EPI	Bechi (2015)[124]	M956T	-	-
958-970 Extracellular									
175	*SCN1A*	C959R	LoF	Ohmori (2006)[30]	EPI	Ohmori (2006)[30]	C959R	-	-
176	*SCN5A*	S910L	LoF	Pambrun (2014)[183]	BrS	Pambrun (2014)[183]	A963L	3.99e-6	NC
177	*SCN10A*	L867F	LoF	Gando (2020)[91]	SUD	Gando (2020)[91]	L969F	2.85e-5	NC
971-991 S6 of D2									
178	*SCN1A*	G979R	LoF	Sugawara (2003)[184] Rhodes (2005)[130]	EPI	Fujiwara (2003)[131]	G979R	-	-
179	*SCN8A*	G964R	LoF	Wagnon (2017)[185]	NDD without epilepsy	Wagnon (2017)[185]		-	-
180	*SCN5A*	N927S	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	N980S	-	NC
181	*SCN5A*	L928P	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	L981P	-	-
182	*SCN1A*	V983A	LoF	Rhodes (2005)[130]	EPI	Fujiwara (2003)[131]	V983A	-	-
183	*SCN1A*	N985I	LoF	Sugawara (2003)[184]	EPI	Fujiwara (2003)[131]	N985I	-	-
184	*SCN1A*	L986F	LoF	Lossin (2003)[186] Thompson (2012)[187]	EPI	Claes (2001)[188]	L986F	-	-
185	*SCN4A*	L796V	GoF	Elia (2020)[189]	PMC	Elia (2020)[189]	L986V	-	-
992-1219 Cytoplasmic									
186	*SCN5A*	S941N	GoF	Ruan (2007)[190]	LQT3	Schwarz (2000)[191]	S994N	-	-
187	*SCN11A*	N816K	GoF	Huang (2019)[192]	FEP	Huang (2019)[192]	A997K	3.99e-6	NC

188	*SCN2A*	E999K	GoF	Miao (2020)[193] Thompson (2020)[54]	EPI	Nakamura (2013)[55] Miao (2020)[193]	E1008K	-	NC
189	*SCN1A*	N1011I	LoF	Rhodes (2005)[130]	EPI	Fujiwara (2003)[131] [compound missense with T808S]	N1011I	-	NC
190	*SCN5A*	R965C	LoF	Hsueh (2009)[194]	BrS	Hsueh (2009)[194]	R1018C	6.49e-5	-
191	*SCN5A*	P1014S	STW	Glazer (2020)[1]	BrS	Glazer (2020)[1]	H1065S	-	NC
192	*SCN5A*	R1023H	LoF	Frustaci (2005)[87]	BrS	Frustaci (2005)[87]	L1073H	2.50-e4	NC
193	*SCN10A*	P1102S	GoF	Gando (2020)[91]	SUD	Gando (2020)[91]	P1167S	4.02e-6	NC
194	*SCN5A*	S1103Y	GoF	Splawski (2002)[195]	LQT3	Splawski (2002)[195] - reported as S1102Y Plant (2006)[196]	-	7.69e-3	NC
195	*SCN1A*	T1174S	Mixed	Cestele (2013)[197]	EPI	Cestele (2013)[197]	T1174S	1.71e-3	NC
196	*SCN9A*	W1150R	GoF	Estacion (2009)[198]	IEM	Drenth (2005)[42] Estacion (2009)[198]	Q1187R	0.88	NC
197	*SCN5A*	P1177L	GoF	Winkel (2012)[199]	LQT3	Winkel (2012)[199]	K1190L	-	NC
198	*SCN1A*	W1204R	Mixed	Lossin (2002)[153] Bechi (2015)[124]	EPI	Escayg (2001)[200] Marini (2007)[201]	W1204R	-	NC
199	*SCN5A*	R1193Q	LoF	Wang (2004)[202] Huang (2006)[203] Abdelsayed (2015)[204] Peters (2016)[88] Abe (2018)[205] Li (2019)[206]	LQT3; BrS	Takahata (2003)[207] Wang (2004)[202] Huang (2006)[203] Li (2019)[206]	N1206Q	5.18-e3	NC
1220-1237 S1 of D3									
200	*SCN2A*	E1211K	Mixed	Ogiwara (2009)[208]	EPI	Ogiwara (2009)[208]	E1221K	-	-
201	*SCN5A*	S1218I	LoF	Calloe (2013)[114]	BrS	Calloe (2013)[114]	S1231I	-	-
1238-1250 Extracellular									
202	*SCN5A*	E1225K	LoF	Glazer (2020)[1]	LQT3; BrS	Schulze-Bahr (2003)[209] Tester (2005)[6] Crotti (2012)[210] Sommariva (2013)[68] Andorin (2016)[71] Yamagata (2017)[21] Van Malderen (2017)[74]	E1238K	4.01e-6	-
203	*SCN5A*	R1232W	LoF	Baroudi (2002)[211] Makita (2008)[212]	BrS	Chen (1998)[213] Baroudi (2002)[211]	R1245W	-	NC
1251-1269 S2 of D3									

204	*SCN4A*	D1069N	LoF/Mixed	Zaharieva (2016)[14]	CMS	Zaharieva (2016)[14]	D1256N	1.20e-5	-
205	*SCN5A*	D1243N	LoF/Mixed	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]		1.45e-4	-
206	*SCN1A*	M1267I	LoF	Nissenkorn (2019)[29]	EPI	Nissenkorn (2019)[29]	M1267I	-	-
1270-1283 Cytoplasmic									**-**
207	*SCN1A*	A1273V	Mixed	Peters (2016)[214]	EPI	Peters (2016)[214]	A1273V	-	-
208	*SCN5A*	G1262S	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	G1275S	2.83e-5	-
1284-1302 S3 of D3									
209	*SCN3A*	V1280I	STW	Zaman (2020)[147]	EPI	Zaman (2020)[147]	V1292I	1.2e-5	NC
210	*SCN5A*	V1281F	Mixed	Glazer (2020)[1]	BrS	Hermida (2013)[215]	V1294F	-	-
1303-1310 Extracellular									
211	*SCN5A*	A1294G	LoF	Zaytseva (2019)[216]	BrS	Zaytseva (2019)[216]	S1307G	2.86e-5	NC
212	*SCN5A*	E1295K	GoF	Abriel (2001)[217]	LQT3	Abriel (2001)[217]	E1308K	4.02e-6	NC
1311-1329 S4 of D3									
213	*SCN9A*	R1279P	GoF	Huang (2014)[218]	PPN	Huang (2014)[218]	R1316P	-	-
214	*SCN5A*	T1304M	GoF	Wang (2007)[36]	LQT3	Wang (2007)[36] Kapplinger (2009)[19] Olesen (2012)[219]	T1317M	1.65e-4	-
215	*SCN5A*	L1308F	STW	Barajaz-Martinez (2008)[51]	BrS	Barajaz-Martinez (2008)[51] Kapplinger (2010)[12] [compound missense with V232I]	L1321F	4.71e-4	NC
216	*SCN2A*	R1312T	LoF	Lossin (2012)[220]	EPI	Shi (2009)[221]	R1322T	-	-
217	*SCN11A*	L1158P	GoF	Huang (2014)[90]	SFN	Huang (2014)[90]	L1327P	4.71e-4	-
218	*SCN2A*	R1319Q	LoF	Misra (2008)[222]	EPI	Berkovic (2004)[223] Wolff (2017)[96]	R1329Q	-	NC
1330-1346 Cytoplasmic									
219	*SCN5A*	G1319V	LoF	Casini (2007)[224]	BrS	Casini (2007)[224]	G1332V	4.08e-5	-
220	*SCN9A*	V1298F	GoF	Jarecki (2008)[225] Cheng (2010)[226] Estacion (2010)[167]	PEPD	Fertleman (2006)[227]	V1335F	-	-

221	*SCN9A*	V1299F	GoF	Jarecki (2008)[225] Thiele (2011)[159]	PEPD	Fertleman (2006)[227]	V1336F	-	-
222	*SCN5A*	N1325S	GoF	Wang (1996)[228] Tian (2004)[229] Glazer (2020)[1] Li (2020)[230]	LQT3	Wang (1995)[231]	N1338S	-	NC
223	*SCN2A*	L1330F	LoF	Misra (2008)[222]	EPI	Heron (2002)[232]	L1340F	-	-
224	*SCN5A*	V1328M	GoF	Turker (2016)[233]	BrS	Turker (2016)[233]	L1341M	-	NC
225	*SCN5A*	A1330P	GoF	Wedekind (2001)[234] Berecki (2006)[235]	LQT3	Wedekind (2001)[234]	A1343P	-	-
226	*SCN4A*	A1156T	GoF	Palmio (2017)[236]	HyperPP; PMC	McClatchey (1992)[237]	A1343T	5.33e-5	-
227	*SCN5A*	A1330T	GoF	Smits (2005b)[238]	LQT3	Smits (2005b)[238]		-	-
228	*SCN3A*	P1333L	GoF	Zaman (2018)[155] Zaman (2020)[147]	EPI	Zaman (2018)[155]	P1345L	-	-
229	*SCN4A*	P1158L	GoF	Desaphy (2016)[239]	PAM	Desaphy (2016)[239]		-	-
230	*SCN5A*	P1332L	GoF	Ruan (2007)[190]	LQT3	Ruan (2007)[190] Schulze-Bahr (2004)[240]		-	-
231	*SCN9A*	P1308L	GoF	Cheng (2010)[226]	IEM	Cheng (2010)[226]		-	-
232	*SCN4A*	P1158S	Mixed	Sugiara (2003)[241] Webb (2008)[242]	HypoPP	Sugiara (2003)[241]	P1345S	-	-
233	*SCN5A*	S1333Y	GoF	Huang (2009)[243]	LQT3	Huang (2009)[243]	S1346Y	-	NC
234	*SCN2A*	S1336Y	GoF	Thompson (2020)[54]	EPI	Nakamura (2013)[55]		-	NC
1347-1366 S5 of D3									
235	*SCN8A*	I1327V	GoF	Barker (2016)[244]	EPI	Vaher (2014)[245] Singh (2015)[246]	I1347V	-	-
236	*SCN2A*	N1339D	GoF	Miao (2020)[193]	EPI	Miao (2020)[193]	N1349D	-	-
237	*SCN8A*	L1331V	GoF	Patel (2016)[247]	EPI	Carvill (2013)[248] - reported as L1290V	L1351V	-	-
238	*SCN2A*	L1342P	Mixed	Begemann (2019)[180]	EPI	Hackenberg (2014)[249] Matalon (2014)[250] Dimassi (2016)[251] Wolff (2017)[96] Begemann (2019)[180]	L1352P	-	-
239	*SCN9A*	V1316A	GoF	Wu (2013)[252] Estacion (2013)[253]	IEM	Huang (2016)[254] Estacion (2013)[253]	V1353A	-	-
240	*SCN11A*	V1184A	GoF	Leipold (2015)[255]	PPN	Leipold (2015)[255]		-	-

241	*SCN5A*	V1340I	LoF	Samani (2009)[256]	BrS	Samani (2009)[256]	V1353I	4.60e-5	-
242	*SCN1A*	V1353L	LoF	Lossin (2003)[186]	EPI	Wallace (2001)[257]	V1353L	-	-
243	*SCN5A*	F1344S	LoF	Keller (2006)[258]	BrS	Keller (2006)[258]	F1357S	-	-
244	*SCN5A*	W1345C	LoF	Glazer (2020)[1]	BrS	Lee (2010)[259]	W1358C	-	-
245	*SCN5A*	L1346P	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	L1359P	-	-
246	*SCN1A*	V1366I	LoF	Bechi (2015)[124]	EPI	Osaka (2007)[260]	V1366I	-	-
247	*SCN5A*	V1353M	STW	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	V1366M	2.78e-5	NC
1367-1418 Extracellular									
248	*SCN10A*	A1304T	GoF	Faber (2012)[111]	PPN	Faber (2012)[111]	A1370T	4.60e-5	NC
249	*SCN8A*	T1360N	LoF	Wengert (2019)[65]	NDD without epilepsy	Wengert (2019)[65]	T1380N	-	-
250	*SCN5A*	V1378M	LoF	Moreau (2012)[18]	BrS	Moreau (2012)[18]	V1390M	3.99e-6	NC
251	*SCN5A*	N1380K	LoF	Glazer (2020)[1]	BrS	Rudnik-Schöneborn (2011)[261]	N1392K	-	-
252	*SCN5A*	S1382I	LoF	Glazer (2020)[1]	BrS	Probst (2009)[128]	T1394I	-	NC
253	*SCN4A*	C1209F	LoF	Zaharieva (2016)[14]	CMS	Zaharieva (2016)[14]	C1396F	-	-
254	*SCN2A*	C1386R	LoF	Ben-Shalom (2017)[5]	ASD	Ben-Shalom (2017)[5]	C1396R	-	-
255	*SCN5A*	V1405L	LoF	Glazer (2020)[1]	BrS	Amin (2011)[82]	V1418L	-	-
256	*SCN5A*	V1405M	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12] Zumhagen (2016)[262] Yamagata (2017)[21]	V1418M	-	-
1419-1440 Pore-forming									
257	*SCN5A*	G1406E	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	G1419E	-	NC
258	*SCN5A*	G1406R	LoF	Tan (2006)[263]	BrS	Kyndt (2001)[264]	G1419R	-	NC
259	*SCN1A*	G1421W	LoF	Kim (2018)[265]	EPI	Kim (2018)[265]	G1421W	-	NC
260	*SCN2A*	T1420M	LoF	Ben-Shalom (2017)[5]	ASD	Ben-Shalom (2017)[5]	T1430M	-	-

261	*SCN5A*	G1420R	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	G1433R	-	-
262	*SCN5A*	G1420V	LoF	Glazer (2020)[1]	BrS	Hermida (2010)[266]	G1433V	-	-
1441-1457 Extracellular									
263	*SCN5A*	A1428S	LoF	Zhu (2015)[267]	BrS	Zhu (2015)[267]	A1441S	3.19e-5	-
264	*SCN5A*	A1428V	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12] Van Malderen (2017)[74]	A1441V	-	-
265	*SCN5A*	D1430N	LoF	Maury (2013)[268]	BrS	Maury (2013)[268]	D1443N	-	-
266	*SCN5A*	R1432G	LoF	Deschenes (2000)[269] Glazer (2020)[1]	BrS	Deschenes (2000)[269]	R1445G	-	NC
1458-1479 S6 of D3									
267	*SCN5A*	Y1449C	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12] Hothi (2015)[270] Van Malderen (2017)[74]	Y1462C	-	-
268	*SCN5A*	T1461S	LoF	Glazer (2020)[1]	BrS	Sacilotto (2017)[271]	T1474S	-	-
1480-1542 Cytoplasmic									
269	*SCN4A*	V1293I	GoF	Farinato (2019)[272]	PMC	Koch (1995)[273]	V1481I	-	-
270	*SCN2A*	I1473M	GoF	Ogiwara (2009)[208]	EPI	Ogiwara (2009)[208]	I1483M	-	-
271	*SCN3A*	I1468R	Mixed	Zaman (2020)[147]	EPI	Zaman (2020)[147]	I1483R	-	-
272	*SCN4A*	N1297K	GoF	Farinato (2019)[272]	PMC	Farinato (2019)[272] Gay (2008)[274]	N1485K	-	-
273	*SCN4A*	N1297S	GoF	Maggi (2017)[275] Farinato (2019)[272]	PMC	Maggi (2017)[275]	N1485S	-	-
274	*SCN4A*	F1298C	GoF	Farinato (2019)[272]	PAM	Farinato (2019)[272]	F1486C	-	-
275	*SCN5A*	F1473C	GoF	Bankston (2007)[276]	LQT3	Bankston (2007)[276]		-	-
276	*SCN5A*	F1473S	GoF	Cai (2016)[277]	LQT3	Ruan (2010)[278]	F1486S	-	-
277	*SCN9A*	F1449V	GoF	Dib-Hajj (2005)[279] Gurkiewicz (2011)[280]	IEM	Dib-Hajj (2005)[279]	F1486V	-	-
278	*SCN5A*	Q1475P	GoF	Gando (2020b)[281]	LQT3	Tan (2017)[282]	Q1488P	-	-
279	*SCN1A*	Q1489H	GoF	Barbieri (2019)[283]	FHM	Vahedi (2009)[284]	Q1489H	-	-

280	*SCN1A*	Q1489K	GoF	Kahlig (2008)[64] Cestèle (2008)[285]	FHM	Kahlig (2008)[64] Cestèle (2008)[285]	Q1489K	-	-
281	*SCN5A*	Q1476R	GoF	Moreau (2013)[286]	LQT3	Moreau (2013)[286]	Q1489R	-	-
282	*SCN4A*	G1306E	GoF	Farinato (2019)[272]	PAM	Lerche (1993)[287]	G1494E	-	-
283	*SCN8A*	G1475R	GoF	Liu (2019)[288] Zaman (2019)[22]	EPI	Parrini (2017)[289] Wang (2017)[290] Xiao (2018)[291] Gardella (2018)[292] Liu (2019)[288] Zaman (2019)[22]	G1494R	-	-
284	*SCN1A*	I1498M	LoF	Barbieri (2019)[283]	FHM	Weller (2014)[293]	I1498M	-	-
285	*SCN4A*	I1310N	GoF	Farinato (2019)[272]	PMC	Farinato (2019)[272]	I1498N	-	-
286	*SCN9A*	I1461T	GoF	Fertleman (2006)[227]	PEPD	Fertleman (2006)[227]	I1498T	-	-
287	*SCN5A*	F1486L	GoF	Wang (2007)[36]	LQT3	Wang (2007)[36]	F1499L	-	-
288	*SCN1A*	F1499L	GoF	Barbieri (2019)[283]	FHM	Vahedi (2009)[284]		-	-
289	*SCN1A*	M1500V	GoF	Barbieri (2019)[283]	FHM	Domitrz (2016)[294]	M1500V	-	-
290	*SCN4A*	T1313A	GoF	Bouhours (2004)[295]	PMC	Bouhours (2004)[295]	T1501A	-	-
291	*SCN4A*	T1313M	GoF	Farinato (2019)[272]	PMC	Farinato (2019)[272]	T1501M	4.00e-6	-
292	*SCN9A*	T1464I	GoF	Fertleman (2006)[227] Thiele (2011)[159]	PEPD	Fertleman (2006)[227]	T1501I	-	-
293	*SCN3A*	T1486I	GoF	Zaman (2020)[147]	EPI/PMG	Zaman (2020)[147]		-	-
294	*SCN8A*	A1491V	GoF	Zaman (2019)[22]	EPI	Zaman (2019)[22]	A1510V	-	-
295	*SCN5A*	P1506S	LoF	Saber (2015)[296]	BrS	Saber (2015)[296]	P1519S	-	-
296	*SCN5A*	R1512W	LoF	Deschenes (2000)[269] Zheng (2016)[297]	BrS	Deschenes (2000)[269] Smits (2002)[127] Zheng (2016)[297]	R1525W	5.57e-5	-
297	*SCN1A*	R1525Q	LoF	Binini (2017)[72]	EPI	Binini (2017)[72]	R1525Q	3.99e-6	-
1543-1560 S1 of D4									
298	*SCN5A*	N1541D	LoF	Dharmawan (2019)[298]	BrS	Dharmawan (2019)[298]	N1554D	-	-
299	*SCN4A*	N1366S	GoF	Ke (2017)[299]	PMC	Ke (2017)[299]	N1554S	-	-

1561-1571 Extracellular									
1572-1590 S2 of D4									
300	*SCN2A*	L1563V	Mixed	Misra (2008)[222] Berecki (2018)[141] Begemann (2019)[180]	EPI	Lewis (1996)[300] Heron (2002)[232]	L1573V	-	-
301	*SCN9A*	W1538R	GoF	Cregg (2013)[301]	IEM	Cregg (2013)[301]	R1575R	2.02e-3	NC
302	*SCN1A*	R1575C	GoF	Ohmori (2008)[302]	EPI	Ohmori (2008)[302]	R1575C	7.18e-5	NC
303	*SCN2A*	I1571T	GoF	Miao (2020)[193]	EPI	Miao (2020)[193]	I1581T	-	NC
304	*SCN10A*	V1518I	LoF	Gando (2020)[91]	SUD	Gando (2020)[91]	L1583I	7.78e-5	NC
305	*SCN1A*	E1587K	LoF	Kluckova (2020)[10]	EPI	Kluckova (2020)[10]	E1587K	-	-
306	*SCN5A*	E1574K	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]		-	-
1591-1602 Cytoplasmic									
307	*SCN1A*	R1596C	LoF	Kluckova (2020)[10]	EPI	Harkin (2007)[303] Depienne (2009)[137] Kim (2014)[304]	R1596C	-	-
308	*SCN5A*	R1583C	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]		8.03e-6	-
309	*SCN2A*	Y1589C	GoF	Lauxmann (2013)[305]	EPI	Lauxmann (2013)[305]	Y1599C	-	-
1603-1620 S3 of D4									
310	*SCN5A*	I1593M	STW	Kapplinger (2015)[8]	LQT3	Kapplinger (2015)[8]	I1606M	4.02e-6	NC
311	*SCN2A*	F1597L	GoF	Wolff (2017)[96]	EPI	Wolff (2017)[96]	F1607L	-	-
312	*SCN5A*	D1595N	LoF	Wang (2002)[306]	PCCD; BrS	Wang (2002)[306]	D1608N	-	-
313	*SCN1A*	V1611F	GoF	Rhodes (2005)[130]	EPI	Fujiwara (2003)[131]	V1611F	4.03e-6	-
1621-1633 Extracellular									
314	*SCN5A*	S1609L	GoF	Winkel (2015)[103]	LQT3	Winkel (2015)[103]	A1622L	-	NC
315	*SCN1A*	L1624P	GoF	Fan (2016)[307]	FHM	Fan (2016)[307]	L1624P	-	NC
316	*SCN4A*	V1442E	LoF	Tsujino (2003)[57]	CMS	Tsujino (2003)[57]	V1630E	-	NC

317	*SCN1A*	P1632S	LoF	Rhodes (2005)[130]	EPI	Fujiwara (2003)[131]	P1632S	-	-
318	*SCN2A*	P1622S	LoF	Wolff (2017)[96]	EPI	Wolff (2017)[96]		-	-
319	*SCN5A*	T1620K	Mixed	Surber (2008)[308]	LQT3	Surber (2008)[308]	T1633K	-	-
320	*SCN2A*	T1623N	GoF	Thompson (2020)[54]	EPI	Nakamura (2013)[55]	T1633N	-	-
321	*SCN5A*	T1620M	LoF	Baroudi (2002)[211] Wang (2000)[309] Makita (2008)[212]	BrS	Chen (1998)[213] Baroudi (2002)[211]	T1633M	3.99e-6	-
1634-1650 S4 of D4									
322	*SCN3A*	R1621G	GoF	Zaman (2020)[147]	EPI/PMG	Zaman (2020)[147]	R1636G	-	-
323	*SCN3A*	R1621Q	GoF	Zaman (2020)[147]	EPI/PMG	Zaman (2020)[147]	R1636Q	3.98e-6	-
324	*SCN5A*	R1623Q	GoF	Kambouris (1998)[310] Tsurugi (2009)[311] Li (2020)[230]	LQT3	Kambouris (2000)[312] Miura (2003)[313]		-	-
325	*SCN8A*	R1617Q	GoF	Wagnon (2015)[314]	EPI	Ohba (2014)[315] Kong (2015)[316] Larsen (2015)[317]		-	-
326	*SCN4A*	R1451C	LoF	Poulin (2018)[318]	HypoPP	Poulin (2018)[318]	R1639C	1.21e-5	-
327	*SCN5A*	R1626P	GoF	Ruan (2007)[190]	LQT3	Ruan (2007)[190]	R1639P	-	-
328	*SCN4A*	R1451L	LoF	Poulin (2018)[318]	PMC	Poulin (2018)[318]	R1639L	4.04e-6	-
329	*SCN8A*	R1620L	LoF	Liu (2019)[288]	ASD	Liu (2019)[288]		-	-
330	*SCN8A*	A1622D	GoF	Liu (2019)[288]	ASD	Liu (2019)[288]	A1641D	-	-
331	*SCN5A*	R1629Q	LoF	Zeng (2013)[319]	BrS	Zeng (2013)[319]	R1642Q	1.19e-5	-
332	*SCN4A*	R1454W	LoF	Habbout (2016)[320]	CMS	Habbout (2016)[320]	R1642W	1.61e-5	-
333	*SCN4A*	I1455T	Mixed	Bednarz (2016)[321]	PMC	Bednarz (2016)[321]	I1643T	1.20e-5	-
334	*SCN5A*	G1631D	GoF	Wang (2008)[322]	LQT3	Wang (2008)[322]	G1644D	-	-
335	*SCN9A*	G1607R	GoF	Choi (2011)[323]	PEPD	Choi (2011)[323]	G1644R	-	-
336	*SCN5A*	R1632C	LoF	Nakajima (2015)[324] Dharmawan (2019)[298]	BrS	Nakajima (2015)[324] García-Molina (2016)[325]	R1645C	3.98e-6	-
337	*SCN4A*	R1457H	LoF	Arnold (2015)[326]	CMS	Arnold (2015)[326]	R1645H	4.01e-6	-

338	*SCN5A*	R1632H	Mixed	Benson (2003)[327] Glazer (2020)[1]	BrS	Robyns (2014)[328]		7.96e-6	-
339	*SCN1A*	R1648C	Mixed	Rhodes (2004)[172] Thompson (2012)[187]	EPI	Ohmori (2002)[173] – reported as R1638C	R1648C	-	-
340	*SCN1A*	R1648H	Mixed	Lossin (2002)[153] Vanoye (2006)[329] Kahlig (2010)[330]	EPI	Escayg (2000)[154]	R1648H	-	-
341	*SCN4A*	R1460Q	Mixed	Elia (2019)[331]	CMS	Elia (2019)[331]	R1648Q	8.01e-6	-
342	*SCN4A*	R1460W	Mixed	Elia (2019)[331]	CMS	Elia (2019)[331]	R1648W	2.13e-5	-
343	*SCN9A*	L1612P	GoF	Suter (2015)[332]	PEPD	Suter (2015)[332]	L1649P	-	-
344	*SCN1A*	L1649Q	Mixed	Kahlig (2008)[64] Cestèle (2013)[333]	FHM	Kahlig (2008)[64] Cestèle (2013)[333]	L1649Q	-	-
1651-1669 Cytoplasmic									
345	*SCN10A*	R1588Q	LoF	Jabbari (2015)[13]	AF	Jabbari (2015)[13]	K1651Q	1.19e-5	NC
346	*SCN5A*	G1642E	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	G1655E	-	-
347	*SCN1A*	I1656M	LoF	Lossin (2003)[186] Liu (2013)[334]	EPI	Wallace (2001)[257]	I1656M	-	-
348	*SCN1A*	R1657C	LoF	Lossin (2003)[186]	EPI	Lossin (2003)[186]	R1657C	-	-
349	*SCN5A*	R1644C	LoF	Frustaci (2005)[87]	BrS	Frustaci (2005)[87]		3.98e-6	-
350	*SCN8A*	R1638C	LoF	Wengert (2019)[65]	NDD without epilepsy	Wengert (2019)[65]		-	-
351	*SCN5A*	R1644H	GoF	Wang (1996)[228] Nieto-Marin (2019)[335]	LQT3	Nieto-Marin (2019)[335]	R1657H	-	-
352	*SCN3A*	F1646C	GoF	Zaman (2020)[147]	EPI/PMG	Zaman (2020)[147]	F1661C	-	-
353	*SCN1A*	F1661L	GoF	Barbieri (2019)[283]	FHM	Weller (2014)[293]	F1661L	-	-
354	*SCN1A*	F1661S	Mixed	Rhodes (2004)[172] Thompson (2012)[187]	EPI	Claes (2003)[89]	F1661S	-	-
355	*SCN4A*	F1473S	GoF	Fleischhauer (1998)[336]	PMC	Fleischhauer (1998)[336]		-	-
356	*SCN1A*	M1664K	LoF	Bechi (2015)[124]	EPI	Depienne (2010)[337]	M1664K	-	-
357	*SCN9A*	M1627K	GoF	Fertleman (2006)[227] Dib-Hajj (2008)[338] Thiele (2011)[159]	PEPD	Fertleman (2006)[227]		-	-
358	*SCN5A*	M1652R	GoF	Ruan (2007)[190] Li (2020)[230]	LQT3	Ruan (2007)[190]	M1665R	-	-

359	*SCN2A*	P1658S	LoF	Miao (2020)[193]	EPI	Miao (2020)[193]	P1668S		-
360	*SCN5A*	A1656D	GoF	Kim (2019)[339]	LQT3	Kim (2019)[339]	A1669D	-	-
361	*SCN9A*	A1632E	GoF	Estacion (2008)[340] Rühlmann (2020)[341]	IEM; PEPD	Estacion (2008)[340]	A1669E	-	-
362	*SCN9A*	A1632G	GoF	Yang (2016)[342]	IEM	Yang (2016)[342]	A1669G	-	-
363	*SCN9A*	A1632T	GoF	Eberhardt (2014)[343]	IEM	Eberhardt (2014)[343]	A1669T	-	NC
1670-1687 S5 of D4									
364	*SCN1A*	L1670W	Mixed	Bertelli (2018)[344] Dhifallah (2018)[345]	FHM	Dhifallah (2018)[345]	L1670W	-	-
365	*SCN5A*	I1660V	LoF	Cordeiro (2006)[75]	BrS	Cordeiro (2006)[75]	I1673V	3.18e-5	-
366	*SCN1A*	G1674R	LoF	Rhodes (2004)[172] Thompson (2012)[187]	EPI	Ohmori (2002)[173] - reported as G1664R	G1674R	-	-
367	*SCN5A*	G1661R	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12] Van Malderen (2017)[74]		-	-
368	*SCN5A*	V1667I	GoF	Nakajima (2020)[346]	LQT3	Nakajima (2020)[346]	V1680I	3.98e-6	NC
369	*SCN4A*	I1495F	Mixed	Bendahhou (1999)[169]	HyperPP	Bendahhou (1999)[169]	I1683F	-	-
370	*SCN3A*	Y1669C	LoF	Zaman (2020)[147]	ASD	Zaman (2020)[147]	Y1684C	-	NC
371	*SCN1A*	A1685D	LoF	Sugiura (2012)[347]	EPI	Fujiwara (2003)[131]	A1685D	-	NC
372	*SCN1A*	A1685V	LoF	Lossin (2003)[186] Sugiura (2012)[347]	EPI	Sugawara (2001)[348]	A1685V	-	NC
373	*SCN5A*	S1672Y	LoF	Glazer (2020)[1]	BrS	Kapplinger (2010)[12] Andorin (2016)[71]	A1685Y	-	NC
1688-1709 Extracellular									
374	*SCN5A*	A1680T	STW	Glazer (2020)[1]	BrS	Kapplinger (2010)[12]	A1693T	4.6e-5	NC
375	*SCN10A*	D1639N	LoF	Kaluza (2018)[349]	SFN	Dabby (2016)[350]	D1702N	8.75e-5	NC
376	*SCN5A*	D1690N	LoF	Zeng (2016)[351] Nunez (2013)[352]	BrS	Zeng (2016)[351] Nunez (2013)[352]	D1703N	3.98e-6	-
377	*SCN1A*	T1709I	LoF	Rhodes (2005)[130]	EPI	Fujiwara (2003)[131]	T1709I	-	-
1710-1732 Pore-forming									

378	*SCN5A*	T1709M	LoF	Glazer (2020)[1]	LQT3; BrS	Kapplinger (2010)[12] Lakshmanadoss (2016)[353]	T1722M	3.98e-6	-
379	*SCN5A*	G1712C	LoF	Chen (2016)[354]	BrS	Kapplinger (2015)[8] Chen (2016)[354]	G1725C	-	-
380	*SCN10A*	G1662S	GoF	Han (2014)[355]	SFN	Han (2014)[355]	G1725S	1.36e-3	-
381	*SCN5A*	D1714G	LoF	Amin (2005)[356]	BrS	Amin (2005)[356]	D1727G	-	-
1733-1762 Extracellular									
382	*SCN5A*	N1722D	LoF	Glazer (2020)[1]	BrS	Probst (2009)[128]	N1735D	-	NC
383	*SCN5A*	P1730H	LoF	Glazer (2020)[1]	BrS	Van Malderen (2017)[74]	P1743H	-	NC
384	*SCN1A*	G1749E	LoF	Rhodes (2004)[172]	EPI	Claes (2003)[89]	G1749E	-	NC
385	*SCN5A*	G1740R	LoF	Baroudi (2004)[357]	BrS	Baroudi (2004)[357] Kapplinger (2010)[12]	G1754R	-	-
386	*SCN5A*	G1743R	LoF	Valdivia (2004)[358]	BrS	Takahata (2003)[207] Valdivia (2004)[358]	G1757R	-	NC
387	*SCN5A*	G1748D	LoF	Nunez (2013)[352]	BrS	Nunez (2013)[352]	G1762D	-	NC
1763-1785 S6 of D4									
388	*SCN1A*	F1765L	LoF	Liao (2010b)[182]	EPI	Liao (2010b)[182]	F1765L	-	NC
389	*SCN10A*	I1706V	GoF	Huang (2013)[359]	SFN	Huang (2013)[359]	I1770V	-	-
390	*SCN1A*	F1774S	GoF	Bertelli (2018)[344]	FHM	Chastan (2016)[360]	F1774S	-	-
391	*SCN5A*	I1762A	GoF	Chang (2004)[361]	LQT3	Chang (2004)[361]	V1776A	-	NC
392	*SCN5A*	V1763M	GoF	Chang (2004)[361]	LQT3	Chang (2004)[361]	V1777M	-	NC
393	*SCN8A*	V1758A	LoF	Zaman (2019)[22]	EPI	Zaman (2019)[22]	V1778A	-	-
394	*SCN5A*	V1764M	GoF	Chang (2004)[361]	LQT3	Chang (2004)[361]	V1778M	-	-
395	*SCN3A*	M1765I	GoF	Zaman (2020)[147]	EPI/PMG	Zaman (2020)[147]	M1780I	-	-
396	*SCN8A*	M1760I	GoF	Liu (2019)[288]	EPI	Liu (2019)[288]		-	-
397	*SCN5A*	M1766L	Mixed	Valdivia (2002)[362] Ye (2003)[106]	LQT3	Valdivia (2002)[362] Ye (2003)[106]	M1780L	-	-

398	*SCN5A*	Y1767C	GoF	Huang (2006)[203] Huang (2011)[363]	LQT3	Huang (2011)[363]	Y1781C	-	-
399	*SCN5A*	I1768V	GoF	Rivolta (2002)[364] Clancy (2003)[365]	LQT3	Rivolta (2002)[364]	I1782V	-	-
400	*SCN9A*	A1746G	GoF	Cregg (2013)[301]	IEM	Cregg (2013)[301]	A1783G	-	-
401	*SCN2A*	A1773T	LoF	Miao (2020)[193]	EPI	Miao (2020)[193]	A1783T	-	-
402	*SCN3A*	V1769A	GoF	Zaman (2018)[155] Zaman (2020)[147]	EPI	Zaman (2018)[155]	V1784A	-	NC
1786-2009 Cytoplasmic									
403	*SCN5A*	N1774D	GoF	Kato (2014)[94]	LQT3	Kato (2014)[94]	N1788D	-	-
404	*SCN8A*	N1768D	GoF	Veeramah (2012)[366] Patel (2016)[247] Baker (2018)[367]	EPI	Veeramah (2012)[366]		-	-
405	*SCN5A*	N1774H	Mixed	Neubauer (2019)[368]	LQT3	Neubauer (2019)[368]	N1788H	-	-
406	*SCN5A*	E1784K	Mixed	Deschenes (2000)[269] Abdelsayed (2015)[204] Peters (2016)[88] Veltmann (2016)[108] Abdelsayed (2017)[369] Abdelsayed (2018)[370] Glazer (2020)[1]	LQT3; BrS	Deschenes (2000)[269] Takahashi (2014)[371] Veltmann (2016)[108]	E1798K	-	NC
407	*SCN5A*	S1787N	GoF	Hu (2015)[372]	LQT3	Splawski (2000)[373]	S1801N	8.29e-4	NC
408	*SCN5A*	D1790G	Mixed	An (1998)[374] Wehrens (2000)[375] Baroudi (2000)[376]	LQT3; BrS	Benhorin (1998)[377] Blich (2015)[378]	D1804G	-	-
409	*SCN1A*	F1808L	Mixed	Rhodes (2005)[130]	EPI	Fujiwara (2003)[131]	F1808L	-	-
410	*SCN5A*	Y1795C	GoF	Rivolta (2001)[379] Berecki (2006)[235] Fredj (2006)[380]	LQT3	Rivolta (2001)[379] Benito (2008)[381] Kapplinger (2015)[8]	Y1809C	-	-
411	*SCN5A*	Y1795H	LoF	Rivolta (2001)[379]	BrS	Rivolta (2001)[379]	Y1809H	-	-
412	*SCN2A*	E1803G	GoF	Begemann (2019)[180]	EPI	Papuc (2019)[382] Begemann (2019)[180]	E1813G	-	-
413	*SCN4A*	Q1633E	GoF	Kubota (2009)[383]	PAM	Kubota (2009)[383]	Q1821E	-	-
414	*SCN1A*	F1831S	LoF	Sugawara (2003)[184]	EPI	Fujiwara (2003)[131]	F1831S	-	-
415	*SCN5A*	L1825P	LoF	Liu (2005)[384]	LQT3	Makita (2002)[385]	L1839P	-	-
416	*SCN5A*	Q1832E	LoF	Gando (2017)[386]	BrS	Gando (2017)[386]	K1846E	9.97e-5	NC

417	*SCN1A*	M1852T	Mixed	Rusconi (2007)[387]	EPI	Annesi (2003)[125]	M1852T	-	NC
418	*SCN5A*	C1850S	LoF	Petitprez (2008)[388]	BrS	Petitprez (2008)[388]	C1864S	-	-
419	*SCN1A*	D1866Y	GoF	Spampanato (2004)[389]	EPI	Spampanato (2004)[389]	D1866Y	-	-
420	*SCN2A*	M1879T	GoF	Adney (2020)[390]	EPI	Adney (2020)[390]	M1889T	-	-
421	*SCN8A*	R1872L	GoF	Wagnon (2015)[314] Zaman (2019)[22]	EPI	Wagnon (2015)[314] Zaman (2019)[22]	R1892L	-	NC
422	*SCN2A*	R1882G	GoF	Schwarz (2016)[63]	EPI	Schwarz (2016)[63]	R1892G	-	NC
423	*SCN2A*	R1882Q	GoF	Wolff (2017)[96] Berecki (2018)[141] Mason (2019)[142]	EPI	Howell (2015)[391] Trump (2016)[392] Wolff (2017)[96] Berecki (2018)[141]	R1892Q	-	NC
424	*SCN8A*	R1872Q	GoF	Wagnon (2015)[314] Aktin (2018)[393]	EPI	Wagnon (2015)[314] Atkin (2018)[393]		4.02e-6	NC
425	*SCN8A*	R1872W	GoF	Liu (2019)[288] Zaman (2019)[22]	EPI	Gardella (2016)[394] Zaman (2019)[22]	R1892W	-	NC
426	*SCN1A*	T1909I	Mixed	Ohmori (2006)[30]	EPI	Ohmori (2002)[30]	T1909I	-	-
427	*SCN5A*	R1897W	LoF	Olesen (2012)[219]	LQT3	Kapplinger (2009)[19]	K1911W	-	NC
428	*SCN5A*	R1898C	LoF	Glazer (2020)[1]	BrS	Selga (2015)[395] Zhang (2016)[396]	R1912C	3.56e-5	NC
429	*SCN1A*	Q1923R	LoF	Nissenkorn (2019)[29]	EPI	Shi (2012)[40] Nissenkorn (2019)[29]	Q1923R	-	-
430	*SCN5A*	Q1909R	Mixed	Winkel (2015)[103] Abdelsayed (2017)[369]	LQT3	Winkel (2015)[103] Kapplinger (2015)[8]		-	-
431	*SCN1A*	R1927G	LoF	Rusconi (2009)[397]	EPI	Rusconi (2009)[397]	R1927G	-	-
432	*SCN1A*	T1934I	LoF	Kluckova (2020)[10]	EPI	Kluckova (2020)[10]	T1934I	3.19e-5	NC
433	*SCN10A*	A1886V	GoF	Savio-Galimberti (2014)[28]	AF	Savio-Galimberti (2014)[28]	G1950V	1.20e-3	NC
434	*SCN5A*	I1968S	LoF	Frustaci (2005)[87]	BrS	Frustaci (2005)[87]	M1977S	1.64e-5	NC
435	*SCN5A*	Y1977N	Mixed	Casini (2019)[398]	LQT3	Casini (2019)[398]	Y1986N	-	NC
436	*SCN5A*	F2004L	LoF	Bebarova (2008)[399]	LQT3; BrS	Bebarova (2008)[399] Arnestad (2007)[400]	-	1.02e-5	NC
437	*SCN5A*	P2006A	GoF	Shinlapawittayatorn (2011)[401]	LQT3	Shinlapawittayatorn(2011)[401]	-	1.11e-3	NC

Legend:

gnomAD frequencies (marked in grey)

NC = not conserved (marked in grey) = corresponding position of variants do not share the same amino acid

STW = Similar to Wildtype function (variant marked in grey)

Phenotypical features: AF = atrial fibrillation, ASD = autism spectrum disorder, BrS = Brugada syndrome, CAP = cold aggravated pain, CMS = congenital myasthenic syndrome, DEE = developmental and epileptic encephalopathy, DS = Dravet syndrome, ECG = electrocardiogram, echo = echocardiogram, EPI = epilepsy, FHM3 = familial hemiplegic migraine type 3, GEFS+ = genetic epilepsy with febrile seizures plus, Hyper-PP = hyperkalaemic periodic paralysis, Hypo-PP = hypokalaemic periodic paralysis, IEM = inherited erythromelalgia, LQT3 = long QT3 syndrome, NDD = neurodevelopmental disorder, PAM = potassium-aggravated myotonia, PDN = painful diabetic neuropathy, PEPD = paroxysmal extreme pain disorder, PMC = paramyotonia congenita, PMG = polymicrogyria, PPN = painful peripheral neuropathy, SCB = sodium channel blocker, SCD = sudden cardiac death, SIDS = sudden infant death syndrome, SSS = sick sinus syndrome, SUD = sudden unexplained death, Sz = seizure, TdP = torsade de pointes, VT = ventricular tachycardia

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Supplementary Table 2: Corresponding variants, phenotypes, and function across different sodium channels

Pair	*SCN1A Position*	Gene/ Variant	Function	Phenotype	Reference*	Corresponding Gene/Variant	Function	Phenotype	Reference*
1	I138V	***SCN4A***; I141V D1 S1	GoF; WCC: Y, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$	Sodium channel myotonia	Petitprez (2008)[23]	***SCN9A***; I136V D1 S1	GoF; WCC: Y, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$	IEM	Cheng (2008)[24]
2	R222W	***SCN4A***; R225W D1 S4	LoF; WCC: Y, $\downarrow$CD, $\rightarrow V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$	Congenital Myopathy	Zaharieva (2016)[14]	***SCN5A***; R225W D1 S4	LoF; WCC: Y, $\downarrow\downarrow$CD, $\rightarrow V_{1/2\ Act.,} \rightarrow V_{1/2\ Fl}$	Severe conduction disease	Bezzina (2003)[45]
3	S243T	***SCN9A***; S241T D1 S4-5	GoF; WCC: Y, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$	IEM	Lampert (2006)[58]	***SCN10A***; S242T D1 S4-5	GoF; WCC: Y, $\leftarrow V_{1/2\ Act.,} \leftarrow V_{1/2\ Fl}$	PPN, PDN; carbamazepine responder	Han (2018)[60]
4	Q267K	***SCN4A***; Q270K D1 S5	GoF/Mixed; WCC: Y, $\rightarrow V_{1/2\ Act.,} \rightarrow V_{1/2\ Fl}$	PMC	Carle (2009)[66]	***SCN5A***; Q270K D1 S5	GoF/Mixed; WCC: Y, $\downarrow$CD, $\uparrow I_{NaP}$, $\rightarrow V_{1/2\ Act.,} \rightarrow V_{1/2\ Fl}$	LQT3/BrS overlap syndrome; ECG: fetal tachycardia/ fibrillation TdP, LQT	Calloe (2011)[67]
5	R377H	***SCN2A***; R379H D1 S5-6	LoF; WCC: None	ASD	Ben-Shalom (2017)[5]	***SCN5A***; R367H D1 S5-6	LoF; WCC: None	BrS; SCD; ECG: ST elevation	Hong (2004)[83]
6	N416K	***SCN4A***; N440K D1 S6	GoF; WCC: Y, $\uparrow I_{NaP}$, $_{no\ change} V_{1/2\ Act.,} \rightarrow V_{1/2\ Fl}$	PMC	Lossin (2012)[92]	***SCN9A***; N395K D1 S6	GoF; WCC: Y, $\leftarrow V_{1/2\ Act.,}$ $_{no\ change} V_{1/2\ Fl}$	IEM	Sheets (2007)[41]
						SCN5A; N406K D1 S6	GoF/Mixed; WCC: Y, $\downarrow$CD, $\uparrow I_{NaP}$, $_{no\ change} V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$,	LQT3; ECG: TdP, LQT, polymorphic VT, mexiletine responder	Hu (2018)[93] Kato (2014)[94]
7	V421M	***SCN4A***; V445M D1 S6	GoF; WCC: Y, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,} \leftarrow V_{1/2\ Fl}$	PMC	Wang (1999)[97] Huang (2020)[98]	***SCN5A***; V411M D1 S6	GoF; WCC: Y, $\uparrow$CD, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$	LQT3; ECG: neonatal LQT with 2:1 block	Horne (2011)[100] Zhou (2015)[101]
						SCN9A; V400M D1 S6	GoF; WCC: Y, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,} \rightarrow V_{1/2\ Fl}$	IEM; carbamazepine responder	Fischer (2009)[102]
8	T782I	***SCN2A***; T773I D2 S1	GoF; WCC: Y, $_{no\ change}$CD, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$	DEE, Sz onset 1 day	Lauxmann (2018)[33]	***SCN8A***; T767I D2 S1	GoF; WCC: Y, $\downarrow$CD, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$	DEE, Sz onset 2 weeks	Pan (2020)[118] Estacion (2014)[119]
9	R859H	***SCN1A***; R859H D2 S4	LoF/mixed; WCC: Y, $\uparrow I_{NaP}$, $_{no\ change}$CD, $\leftarrow V_{1/2\ Act.,} \leftarrow V_{1/2\ Fl}$	GEFS+	Volkers (2011)[134]	***SCN4A***; R669H D2 S4	LoF/mixed; WCC: Y, $\downarrow$CD, $_{no\ change} V_{1/2\ Act.,} \leftarrow V_{1/2\ Fl}$	HypoPP	Kuzmenkin (2002)[135]
10	R859C	***SCN1A***; R859C D2 S4	LoF; WCC: Y, $\downarrow$CD, $_{no\ change} V_{1/2\ Act.,\ no\ change} V_{1/2\ Fl}$	EPI	Bechi (2015)[124]	***SCN5A***; R808C D2 S4	LoF; WCC: Y, $\downarrow$CD, $_{no\ change} V_{1/2\ Act.,} \leftarrow V_{1/2\ Fl}$	BrS	Glazer (2020)[1]

11	R862H	***SCN4A***; R672H D2 S4	LoF; WCC: Y, ↓CD; $\rightarrow V_{1/2\ Act.}$, $\leftarrow V_{1/2\ Fl}$	Hypo-PP	Jurkatt-Rott (2000)[140] Kuzmenkin (2002)[135]	***SCN5A***; R811H D2 S4	LoF; WCC: Y, ↓CD; $_{no\ change}V_{1/2\ Act.}$, $\leftarrow V_{1/2\ Fl}$	BrS; family history of sudden death,	Calloe (2013)[114]
12	R865Q	***SCN4A***; R675Q D2 S4	Mixed; WCC: Y, $_{no\ change}$CD, $_{no\ change}V_{1/2\ Act.,\ no\ change}V_{1/2\ Fl}$, $\leftarrow V_{1/2\ Sl}$	Potassium sensitive normoPP	Wu (2014)[149]	***SCN5A***; R814Q D2 S4	Mixed; WCC: Y, $_{no\ change}$CD, $_{no\ change}V_{1/2\ Act.,\ no\ change}V_{1/2\ Fl}$	LQT3; BrS	Glazer (2020)[1]
13	I883T	***SCN3A***; I875T D2 S4-5	GoF; WCC: Y, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	EPI/PMG	Zaman (2018)[155]	***SCN9A***; I848T D2 S4-5	GoF; WCC: Y, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.,\ no\ change}V_{1/2\ Fl}$	IEM	Cummins (2004)[157] Namer (2015)[158] Theile (2011)[159]
14	R946C	***SCN1A***; R946C; D2 S5-6	LoF; WCC: None	DS	Volkers (2011)[134]	***SCN2A***; R937C; D2 S5-6	LoF; WCC: None	ASD	Begemann (2019)[180]
15	R946H	***SCN1A***; R946H; D2 S5-6	LoF; WCC: None	DS	Liao (2010)[182] Volkers (2011)[134]	***SCN2A***; R937H; D2 S5-6	LoF; WCC: None	ASD	Ben-Shalom (2017)[5]
16	G979R	***SCN1A***; G979R; D2 S6	LoF; WCC: None	DS	Sugawara (2003)[184] Rhodes (2005)[130]	***SCN8A***; G964R; D2 S6	LoF; WCC: None	NDD without EPI	Wagnon (2017)[185]
17	D1256N	***SCN4A***; D1069N D3 S2	LoF/Mixed; WCC: Y, $_{no\ change}$CD, $\rightarrow V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	Congenital myopathy	Zaharieva (2016)[14]	***SCN5A***; D1243N D3 S2	LoF/Mixed; WCC: Y, $_{no\ change}$CD, $\rightarrow V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	BrS	Glazer (2020)[1]
18	A1343T	***SCN4A***; A1156T D3 S4-5	GoF; WCC: Y, $_{no\ change}V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	PMC with prominent myalgia	Palmio (2017)[236]	***SCN5A***; A1330T D3 S4-5	GoF; WCC: Y, $_{no\ change}V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	LQT3; SCD	Smits (2005)[238]
19	P1345L	***SCN3A***; P1333L D3 S4-5	GoF; WCC: Y, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.}$, $_{no\ change}V_{1/2\ Fl}$	EPI	Zaman (2018)[155]	***SCN4A***; P1158L D3 S4-5	GoF; WCC: Y, $_{no\ change}V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	Sodium channel myotonia	Desaphy (2016)[239]
						SCN5A; P1332L D3 S4-5	GoF/mixed; WCC: Y, $\leftarrow V_{1/2\ Act.}$, $\leftarrow V_{1/2\ Fl}$	LQT3, ECG: TdP, LQT, mexiletine responder	Ruan (2007)[190]
						SCN9A; P1308L D3 S4-5	GoF; WCC: Y, ↓CD, $\leftarrow V_{1/2\ Act.,\ no\ change}V_{1/2\ Fl}$	IEM	Cheng (2010)[226]
20	S1346Y	***SCN2A***; S1336Y D3 S4-5	GoF/Mixed ($Na_V1.2N$); WCC: Y, ↓CD, $\leftarrow V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	DEE	Thompson (2020)[54]	***SCN5A***; S1333Y D3 S4-5	GoF; WCC: Y, $_{no\ change}$CD, $\leftarrow V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	SIDS; LQT3	Huang (2009)[243]
21	V1353A	***SCN9A***; V1316A D3 S4-5	GoF; WCC: Y, $\leftarrow V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	IEM	Wu (2013)[252], Estacion (2013)[253]	***SCN11A***; V1184A D3 S5	GoF; WCC: Y, ↑CD, $\uparrow I_{NaP}$, $\leftarrow V_{1/2\ Act.}$, $_{no\ change}V_{1/2\ Fl}$	PPN, CAP	Leipold (2015)[255]
22	F1486C	***SCN4A***; F1298C D3-D4 linker	GoF/Mixed; WCC: Y, $\rightarrow V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	Sodium channel myotonia	Farinato (2019)[272]	***SCN5A***; F1473C D3-D4 linker	GoF; WCC: Y, $\uparrow I_{NaP}$, $_{no\ change}V_{1/2\ Act.}$, $\rightarrow V_{1/2\ Fl}$	LQT3; ECG: TdP, LQT with 2:1 block, mexiletine responder	Bankston (2007)[276]

23	F1499L	***SCN1A***; F1499L D3-D4 linker	GoF; WCC: Y, ↑I_{NaP}, no change$V_{1/2\ Act.}$, →$V_{1/2\ FI}$	FHM	Barbieri (2019)[283]	***SCN5A***; F1486L D3-D4 linker	GoF; WCC: Y, ↑I_{NaP}, no change$V_{1/2\ Act.}$, →$V_{1/2\ FI}$	LQT3	Wang (2007)[36]
24	T1501I	***SCN3A***; T1486I D3-D4 linker	GoF; WCC: Y, ↑I_{NaP}, no change$V_{1/2\ Act.}$, →$V_{1/2\ FI}$	EPI/PMG	Zaman (2020)[147]	***SCN9A***; T1464I D3-D4 linker	GoF; WCC: Y, ↑I_{NaP}, →$V_{1/2\ Act.}$, →$V_{1/2\ FI}$	PEPD, responsive to SCB	Fertleman (2006)[227] Theile (2011)[159]
25	E1587K	***SCN1A*;** E1587K D4 S2	LoF; WCC: None	EPI	Kluckova (2020)[10]	***SCN5A*;** E1574K D4 S2	LoF; WCC: Y, ↓↓CD, →$V_{1/2\ Act.}$	BrS	Glazer (2020)[1]
26	R1596C	***SCN1A*;** R1596C D4 S2-3	LoF; WCC: None	EPI	Kluckova (2020)[10]	***SCN5A*;** R1583C D4 S2-3	LoF; WCC: Y, ↓CD, no changeI_{NaP}, no change$V_{1/2\ Act.}$, no change$V_{1/2\ FI}$	BrS	Glazer (2020)[1]
27	P1632S	***SCN1A***; P1632S; D4 S3-4	LoF; WCC: Y, ←$V_{1/2\ Act.}$, ←$V_{1/2\ FI}$	DS	Rhodes (2005)[130]	***SCN2A***; P1622S; D4 S3-4	LoF; WCC: Y, ←$V_{1/2\ FI}$	ASD and Sz onset 21 months	Wolff (2017)[96]
28	R1636Q	***SCN3A*:** R1621Q D4 S4	GoF; WCC: Y, no changeCD, ↑I_{NaP}, ←$V_{1/2\ Act.}$, no change$V_{1/2\ FI}$	EPI/PMG	Zaman (2020)[147]	***SCN8A***; R1617Q D4 S4	GoF; WCC: Y, ↑I_{NaP}, ←$V_{1/2\ Act.}$, →$V_{1/2\ FI}$	DEE, Sz onset 3 months	Wagnon (2015)[314]
						SCN5A; R1623Q D4 S4	GoF; WCC: Y, ↑I_{NaP}, ←$V_{1/2\ Act.}$	LQT3; ECG: TdP, LQT, mexiletine responder	Kambouris (1998)[310] Tsurugi (2009)[311]
29	R1639L	***SCN4A***; R1451L D4 S4	LoF; WCC: Y, ↓CD, no change$V_{1/2\ Act.}$, ←$V_{1/2\ FI}$	Complex phenotype including myotonia and paralysis (both potassium sensitive and hypoPP	Poulin (2018)[318]	***SCN8A***; R1620L D4 S4	LoF; WCC: Y, ↓↓CD, no change$V_{1/2\ Act.}$, ←$V_{1/2\ FI}$	ASD	Liu (2019)[288]
30	R1645H	***SCN4A***; R1457H D4 S4	LoF; WCC: Y, no change$V_{1/2\ Act.}$, ←$V_{1/2\ FI}$	CMS (in patient homozygous for R1457H variant)	Arnold (2015)[326]	***SCN5A***; R1632H D4 S4	LoF; WCC: Y, no changeCD, no change$V_{1/2\ Act.}$, ←$V_{1/2\ FI}$	SSS; ECG: bradycardia, absent atrial depolarizations, prolonged QRS, 1° heart block	Benson (2003)[327]
31	R1657C	***SCN1A***; R1657C; D4 S4-5	LoF; WCC: Y, ↓CD, →$V_{1/2\ Act.}$, no change$V_{1/2\ FI}$	GEFS+	Lossin (2003)[186]	***SCN5A***; R1644C D4 S4-5	LoF; WCC: Y, →$V_{1/2\ Act.}$, no change$V_{1/2\ FI}$	BrS; ECG: ST elevation, echo: CM changes	Frustaci (2005)[87]
						SCN8A; R1638C; D4 S4-5	LoF; WCC: Y, →$V_{1/2\ Act.}$, no change$V_{1/2\ FI}$	NDD without epilepsy	Wengert (2019)[65]
32	F1661S	***SCN1A***; F1661S D4 S4-5	Mixed; 50% reduction in trafficking WCC: Y, ↓CD, ↑I_{NaP}, no change$V_{1/2\ Act.}$, →$V_{1/2\ FI}$	DS	Rhodes (2004)[172] Thompson (2012)[187]	***SCN4A***; F1473S D4 S4-5	GoF; WCC: Y, CD not reported, ↑I_{NaP}, no change$V_{1/2\ Act.}$, →$V_{1/2\ FI}$	PMC	Fleischhauer (1998)[336]
33	M1664K	***SCN1A***; M1664K D4 S4-5	LoF; 90% reduction in peak current and trafficking not allowing for detailed *SCN1A* biophysics	GEFS+/DS	Bechi (2015)[124]	***SCN9A***; M1627K D4 S4-5	GoF; WCC: Y, no changeCD, no change$V_{1/2\ Act.}$, →$V_{1/2\ FI}$	PEPD	Fertleman (2006)[227] Dib-Hajj (2008)[338] Theile (2011)[159]

34	G1674R	***SCN1A***; G1674R D4 S5	LoF; WCC: None ↓↓CD	EPI	Rhodes (2004)[172] Thompson (2012)[187]	***SCN5A***; G1661R D4 S5	LoF; WCC: Y (barely) ↓↓CD	BrS	Glazer (2020)[1]
35	M1780I	***SCN3A***; M1765I D4 S6	GoF; WCC: Y, ↑I_{NaP}, ←$V_{1/2\ Act.,\ no\ change}V_{1/2\ FI}$	EPI/PMG	Zaman (2020)[147]	***SCN8A***; M1760I D4 S6	GoF; WCC: Y, ←$V_{1/2\ Act.,\ no\ change}V_{1/2\ FI}$	EPI	Liu (2019)[288]
36	N1788D	***SCN5A***; N1774D C-Term	GoF; WCC: Y, ↑CD, ↑I_{NaP}, ←$V_{1/2\ Act.,\ no\ change}V_{1/2\ FI}$	LQT3; ECG: TdP, LQT with 2:1 block, mexiletine responder	Kato (2014)[94]	***SCN8A***; N1768D C-Term	GoF; WCC: Y, ↑I_{NaP}, $_{no\ change}V_{1/2\ Act.,}$ →$V_{1/2\ FI}$	DEE, Sz onset 6 months	Veeramah (2012)[366] Patel (2016)[247] Baker (2018)[367]
37	R1892Q	***SCN2A***; R1882Q; C-Term	GoF; WCC: Y, ↑CD, ↑I_{NaP}, ←$V_{1/2\ Act.,}$ →$V_{1/2\ FI}$	DEE, Sz onset 1 day	Berecki (2018)[141] Mason (2019)[142] Wolff (2017)[96]	***SCN8A***; R1872Q; C-Term	GoF; WCC: Y, ↑CD, ←$V_{1/2\ Act.,}$ →$V_{1/2\ FI}$	DEE, Sz onset 4 months	Wagnon (2015)[314] Aktin (2018)[393]
38	Q1923R	***SCN1A***; Q1923R C-Term	LoF; WCC: None	DS	Nissenkorn (2019)[29]	***SCN5A***; Q1909R C-Term	Mixed; ←$V_{1/2\ Act.,\ no\ change}V_{1/2\ FI}$ decrease in peak current by 50%.	SIDS (not a known cardiac patient)	Winkel (2015)[103] Abdelsayed (2017)[369]

Corresponding variant = identical variant among different *SCN* at the same position/location in the SCN protein (the corresponding sequence numbers are not identical as the amino acid sequence between *SCN* variants differs slightly).

Rows marked in grey denote variant pairs with divergent functional properties.

*References relate to those detailed in Supplementary Table 1.

Phenotypical features: ASD = autism spectrum disorder, BrS = Brugada syndrome, CAP = cold aggravated pain, CM changes = cardiomyopathic changes, CMS = congenital myasthenic syndrome, DEE = developmental and epileptic encephalopathy, DS = Dravet syndrome, ECG = electrocardiogram, echo = echocardiogram, EPI = epilepsy, FHM3 = familial hemiplegic migraine type 3, GEFS+ = genetic epilepsy with febrile seizures plus, Hyper-PP = hyperkalaemic periodic paralysis, Hypo-PP = hypokalaemic periodic paralysis, IEM = inherited erythromelalgia, LQT3 = long QT3 syndrome, $Na_v1.2N$ = neonatal proteoform, NDD = neurodevelopmental disorder, PAM = potassium-aggravated myotonia, PDN = painful diabetic neuropathy, PEPD = paroxysmal extreme pain disorder, PMC = paramyotonia congenita, PMG = polymicrogyria, PPN = painful peripheral neuropathy, SCB = sodium channel blocker, SCD = sudden cardiac death, SIDS = sudden infant death syndrome, SSS = sick sinus syndrome, SUD = sudden unexplained death, Sz = seizure, TdP = torsade de pointes, VT = ventricular tachycardia

Electrophysiological key features: Arrows (→) are used for electrophysiological parameters. The direction of the arrows indicates hyperpolarizing (←) or depolarizing shifts (→), as well as an increase (↑) or decrease (↓) of parameters, (↓↓ = >50% decrease)

Electrophysiological abbreviations: GoF: gain-of-function, LoF: loss-of-function, WCC: whole cell current (Y = measurable, N = not measurable), Act: activation, CD: current density, FI: fast inactivation, SI: slow inactivation, I_{NaP}: persistent sodium current, $V_{1/2\ Act.}$: half-activation of steady-state activation curve, $V_{1/2\ FI}$: half-inactivation of steady-state fast inactivation curve.

Supplementary Table 3: Detailed *SCN1-11A* Analysis

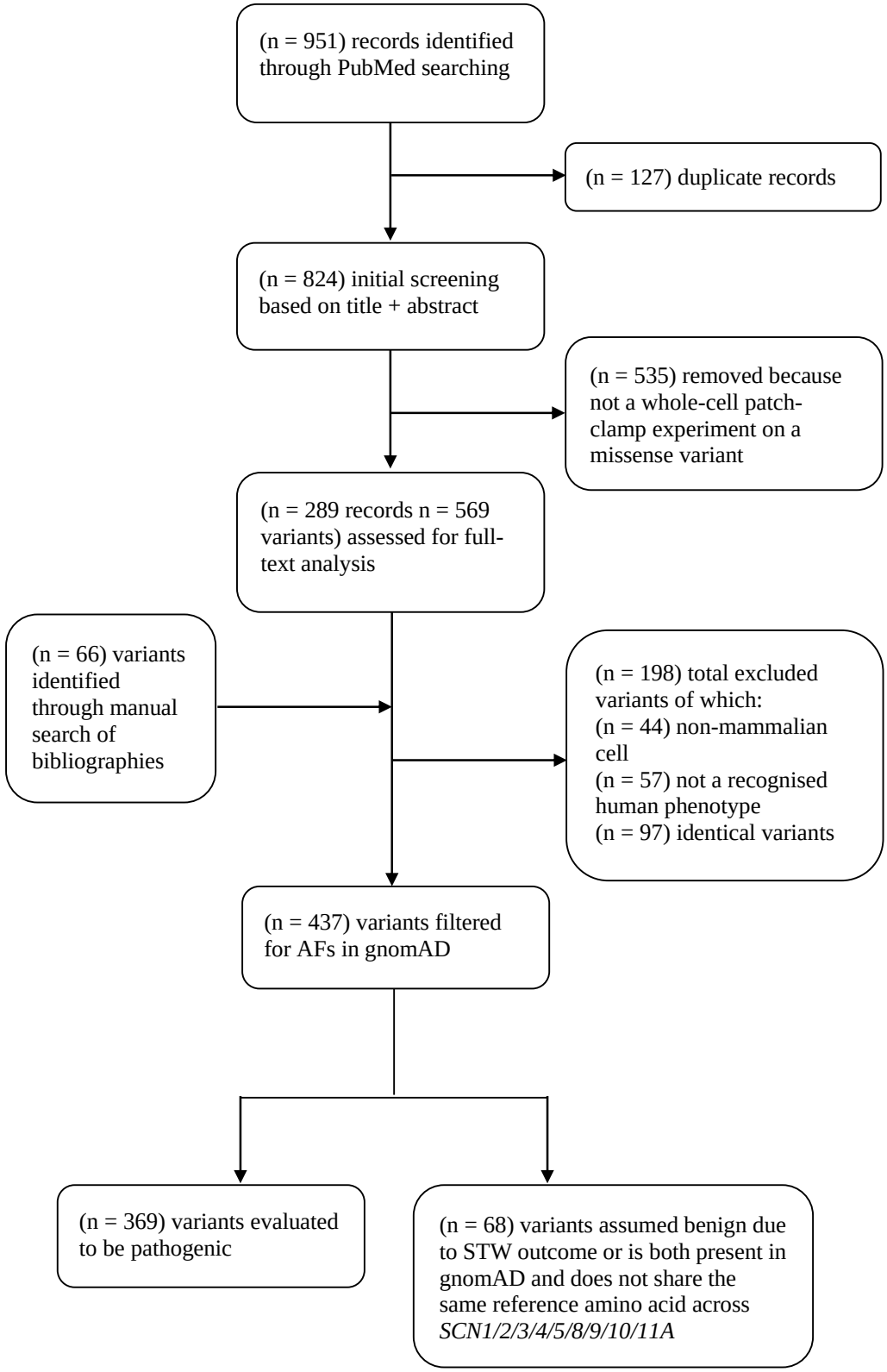
SCN1A				
Disorder	**No.**	**Functional Effects**	**Distribution**	**Clinical Context**
EPI	60 (85%)	• GoF – (3/60, 5%) • LoF – (47/60, 78%) • Mixed – (10/60, 17%)	*SCN1A variants clustered across pore-loop regions (S5, S5-6 & S6) and 88% of variants showed LoF (23/26)*	Variants displaying LoF were more frequently associated with DS, whereas variants showing GoF were FHM3-associated (p<0.001)
FHM3	11 (15%)	• GoF – (8/11, 73%) • LoF – (1/11, 9%) • Mixed – (2/11, 18%)	55% (6/11) of FHM3-associated variants occurred in sites implicated in channel inactivation, including the DIII-IV linker, DIVS4-5 and DIVS6, predominantly showing GoF effects. Of these, 83% were GoF (5/6). While most FHM3-associated variants are associated with GoF effects, the variant located in DIVS4 was clearly mixed. The other mixed variant was located in DIVS5	
SCN2A				
Disorder	**No.**	**Functional Effect**	**Distribution**	**Clinical Context**
EPI	29 (81%)	• GoF – (17/29, 59%) • LoF – (7/29, 24%) • Mixed – (5/29, 17%)	*SCN2A* epilepsy-associated variants were evenly distributed across homologous domains but very few were found in pore-forming regions	Variants displaying LoF effects were frequently associated with ASD, while GoF variants were epilepsy-associated (p = 0.001)
ASD	7 (19%)	All variants showed LoF	71% of ASD-associated variants clustered in pore-loop regions (5/7), all displaying LoF	
SCN3A				
Disorder	**No.**	**Functional Effect**	**Distribution**	**Clinical Context**
EPI	5 (38%)	• GoF – 3/5 (60%) • LoF – 1/5 (20%) • Mixed – 1/5 (20%)	Variants associated with an epilepsy or mixed phenotype were evenly distributed across the protein and only two were observed in pore-forming regions	Epilepsy and PMG variants appear to be mainly GoF
EPI/PMG	6 (46%)	All variants showed GoF		
ASD	1 (8%)	LoF	DIVS5	
Fetal Akinesia	1 (8%)	GoF	DIIS4	

SCN4A				
Disorder	**No.**	**Functional Effect**	**Distribution**	**Clinical Context**
PMC	14 (36%)	• GoF – (11/14, 86%) • LoF – (1/14, 7%) • Mixed – (2/14, 7%)	43% occurred in the DIII-IV linker (6/14) and the remainder across the protein	GoF variants were frequently PAM/PMC-associated, whereas LoF variants were CMS-associated ($p<0.001$). Overall, 32% of variants occurred in inactivation sites (12/38), 92% of which showed GoF (11/12). 29% of variants were found in S4 sites (11/38), 70% of which showed LoF (8/11). 18% occurred in pore-forming regions (7/38) and the remainder across the protein.
CMS	10 (26%)	• LoF – (8/10, 80%) • Mixed – (2/10, 20%)	Two variants occurred in pore-loops and two in voltage-sensing regions.	
PAM	4 (11%)	All variants showed GoF	Three variants were found in inactivation sites and one in the C-terminus	
HypoPP	5 (13%)	Four variants displayed LoF and one variant showed mixed function	All four variants displaying LoF were found in S4 sites while the LoF variant was found in DIIIS4-5	
HyperPP	1 (3%)	Mixed	DIVS5	
NormoPP	1 (3%)	Mixed	DIIS4	
Mixed Phenotype	3 (8%)	All variants showed GoF	Variants occurred in DIS6, DIIS5 and DIIIS4-5	
SCN5A				
Disorder	**No.**	**Functional Effect**	**Distribution**	**Clinical Context**
BrS	100 (69%)	96% of variants showed LoF (96/100), three were mixed effect and one displayed GoF	52% of BrS-associated variants occurred in pore-loop regions (S5, S5-6 & S6) (52/100), while only 6% were found at sites of channel inactivation (6/100)	Variants displaying LoF effects were more frequently BrS-associated, while GoF variants were LQT3-associated, ($p<0.001$)
LQT3	38 (26%)	• GoF – (30/38, 79%) • LoF – (2/38, 5%) • Mixed – (6/38, 16%)	47% of LQT3 variants clustered in sites of inactivation (18/38), showing predominantly GoF (94%, 17/18)	
Mixed	8 (5%)	• LoF – 4/8 (50%) • Mixed – 4/8 (50%)	Two variants occurred in the C-terminus, one in DIS4, one in DIIS4 and the rest across the protein	

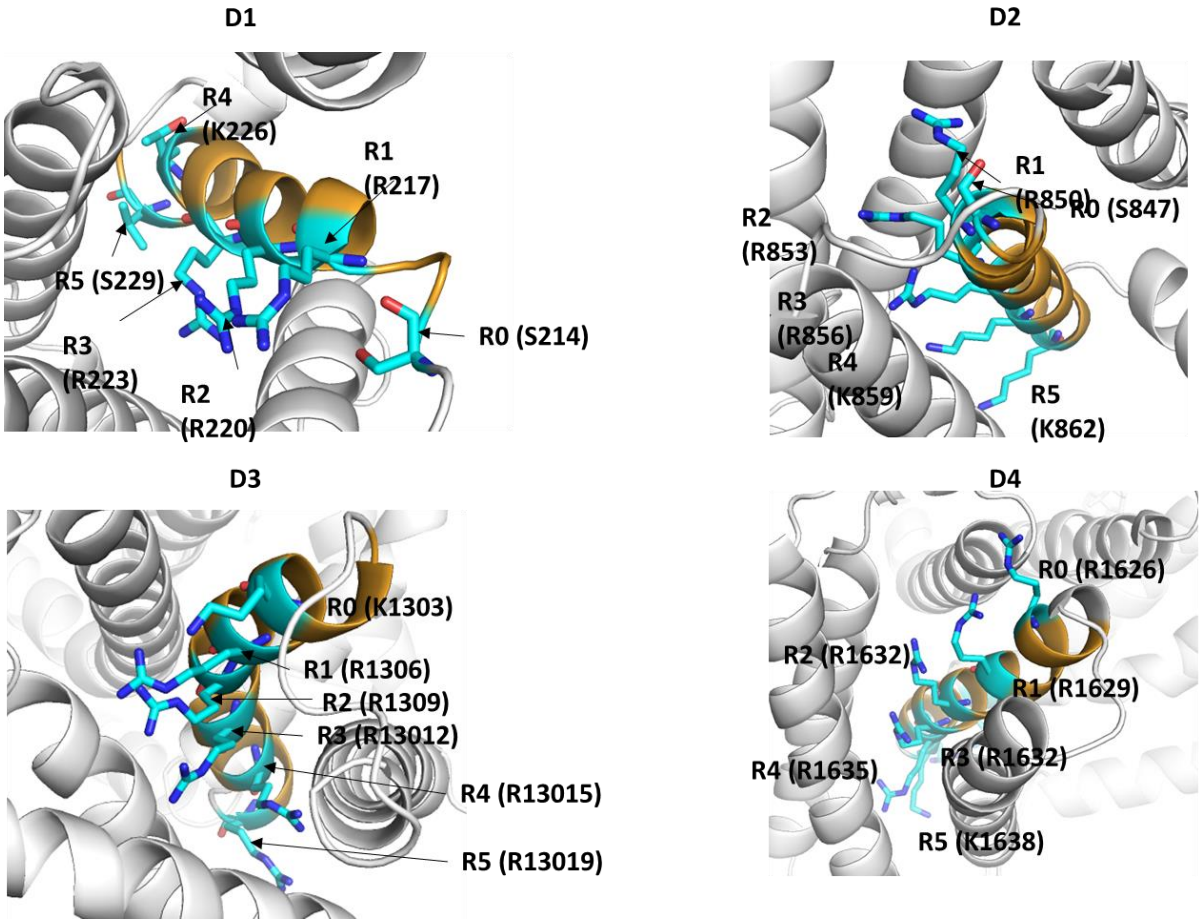
SCN8A				
Disorder	**No.**	**Functional Effect**	**Distribution**	**Clinical Context**
EPI	14 (67%)	• GoF – (12/14, 86%) • LoF – (2/14, 14%)	29% occurred in S4 regions (4/14), 14% in the C-terminus (2/14), 14% in inactivation sites (2/14) and the remainder across the protein. None occurred in cytoplasmic regions.	Variants displaying LoF effects were frequently NDD/ASD-associated, while GoF variants were epilepsy-associated, (p=0.003).
NDD	5 (23%)	All variants showed LoF	Three were found in pore-forming regions, one in DIVS4-5 and one in DIIS3	
ASD	2 (9%)	One variant showed GoF while the other LoF	Both variants were located in DIVS4	
SCN9A				
Disorder	**No.**	**Functional Effect**	**Distribution**	**Clinical Context**
PPN	34	• GoF – 33/34 (97%) • Mixed – 1/34 (3%)	Of 33 GoF variants, 33% were found in inactivation sites (11/33), 18% in DIIS5 (6/33), 15% in S4 regions (5/33) and the remainder across the protein. The mixed effect variant was located in DIIS4.	The majority of variants appear to be GoF
SCN10A				
Disorder	**No.**	**Functional Effect**	**Distribution**	**Clinical Context**
AF	1	LoF	The LoF variant was observed in the N-terminus	GoF variants appear to be associated with PPN
SUD	2	Both variants showed LoF	Variants were observed in D1S6 and DIIS4	
PPN	3	All variants showed GoF	Variants were found at DIS4-S5, DIVS5-6 and DIVS6	
SCN11A				
Disorder	**No.**	**Functional Effect**	**Distribution**	**Clinical Context**
PPN	4	All variants showed GoF	PPN-associated variants were found in DIS4, DIIS4-5, DIIIS4 and DIIIS5	The majority of variants appear to be GoF.

Phenotypical features: FHM3 = familial hemiplegic migraine type 3, EPI = epilepsy, ASD = autism spectrum disorder, NDD = neurodevelopmental disorder, PMG = polymicrogyria, Hypo-PP = hypokalaemic periodic paralysis, Hyper-PP = hyperkalaemic periodic paralysis, PMC = paramyotonia congenita, CMS = congenital myasthenic syndrome, PAM = potassium-aggravated myotonia, BrS = Brugada syndrome, LQT3 = long QT3 syndrome, SCD = sudden cardiac death, PPN = peripheral painful neuropathy (including, PEPD = paroxysmal extreme pain disorder, IEM = inherited erythromelalgia and SFN = small fibre neuropathy), AF = atrial fibrillation, SUD = sudden unexpected death.

Supplementary Figure 1: Study Selection



Supplementary Figure 2: Voltage sensing regions (S4) structure zoom across D1-D4



Voltage sensing regions (S4) structure zoom across D1-D4. Close-up view of S4 voltage sensing regions across all four domains (D1-D4) illustrating conserved Arginines R0-R4.