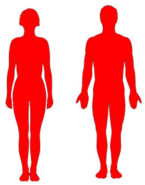


Recruitment and deep phenotyping

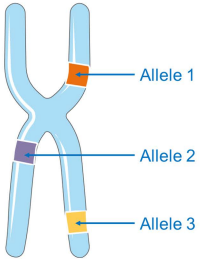
Whole genome sequencing

Multi disciplinary team meeting

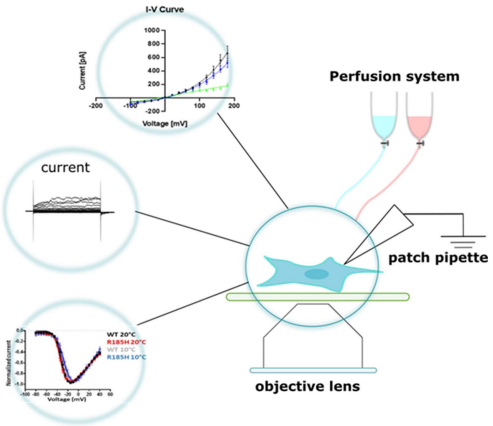
Reporting of clinically relevant (medical actionable) variants, results reported back to local neurology team (Only Tier 1 genes)

Clinical

Research



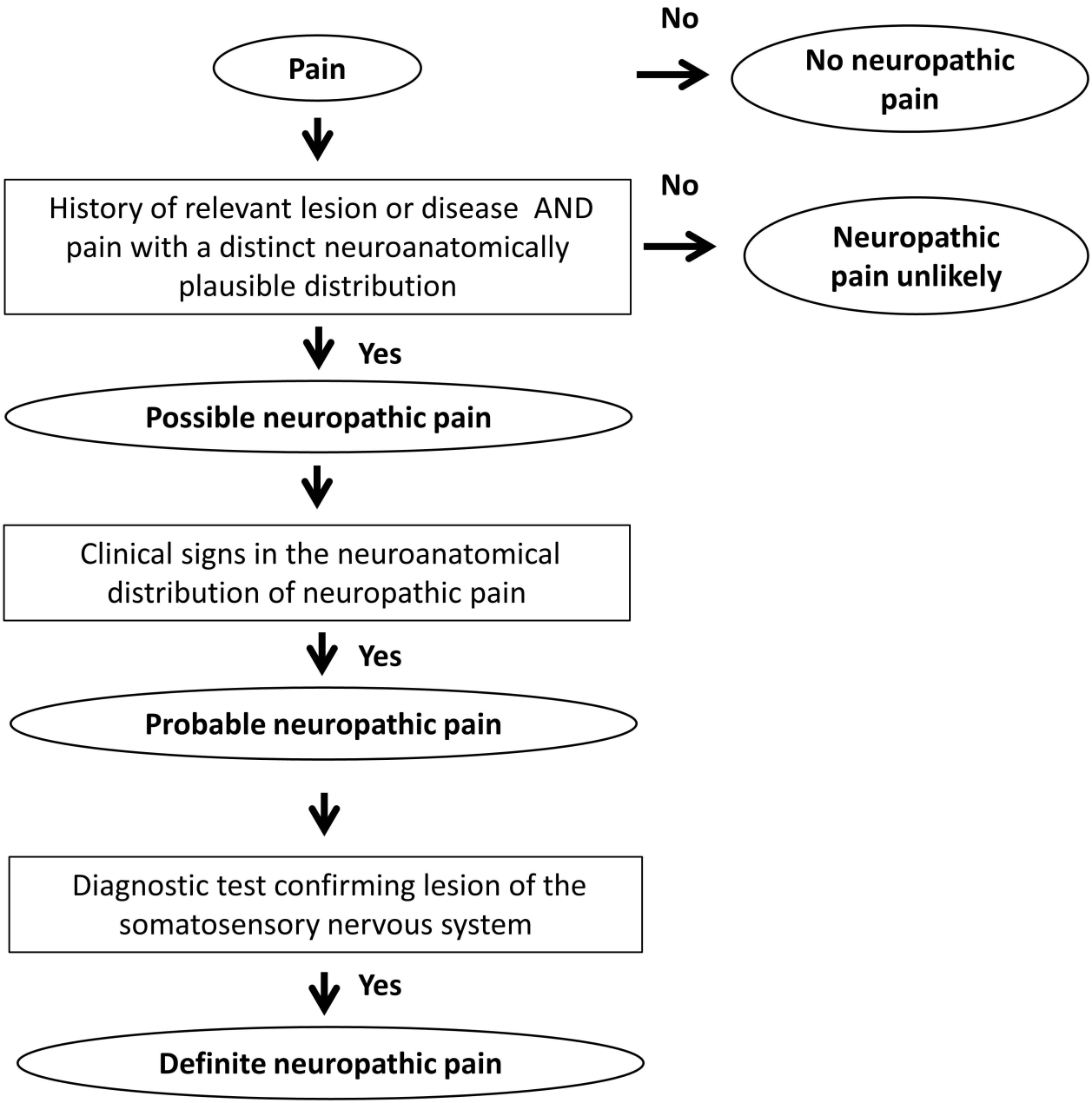
Identification of novel variants in Tier 2/3 genes



Functional studies for further neurophysiological characterisation of Tier 1 gene variants and novel Tier 2/3 variants

Supplementary figure 1
Flow diagram outlining steps in the project.

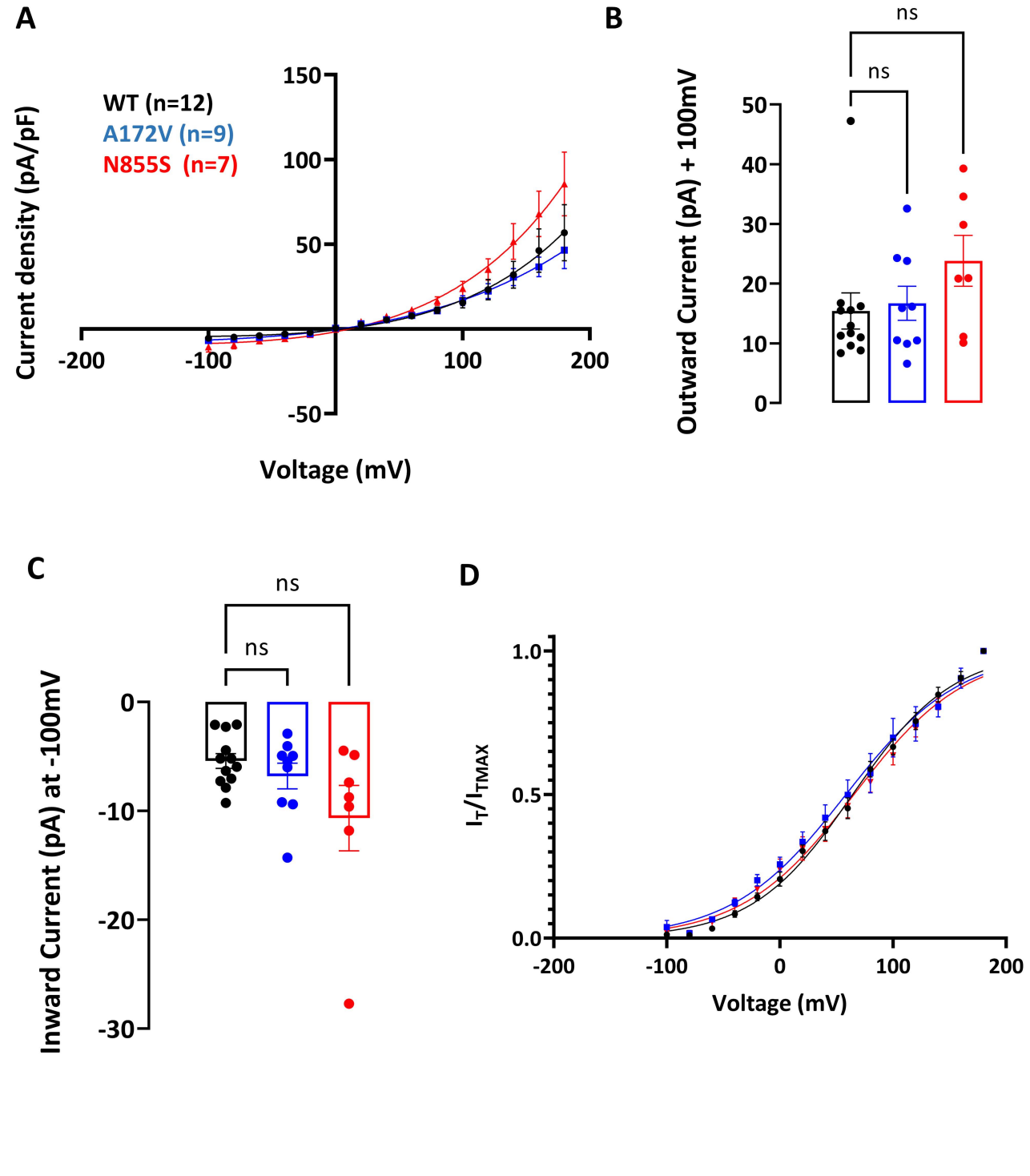
The flow diagram outlines recruitment of participants, analysis pipeline, genetic testing and the difference between the clinical reporting of relevant gene variants versus the exploratory gene analysis and in vitro functional assessment of variants of interest


Pain
No
No neuropathic pain
History of relevant lesion or disease AND pain with a distinct neuroanatomically plausible distribution
No
Neuropathic pain unlikely
Yes
Possible neuropathic pain
Clinical signs in the neuroanatomical distribution of neuropathic pain
Yes
Probable neuropathic pain
Diagnostic test confirming lesion of the somatosensory nervous system
Yes
Definite neuropathic pain

Supplementary figure 2
Flow diagram outlining neuropathic pain grading .

Possible neuropathic pain must fulfil criteria 1 and 2.
Probable neuropathic pain must fulfil criteria 1, 2 and 3.
Definite neuropathic pain must fulfil all 4 criteria.

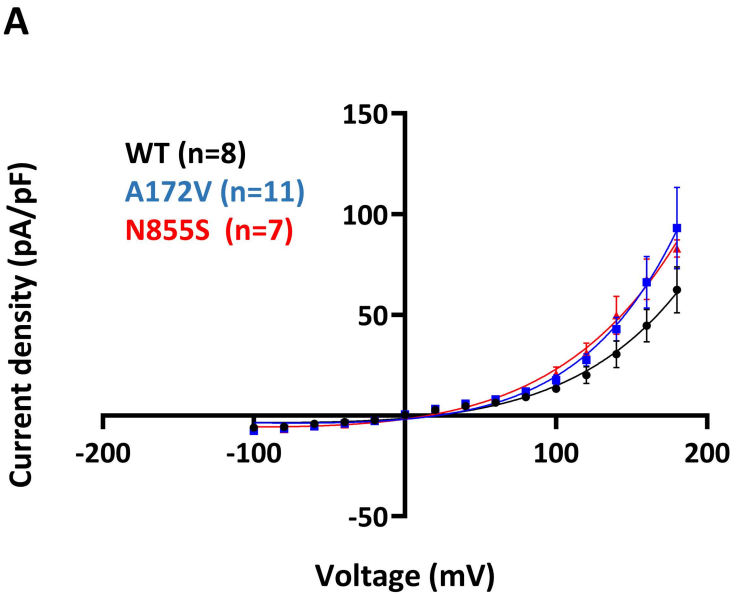
1. Pain with a distinct neuroanatomically plausible distribution e.g. pain symmetrically distributed in the extremities, pain in erythematous areas
2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system e.g. a history of neuropathy symptoms including decreased sensation, or positive sensory symptoms e.g. burning, aching pain mainly in the toes, feet or legs.
3. Demonstration of distinct neuroanatomically plausible distribution of neuropathic pain e.g. presence of clinical signs of peripheral neuropathy such as decreased distal sensation or decreased/absent ankle reflexes.
4. Demonstration of the relevant lesion or disease by at least one confirmatory test e.g. abnormality on either nerve conduction tests, thermal thresholds or intra-epidermal nerve fibre density.

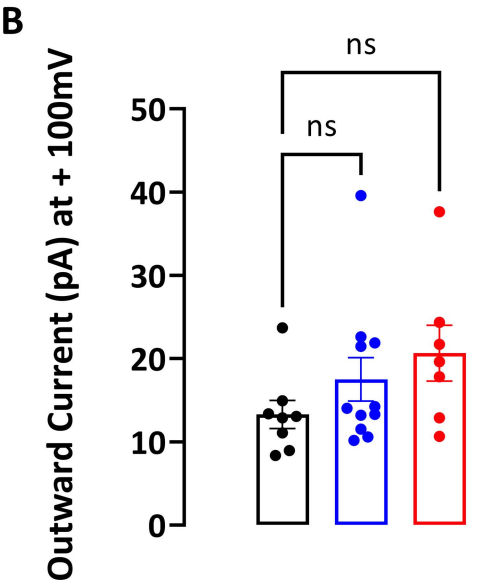

A
WT (n=12)
A172V (n=9)
N855S (n=7)
Current density (pA/pF)
150
100
50
-50
-200
-100
100
200
Voltage (mV)
B
ns
ns
Outward Current (pA) + 100mV
50
40
30
20
10
0
C
ns
ns
Inward Current (pA) at -100mV
0
-10
-20
-30
D
I_T/I_{TMAX}
1.0
0.5
0.0
-200
-100
0
100
200
Voltage (mV)

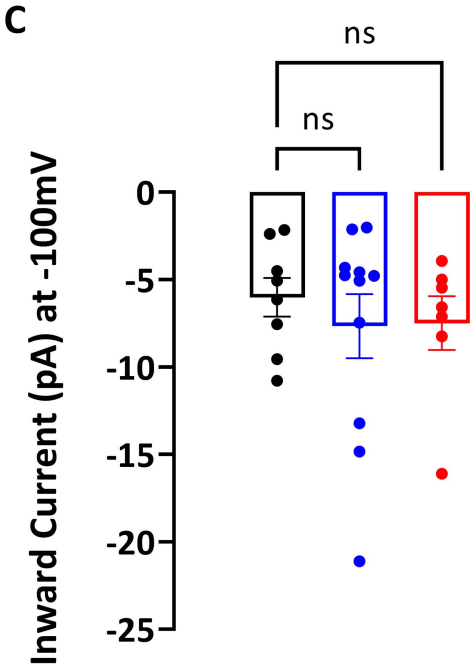
Supplementary figure 3
Biophysical characterisation of hTRPA1 WT, p.Ala172Val and p.Asn855Ser variant in control conditions shows no significant differences.

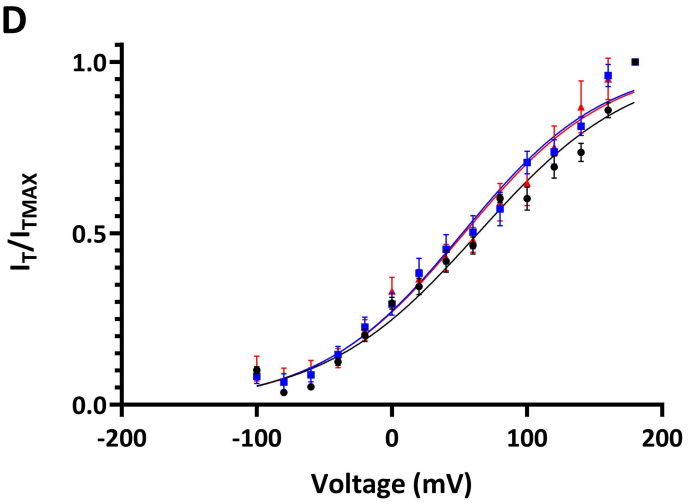
Voltage step protocol consisted of 400 ms voltage steps to test potentials ranging from –100 mV to +180 mV, followed by a final invariant step to -75 mV (400 ms to measure tail currents). The holding potential was set at -0 mV.
A) Current density measured in WT and mutant channels were not statistically different as quantified in b) and c)
B) Outward currents at (+100mV, WT = 15.41 ± 3.01pA/pF, p.Ala172Val = 16.69 ± 2.85pA/pF, p. Asn855Ser = 23.81 ± 4.25pA/pF) were not significantly different between WT and the respective variants (p = 0.77 WT versus p.Ala172Val, p = 0.17 WT versus p.Asn855Ser)
C) Inward currents (at -100mV, WT = -5.42 ± 0.68pA/pF, p.Ala172Val = -6.80 ± 1.18pA/pF and p.Asn855Ser = -10.66 ± 3.00pA/pF), were not significantly different between WT and the respective variants (p = 0.75 WT versus p.Ala172Val, and p = 0.05 WT versus p.Asn855Ser).
D) Voltage of half-maximal activation for WT n = 12, p.Ala172Val n = 9 and p.Asn855Ser n = 7 ($V_{1/2}$, WT = 59.70 ± 4.59mV, p.Ala172Val = 59.45 ± 8.91mV, p.Asn855Ser = 64.85 ± 8.09mV; p= 0.99, and p = 0.85, respectively) and slopes of the voltage-activation curve (k, WT = 42.51 ± 2.01mV, p.Ala172Val = 46.19 ± 2.60mV, p.Asn855Ser = 47.45 ± 1.88mV; p = 0.41 and p = 0.26, respectively) were not statistically different.

WT – Wild Type
Data are presented as mean ± SEM.
Statistical analysis for group comparisons - One way ANOVA with Sidak's multiple comparison test (* - indicates statistically significant differences, $P < 0.05$)


A
WT (n=8)
A172V (n=11)
N855S (n=7)
Current density (pA/pF)
150
100
50
-50
-200
-100
100
200
Voltage (mV)


B
ns
ns
Outward Current (pA) at + 100mV
50
40
30
20
10
0


C
ns
ns
Inward Current (pA) at -100mV
0
-5
-10
-15
-20
-25


D
1.0
0.5
0.0
I_T/I_{TMAX}
-200
-100
0
100
200
Voltage (mV)

Supplementary figure 4
Application of 100µM of Menthol, with extracellular calcium alone, did not alter hTRPA1 p.Ala172Val nor p.Asn855Ser channel excitability.

Voltage-dependence activation of hTRPA1 p.Ala172Val and p.Asn855Ser was measured in response to Menthol. Current-voltage curves were measured with a two voltage-step protocol (voltage-ramps ranging from -100 mV to + 100 mV for 500 ms, every 5 seconds; holding potential was set at -70 mV).

A) Current densities were not statistically different for the variant channels when compared to WT as quantified in b) and c)
B) Outward current (at +100mV, WT = 13.29 ± 1.69pA/pF, p.Ala172Val = 17.51 ± 2.60pA/pF, p.Asn855Ser = 20.66 ± 3.35pA/pF were not significantly different (p = 0.44, and p = 0.15, respectively).
C) Inward currents (at -100mV, WT = -6.02 ± 1.11pA/pF, p.Ala172Val = -7.66 ± 1.83pA/pF, p.Asn855Ser = -7.49 ± 1.53pA/pF) were not significantly different (p = 0.72, p = 0.80, respectively).
D) Half-maximal activation voltage for WT n = 8, p.Ala172Val n = 8, and p.Asn855Ser n = 7 ($V_{1/2}$, WT= 65.39 ± 5.79mV, p.Arg185His= 56.61 ± 9.25mV, p.Asn855Serp.Asn855Ser= 58.62 ± 7.31mV, p = 0.69, and p = 0.83, respectively) were not statistically different. Slopes of the voltage-activation curve (k = 56.66 ± 1.40mV WT, 49.01 ± 1.53mV p.Arg185His, 49.73 ± 3.28mV p.Asn855Ser, p= 0.022 and p = 0.069, respectively) were reduced for both p.A712V and p.Asn855Ser .

WT – Wild Type
Data are presented as mean ± SEM.
Statistical analysis for group comparisons - One way ANOVA with Sidak's multiple comparison test (* - indicates statistically significant differences, P <0.05).

Supplementary table 1

No	Clinical phenotype	Neuropathic pain grading	Gene	Nucleotide change	Amino acid change	Assigned pathogenicity	Alle frequency of variants in databases				In silico analysis		Previous study demonstrating altered channel function (PMID Reference)
							gnomAD	WGS10K	NPD European (African)	NIHR Bioresources controls European (African)	SIFT score	Polyphen	
1	Erythromelalgia	Definite	SCN9A	c.2543T>C	p.Ile848Thr	Pathogenic	.	0.0001	0.0039 (0)	0 (0)	0.00	probably damaging	Yes (15385606)
2	Erythromelalgia	Definite	SCN9A	c.2543T>C	p.Ile848Thr	Pathogenic	.	0.0001	0.0039 (0)	0 (0)	0.00	probably damaging	Yes (15385606)
3	Sensorimotor neuropathy	Probable	SPTLC1	c.399T>G	p.Cys133Trp	Pathogenic	.	0.0000	0.0039 (0)	0 (0)	0.00	probably damaging	Yes (16210380)
4	Small fibre neuropathy	Definite	SCN10A	c.4984G>A	p.Gly1662Ser	Likely pathogenic	0.0014	0.0010	0.0039 (0)	0.0005 (0)	0.00	probably damaging	Yes (23115331)
5	Small fibre neuropathy	Definite	SCN11A	c.4628G>A	p.Cys1543Tyr	Likely pathogenic	0.0001	0.00004	0.0039 (0.0131)	0 (0)	0.01	probably damaging	No studies for this variant
6	Painful sensory neuropathy	Definite	SPTLC2	c.886A>C	p.Ile296Leu	VUS	.	0.0000	0.0039 (0)	0 (0)	0.04	possibly damaging	No studies for this variant
7	Non-freezing cold injury	Definite	SCN9A	c.554G>A	p.Arg185His	VUS	0.0031	0.0016	0 (0.0921)	0.0015 (0.0064)	0.01	probably damaging	Yes (21698661, 22826602)
8	Non-freezing cold injury	Definite	SCN9A	c.554G>A	p.Arg185His	VUS	0.0031	0.0016	0 (0.0921)	0.0015 (0.0064)	0.01	probably damaging	Yes (21698661, 22826602)
9	Non-freezing cold injury	Definite	SCN9A	c.554G>A	p.Arg185His	VUS	0.0031	0.0016	0 (0.0921)	0.0015 (0.0064)	0.01	probably damaging	Yes (21698661, 22826602)
10	Non-freezing cold injury	Definite	SCN9A	c.554G>A	p.Arg185His	VUS	0.0031	0.0016	0 (0.0921)	0.0015 (0.0064)	0.01	probably damaging	Yes (21698661, 22826602)
11	Non-freezing cold injury	Definite	SCN9A	c.554G>A	p.Arg185His	VUS	0.0031	0.0016	0 (0.0921)	0.0015 (0.0064)	0.01	probably damaging	Yes (21698661, 22826602)
12	Non-freezing cold injury	Definite	SCN9A	c.554G>A	p.Arg185His	VUS	0.0031	0.0016	0 (0.0921)	0.0015 (0.0064)	0.01	probably damaging	Yes (21698661, 22826602)
13	Small fibre neuropathy	Definite	SCN9A	c.4612T>C	p.Trp1538Arg	VUS	0.0020	0.0018	0.0039 (0)	0.0018 (0)	0.71	benign	Yes (23292638)
14	Small fibre neuropathy	Definite	SCN9A	c.1445A>G	p.Lys482Arg	VUS	0	0.00004	0.0039 (0)	0 (0)	0.18	benign	No studies for this variant
15	Small fibre neuropathy	Probable	SCN9A	c.2215A>G	p.Ile739Val	VUS	0.0024	0.0032	0.0078 (0)	0.0041 (0)	0.03	benign	Yes (22826602)
16	Small fibre neuropathy	Definite	SCN9A	c.2215A>G	p.Ile739Val	VUS	0.0024	0.0032	0.0078 (0)	0.0041 (0)	0.03	benign	Yes (22826602)
17	Painful sensory neuropathy	Probable	SCN9A	c.2215A>G	p.Ile739Val	VUS	0.0024	0.0032	0.0078 (0)	0.0041 (0)	0.03	benign	Yes (22826602)
18	Sensorimotor neuropathy	Definite	SCN9A	c.2215A>G	p.Ile739Val	VUS	0.0024	0.0032	0.0078 (0)	0.0041 (0)	0.03	benign	Yes (22826602)
19	Small fibre neuropathy	Definite	SCN9A	c.4982A>G	p.Glu1661Gly	VUS	0.0000	0.0001	0.0039 (0)	0.0018 (0)	0.10	benign	No studies for this variant
20	Traumatic neuropathy	Probable	SCN9A	c.554G>A	p.Arg185His	VUS	0.0031	0.0016	0 (0.0921)	0.0015 (0.0064)	0.01	probably damaging	Yes (21698661, 22826602)
21	Painful Sensory neuropathy	Definite	SCN10A	c.3445G>A	p.Pro1149Met	VUS	0.0001	0.0003	0.0039 (0)	0.00008 (0)	0.00	probably damaging	No studies for this variant
22	Small fibre neuropathy	Definite	SCN10A	c.2428G>T	p.Gly810Trp	VUS	0.0003	0.0005	0.0039 (0)	0.0004 (0)	0.00	probably damaging	No studies for this variant
23	Painful Sensory neuropathy	Definite	SCN10A	c.2737G>A	p.Ala913Thr	VUS	0.0003	0.0006	0.0039 (0)	0.0003 (0)	0.01	probably damaging	No studies for this variant
24	Erythromelalgia	Probable	SCN10A	c.968A>G	p.Tyr323Cys	VUS	.	0.00004	0.0039 (0)	0 (0)	0.00	probably damaging	No studies for this variant
25	Small fibre neuropathy	Definite	SCN11A	c.2471A>G	p.Glu824Gly	VUS	.	0.00004	0.0039 (0)	0 (0)	0.02	possibly damaging	No studies for this variant
26	Episodic pain	Possible	SCN11A	c.1730C>T	p.Pro577Leu	VUS	0.0002	0.0006	0.0039 (0)	0.0005 (0)	0.00	probably damaging	No studies for this variant

Supplementary table 1

List of gene variants that were reported and were deemed medically actionable i.e. variants that result in specific, defined medical recommendations. Clinically relevant, medically actionable, variants were reported to the referring clinician.

All participants were heterozygous for the relevant variants

All variants were predicted by Ensembl Variant Effect Predictor as missense variants

VUS – variant of uncertain significance

gnomAD - Genome Aggregation Database, open resource that aggregates and harmonises both exome and genome sequencing data; current status lists 125,748 exome sequences and 15,708 whole-genome sequences from unrelated individuals sequenced as part of various disease-specific and population genetic studies.

Allele Frequencies are shown in the Neuropathic Pain Disorders (NPD) cohort and in NIHR BioResource control cohorts.

WGS10K – NIHR Bioresources database with 13,037 whole genome sequences.

NPD- Neuropathic Pain Disorders

In silico analysis, SIFT and Polyphen, results shown.

SIFT score predicts whether an amino acid substitution affects protein function. The SIFT score ranges from 0.0 (deleterious) to 1.0 (tolerated).

The score can be interpreted as follows:

0.0 to 0.05 - Variants with scores in this range are considered deleterious. Variants with scores closer to 0.0 are more confidently predicted to be deleterious.

0.05 to 1.0 -Variants with scores in this range are predicted to be tolerated (benign). Variants with scores very close to 1.0 are more confidently predicted to be tolerated.

Genomic coordinates and the HGNC gene symbol for gene models	Fraction with rare variants	Variants considered	P Value	Rho
Tier 1-3 pain genes				
Europeans				
Probable/Definite Neuropathic pain vs Controls				
1:212733740-213037331_FLVCR1_promoter	0.078509	704	2.0274e-07	0
2:241656788-241737150_KIF1A	0.038265	180	2.7235e-09	0
2:241757820-241808205_KIF1A_promoter	0.01171	182	2.4975e-07	
1:115828713-115836247_NGF	0.002639	14	2.6429e-09	0
12:52056606-52201160_SCN8A	0.0097312	44	1.5018e-09	0
2:167227721-167351474_SCN9A_promoter	0.037605	461	2.3805e-05	0
8:72935185-72987631_TRPA1	0.015009	73	5.2482e-05	0
2:234835229-234916724_TRPM8	0.017978	90	2.825e-07	0
Possible Neuropathic pain vs Controls				
5:10237637-10311587_CCT5_promoter	0.043829	390	2.1646e-10	0
22:19158112-19468896_CLTCL1_promoter	0.12628	755	1.8541e-05	0
2:27272295-27888854_MPV17_promoter	0.14408	1039	1.1537e-06	0
9:132888940-133713656_PRDM12_promoter	0.12242	778	2.5937e-24	0
3:38887266-38992020_SCN11A	0.022166	116	3.2814e-17	0
3:38387651-39150434_SCN11A_promoter	0.036776	182	9.13e-36	0
2:167051740-167168308_SCN9A	0.031066	138	1.0185e-11	0
9:94179481-95733983_SPTLC1_promoter	0.17162	1253	1.4402e-20	0
14:77972340-78045374_SPTLC2	0.023678	113	7.4671e-17	0
17:16188184-16396312_TRPV2_promoter	0.16927	1239	2.8037e-07	0
14:23990197-24004569_ZFHX2	0.037615	195	1.8008e-11	0
Idiopathic vs Controls				
9:111694228-111884278_ELP1_promoter	0.099514	665	0.00010639	0
1:212733740-213037331_FLVCR1_promoter	0.078238	689	3.5673e-11	0
9:111637167-111693371_IKBKAP	0.021612	98	6.0954e-14	0
2:27532377-27548436_MPV17	0.0065338	31	2.3621e-11	0
2:27272295-27888854_MPV17_promoter	0.14492	1039	1.8079e-11	0
17:40688345-40696166_NAGLU	0.0065338	31	2.5867e-11	0
1:156735601-156831188_NTRK1_promoter	0.053443	606	1.2915e-12	0
3:38387651-39150434_SCN11A_promoter	0.03669	181	7.875e-07	0
12:52056606-52201160_SCN8A	0.0093818	42	7.6272e-10	0
2:167227721-167351474_SCN9A_promoter	0.03736	445	3.7788e-07	0
9:94794766-94877614_SPTLC1	0.0073714	41	2.0265e-12	0
8:72935185-72987631_TRPA1	0.01491	72	2.1457e-10	0
Non-freezing cold injury vs Controls				
11:62605687-64041758_ATL3_promoter	0.2605	1807	1.9334e-26	0
22:19158112-19468896_CLTCL1_promoter	0.12622	755	1.7755e-11	0
6:56322787-56765386_DST	0.064706	326	7.2668e-21	0
2:241653211-241737219_KIF1A	0.037479	174	2.6565e-24	0
2:27272295-27888854_MPV17_promoter	0.14437	1036	2.418e-05	0
1:115828571-115836350_NGF	0.002521	13	6.9657e-126	0
1:115257831-115881445_NGF_promoter	0.073613	415	9.0969e-55	0
12:51791830-52209151_SCN8A_promoter	0.073613	593	5.8951e-06	0
9:94179481-95733983_SPTLC1_promoter	0.17143	1244	5.4476e-30	0
14:77768191-78083941_SPTLC2_promoter	0.06084	683	1.1154e-26	0
2:234825742-235408070_TRPM8_promoter	0.058824	421	9.7579e-49	0
12:109567961-110487716_TRPV4_promoter	0.16185	898	1.6927e-12	0
Erythromelalgia vs Controls				
5:10254263-10266494_CCT5	0.013754	63	1.1515e-09	0
19:9647679-11208553_DNMT1_promoter	0.44918	3552	5.0184e-07	0
6:56322787-56765386_DST	0.064743	328	9.2064e-09	0
9:111694228-111884278_ELP1_promoter	0.099631	660	2.6704e-12	0
1:212733740-213037331_FLVCR1_promoter	0.078665	695	4.5875e-62	0

12:5020374-5027410_KCNA1	0.022979	114	8.8721e-09	0
20:43720954-43728938_KCNS1	0.016437	79	5.6901e-10	0
20:43593848-44003217_KCNS1_promoter	0.046964	245	6.3713e-22	0
2:241653211-241737219_KIF1A	0.037571	174	9.983e-40	0
2:27272295-27888854_MPV17_promoter	0.14425	1040	4.0699e-07	0
1:115257831-115881445_NGF_promoter	0.073465	414	4.0189e-19	0
3:38738320-38835432_SCN10A	0.024992	117	2.745e-08	0
12:52078070-52202289_SCN8A	0.0093928	42	6.9227e-19	0
2:167051740-167168308_SCN9A	0.03103	138	0.00011167	0
17:75303232-75496662_SEPT9	0.020798	92	9.6699e-10	0
17:74347488-75883645_SEPTIN9_promoter	0.68031	14656	2.0928e-23	0
9:94179481-95733983_SPTLC1_promoter	0.17159	1249	1.658e-17	0
2:234835229-234928166_TRPM8	0.017612	88	5.975e-10	0
12:936533-1020561_WNK1	0.030191	130	9.9286e-06	0
Post Traumatic Neuropathy vs controls				
14:50777141-51327966_ATL1_promoter	0.094511	689	3.6407e-14	0
11:62605687-64041758_ATL3_promoter	0.2607	1807	7.2586e-06	0
19:9647679-11208553_DNMT1_promoter	0.44972	3553	2.0827e-11	0
1:46215085-47268057_FAAH_promoter	0.10307	553	5.4233e-06	0
9:111629802-111693471_IKBKAP	0.021655	96	1.8508e-18	0
20:43720954-43728938_KCNS1	0.016451	79	1.9211e-10	0
2:241653211-241737219_KIF1A	0.037771	176	2.0856e-38	0
9:132888940-133713656_PRDM12_promoter	0.12187	777	4.1157e-06	0
3:38387651-39150434_SCN11A_promoter	0.036596	182	7.715e-09	0
12:51791830-52209151_SCN8A_promoter	0.073527	596	4.1392e-20	0
2:234835229-234928166_TRPM8	0.017626	88	1.6971e-24	0
18:29077164-29267441_TTR_promoter	0.077052	399	2.057e-07	0
12:678629-1060004_WNK1_promoter	0.1296	1229	3.4161e-11	0
Neuropathic Pain Not Otherwise Specified vs controls				
5:10237637-10311587_CCT5_promoter	0.043807	390	1.7269e-05	0
6:56322787-56765386_DST	0.064787	328	1.2338e-16	0
1:212733740-213037331_FLVCR1_promoter	0.078214	689	3.2979e-10	0
1:115257831-115881445_NGF_promoter	0.073347	411	5.1011e-05	0
1:156735601-156831188_NTRK1_promoter	0.053206	606	4.9332e-07	0
9:132888940-133713656_PRDM12_promoter	0.12219	777	5.1652e-10	0
3:38387651-39150434_SCN11A_promoter	0.036925	183	1.1968e-45	0
12:52078070-52202289_SCN8A	0.0093991	41	9.7448e-23	0
2:167051740-167168308_SCN9A	0.031051	137	1.1055e-07	0
2:167227721-167351474_SCN9A_promoter	0.037261	441	1.2761e-07	0
9:94179481-95733983_SPTLC1_promoter	0.17153	1253	9.4963e-18	0
14:77972340-78045374_SPTLC2	0.023666	113	4.924e-13	0
Africans				
Post Traumatic Neuropathy vs controls				
6:56323823-56819337_DST	0.076923	14	8.3758e-05	0
Small Fibre Neuropathy vs controls				
2:241653211-241737219_KIF1A	0.044586	7	1.9638e-06	0
2:234835229-234928166_TRPM8	0.044586	7	6.7973e-06	0
12:936533-1020561_WNK1	0.031847	5	0.00010244	0
12:678629-1060004_WNK1_promoter	0.17834	64	6.2972e-06	0
Non-freezing cold injury vs Controls				
1:156811877-156851636_NTRK1	0.02139	4	7.1487e-09	0

Supplementary table 2
Significant results from the gene-wise association test for rare variants of Tier 1-3 genes for each ethnicity and phenotype. Significance was set to the Bonferroni adjusted 0.01 threshold for the number of genes considered (0.01/36 = 2.7*10e-4). We report unadjusted P values that passed the Bonferroni corrected significant threshold.

Genomic coordinates and the HGNC gene symbol for gene models	Fraction with rare variants	Variants considered	P Value	Rho
Whole gene set				
Europeans				
All Neuropathic pain vs Controls				
16:16101815-16235133_ABCC1	0.0046106	13	3.57E-10	0
8:107773299-107782388_ABRA	0.0024699	6	8.48E-11	0
7:6713448-6715965_AC073343.1	0.0016466	5	1.53E-07	0.1
14:70989304-70991552_ADAM20	0.0013173	4	6.73E-09	0.1
7:87563806-87822444_ADAM22	0.00098798	3	7.66E-09	0.1
5:178540879-178771007_ADAMTS2	0.0024699	6	2.42E-10	0
1:26648464-26680526_AIM1L	0.0062572	15	9.11E-09	0
10:45869747-45941096_ALOX5	0.001976	5	1.02E-12	0
2:242128052-242163531_ANO7	0.0027993	8	1.72E-12	0
12:99042160-99126330_APAF1	0.0039519	9	1.93E-08	0
2:68694871-68805137_APLF	0.0011526	3	1.26E-14	0
1:94639450-94697137_ARHGAP29	0.0034579	9	6.86E-09	0
10:28067822-28287922_ARMC4	0.0049399	13	5.40E-08	0
19:42470756-42492732_ATP1A3	0.0021406	6	3.93E-13	0
9:33255285-33264660_BAG1	0.0013173	4	3.90E-07	0.1
15:52402005-52404915_BCL2L10	0.0011526	3	2.72E-15	0
5:78373352-78384356_BHMT2	0.0024699	5	4.47E-08	0
17:41197711-41276095_BRCA1	0.0042812	11	4.88E-10	0
11:82625764-82645231_C11orf82	0.0011526	3	1.53E-15	0
12:70272858-70352309_C12orf28	0.001976	4	9.64E-10	0
14:105052787-105055181_C14orf180	0.0023053	7	1.25E-15	0
12:7246446-7261770_C1RL	0.0029639	7	2.59E-12	0.1
3:185431276-185447460_C3orf65	0.001976	3	1.54E-08	0
15:42652136-42704352_CAPN3	0.0026346	5	8.84E-08	0
1:10699139-10725481_CASZ1	0.0051046	14	2.25E-10	0
19:47761828-47774873_CCDC9	0.00098798	3	2.06E-10	0.1
11:35160867-35250840_CD44	0.001482	5	9.59E-10	0.1
8:42559625-42591717_CHRNB3	0.00098798	3	1.23E-09	0.1
20:61926481-61960987_COL20A1	0.0065865	15	3.79E-07	0
19:15752299-15770077_CYP4F3	0.0029639	7	2.24E-07	0
2:118575082-118588191_DDX18	0.0011526	3	6.20E-08	0.2
6:170592107-170598890_DLL1	0.0016466	3	2.16E-10	0.3
5:169081464-169509843_DOCK2	0.0021406	6	4.76E-14	0
19:2189756-2227118_DOT1L	0.0059279	16	1.15E-08	0
1:44435905-44438206_DPH2	0.0013173	4	1.75E-09	0.1
16:22237076-22295307_EEF2K	0.0031286	8	2.20E-10	0
12:10658548-10675292_EIF2S3L	0.001976	6	3.11E-15	0
6:132129287-132211535_ENPP1	0.0032933	7	3.99E-07	0
12:15774255-15835855_EPS8	0.0018113	4	8.99E-11	0
8:614610-681152_ERICH1	0.0027993	6	3.62E-09	0
3:38537860-38583424_EXOG	0.0029639	7	1.93E-07	0.1
4:91229615-92520132_FAM190A	0.0023053	4	6.81E-09	0
15:52874400-52944065_FAM214A	0.0016466	5	1.28E-07	0.1
18:55217969-55253816_FECH	0.00098798	3	2.06E-09	0.1
9:95738584-95797806_FGD3	0.0027993	7	1.26E-15	0
6:76005652-76124663_FILIP1	0.0029639	7	6.31E-08	0
9:14737440-14868953_FREM1	0.0090565	25	1.29E-07	0
21:47556381-47575416_FTCD	0.0034579	7	1.94E-08	0
6:46821758-46874402_GPR116	0.0027993	7	8.74E-10	0

6:142630695-142764637_GPR126	0.0034579	9	9.52E-11	0
17:72363674-72368735_GPR142	0.001976	5	1.89E-24	0.1
2:128407614-128409316_GPR17	0.0016466	4	2.22E-10	0
19:35500042-35517022_GRAMD1A	0.0049399	12	1.15E-07	0.1
4:2965737-3040173_GRK4	0.0013173	4	2.68E-18	0
22:46693331-46725456_GTSE1	0.0044459	11	6.63E-08	0
14:25075829-25078803_GZMH	0.00098798	3	4.47E-10	0.1
17:65074393-65214916_HELZ	0.0042812	11	1.12E-08	0
11:93754556-93845053_HEPHL1	0.0037873	10	7.87E-10	0
3:42734320-42742317_HHATL	0.0034579	7	2.21E-07	0
9:133260072-133309076_HMCN2	0.0047752	11	1.44E-08	0
2:203644274-203735380_ICA1L	0.0018113	4	4.20E-18	0.2
3:129159189-129239058_IFT122	0.0026346	7	2.42E-10	0
1:67786085-67861620_IL12RB2	0.001976	6	2.88E-07	0
6:52101751-52109225_IL17F	0.00098798	3	1.15E-09	0.1
4:128554197-128637586_INTU	0.00098798	3	8.96E-09	0.2
1:156496351-156539238_IQGAP3	0.0057632	13	4.16E-08	0
16:54317544-54319854_IRX3	0.0023053	6	7.95E-13	0
17:45331244-45412723_ITGB3	0.001482	4	3.51E-14	0
14:93407968-93581414_ITPK1	0.001482	4	1.57E-08	0.1
11:64060618-64067210_KCNK4	0.0013173	4	6.24E-18	0
6:73331924-73905055_KCNQ5	0.001482	4	7.64E-17	0.1
2:241656788-241737150_KIF1A	0.0069159	14	2.02E-08	0
5:132032369-132073108_KIF3A	0.0016466	3	1.51E-09	0
X:69510002-69640098_KIF4A	0.0011526	3	7.75E-08	0.1
19:55294383-55295260_KIR2DL1	0.0024699	5	7.74E-12	0.1
11:126294495-126870380_KIRREL3	0.0029639	8	2.96E-16	0
3:189675726-189838468_LEPREL1	0.0026346	7	6.34E-12	0
7:123296025-123303794_LMOD2	0.00098798	3	2.08E-10	0.1
10:85981710-85985273_LRIT2	0.00098798	3	1.15E-10	0
21:30303571-30365237_LTN1	0.0032933	9	1.07E-09	0
19:43965538-43969718_LYPD3	0.0013173	4	3.80E-09	0.1
15:100269338-100272192_LYSMD4	0.0011526	3	3.91E-12	0
10:102762320-102766905_LZTS2	0.001482	4	1.51E-15	0
5:71403450-71500986_MAP1B	0.0046106	12	6.24E-11	0
14:71197219-71267779_MAP3K9	0.0037873	8	5.99E-08	0
9:123367518-123476611_MEGF9	0.0026346	5	1.43E-07	0
17:81042826-81052312_METRNL	0.0018113	4	2.64E-10	0
17:45901575-45908862_MRPL10	0.0013173	3	6.88E-13	0
19:54376827-54377745_MYADM	0.0023053	5	5.80E-11	0
17:10532922-10558356_MYH3	0.0037873	10	1.11E-12	0
14:23851265-23876383_MYH6	0.0023053	7	2.96E-07	0
5:177546645-177548999_N4BP3	0.0018113	5	6.64E-10	0.1
1:46049820-46083784_NASP	0.0018113	5	4.33E-17	0
4:17812738-17844936_NCAPG	0.0021406	5	2.13E-10	0
8:71033608-71128953_NCOA2	0.0024699	6	2.64E-10	0
17:26084316-26125784_NOS2	0.0034579	7	1.73E-10	0
8:27880856-27931905_NUGGC	0.0021406	6	3.02E-12	0
15:41625208-41672367_NUSAP1	0.0016466	5	2.98E-08	0.1
5:140797470-140890735_PCDHGB7	0.0036226	9	1.59E-10	0
1:77558163-77685087_PIGK	0.0011526	3	5.37E-15	0
19:39904703-39915987_PLEKHG2	0.0054339	13	1.01E-07	0
14:65194318-65210406_PLEKHG3	0.0077392	17	2.78E-08	0
19:4504520-4517590_PLIN4	0.0016466	5	9.03E-08	0.1
9:33750530-33799176_PRSS3	0.0018113	4	8.90E-11	0
16:58314167-58327720_PRSS54	0.0026346	6	5.24E-09	0

5:71616283-71654214_PTCD2	0.0011526	3	3.34E-07	0.2
6:47846053-48036289_PTCHD4	0.001482	4	9.82E-08	0
11:450550-490493_PTDSS2	0.0023053	5	1.86E-20	0.1
3:110790965-110912153_PVRL3	0.001976	5	1.49E-12	0
6:107077557-107113791_QRSL1	0.0023053	7	2.22E-07	0
16:12181701-12183753_RP11-276H1.3	0.0011526	3	2.13E-14	0
20:62190630-62203698_RP4-697K14.7	0.011856	30	2.07E-12	0
5:115782325-115840589_SEMA6A	0.0052692	13	1.56E-07	0.1
15:44087238-44092184_SERINC4	0.00098798	3	3.07E-09	0.1
5:150696439-150727020_SLC36A2	0.001976	5	4.05E-11	0
9:115642055-115652961_SLC46A2	0.0016466	5	3.02E-07	0.1
4:139093129-139163217_SLC7A11	0.0021406	4	2.47E-09	0
2:231305272-231407567_SP100	0.001976	6	6.37E-08	0
7:99913463-99917393_SPDYE3	0.0011526	3	7.63E-14	0
2:228846486-229046289_SPHKAP	0.0046106	13	8.40E-12	0
17:79977081-79980514_STRA13	0.0011526	3	4.76E-14	0
3:33194278-33260276_SUSD5	0.0021406	5	1.19E-07	0.2
16:29989477-30002833_TAOK2	0.0031286	8	8.22E-11	0
1:150460442-150479509_TARS2	0.0018113	6	9.51E-12	0
9:100961748-101017784_TBC1D2	0.0021406	6	5.01E-15	0
4:48139449-48230531_TEC	0.0013173	4	1.08E-08	0.1
22:37387239-37398303_TEX33	0.001482	4	8.23E-15	0
7:128597331-128694794_TNPO3	0.0026346	6	2.01E-12	0
9:15172019-15307233_TTC39B	0.0013173	4	8.90E-08	0.1
17:46846397-46894432_TTLL6	0.0039519	9	3.56E-09	0
16:11773077-11836586_TXNDC11	0.0052692	12	2.97E-09	0
2:128848939-128945123_UGGT1	0.0039519	12	1.56E-29	0
2:61415248-61647956_USP34	0.0064219	15	3.39E-21	0
9:136629191-136857358_VAV2	0.0021406	5	1.25E-08	0
19:54544235-54567012_VSTM1	0.0021406	4	2.39E-08	0
7:141408701-141430098_WEE2	0.00098798	3	1.61E-08	0.1
19:15533906-15559106_WIZ	0.0055986	14	3.82E-22	0
1:155629494-155658171_YY1AP1	0.0024699	7	2.34E-15	0
4:25314444-25370677_ZCCHC4	0.0024699	6	3.46E-09	0
5:32355972-32444381_ZFR	0.0011526	3	2.82E-11	0.3
20:62339945-62367201_ZGPAT	0.0021406	6	2.54E-10	0
19:20295169-20308907_ZNF486	0.0013173	4	5.17E-19	0
19:52937314-52954724_ZNF534	0.0016466	5	5.70E-08	0.1
22:24086024-24092897_ZNF70	0.0016466	5	1.22E-18	0
16:31446173-31448153_ZNF843	0.00098798	3	1.48E-08	0.1
10:126631147-126673505_ZRANB1	0.0013173	4	5.25E-08	0.1

Supplementary table 3

Significant results from the gene-wise association test for the whole gene set (5790). For the whole gene set analysis we applied a minor allele count filter of >= 2 and for the Neuropathic Pain Disorders candidate genes a minor allele count filter of >= 1. Only genes with at least two variants which passed the filters were included.

Significance was set to the Bonferroni adjusted 0.01 threshold for the number of genes considered (0.01/5790 = 1.7*10e-6).