Supplementary Material

Number of patients	Nucleotide change	Amino acid change	GoF	Allele Freq (GnomAD)	Allele count (GnomAD)	Type of variation	Classification ACGS guidelines	Overall LCM response	References
1	**c.684C>G**	**p.Ile228Met**	**YES**	**8.58e-4**	**241/281046**	**missense**	**Pathogenic**	**-**	**(Faber *et al.*, 2012) (Persson *et al.*, 2013) (Estacion *et al.*, 2011)**
1	c.1552G>T	p.Val518Phe	UK	4.02e-6	1/249054	missense	Unknown significance	+	(Eijkenboom *et al.*, 2019)
1	c.1592A>C	p.Thr531Asn	UK	-	0	missense	Unknown significance	+	(Eijkenboom *et al.*, 2019)
1	c.1691T>C	p.Ile564Thr	UK	1.21e-5	1/248986	missense	Unknown significance	-	Unpublished data
2	c.1964A>G	p.Lys655Arg	UK	1.90e-3	592/279028	missense	Unlikely to be pathogenic	-	(Singh *et al.*, 2009) (Klein *et al.*, 2003) (Brouwer *et al.*, 2014)
1	**c.2157G>C**	**p.Trp719Cys**	**UK**	**9.81e-4**	**293/243602**	**missense**	Unknown significance	**+**	(Eijkenboom *et al.*, 2019)
6*	**c.2215A>G**	**p.Ile739Val**	**YES**	2.47e-3	**597/241656**	**missense**	**Pathogenic risk factor**	**+**	**(Han *et al.*, 2012b) (Faber *et al.*, 2012) (Devigili *et al.*, 2014)**
1	c.2266C>A	p.Pro756Thr	UK	2.85e-5	7/245266	missense	Uncertain significance	-	(Eijkenboom *et al.*, 2019)
1	c.3734A>G	p.Asn1245Ser	NO	4.4e-3	1224/278244	missense	Unlikely to be pathogenic	+	(Brouwer *et al.*, 2014)
4	**c.3799C>G**	**p.Leu1267Val**	**YES**	**1.31e-3**	**321/245832**	**missense**	**Unknown significance (data available upon request)**	**-**	**(Huang *et al.*, 2014) (Della Mina *et al.*, 2015) (Wadhawan *et al.*, 2017)**
1	c.5260G>T	p.Val1754Phe	UK	-	0	-	Uncertain significance	+	(Eijkenboom *et al.*, 2019)
3*	c.2794A>C and c.2971G>T	p.Met932Leu and p.Val991Leu	YES	3.38e-2 and 3.01e-2	9571/282670 and 7160/237770	missense and missense	Pathogenic	+	(Faber *et al.*, 2012) (Li *et al.*, 2015)
2*	**c.4612T>C**	**p.Trp1538Arg**	**YES**	**2.02e-3**	**565/279548**	**missense**	**Pathogenic**	**-**	(Cregg *et al.*, 2013)
1	c.3595-11T>G	-	UK	-	0	splice-	Uncertain significance	+	Unpublished data
1	c.2842-6_2842-5delinsG	-	UK	-	0	splice	Uncertain significance -	-	Unpublished data

Supplementary Table 1. Summary of *SCN9A* variants reported in the cohort from the de Greef *et al.* (2019) study. All participants were diagnosed with pure (or with Diabetes Mellitus) painful SFN, with an associated $Na_v1.7$ variant.

Variants were classified and reported according the Practice Guidelines of the Association for Clinical Genetic Science (ACGS), Wallis, *et al.* (2013). Whenever the variant has functionally been assessed, the classification is reported accordingly, with appropriate referencing.

The star sign (*) next to the patient number indicates that one or more patients carried at least one additional variant:

One out of the six patients carrying the I739V variant also carries M932L/V991L and W1538R

Two out of the three patients carrying the M932L/V991L double mutation carry additional variants: one patient carries the W1538R, and the other patient, both W1538R and I739V (same as above).

Both patients carrying the W1538R carry additional variants (as described above, the M932L/V991L variant, and the M932L/V991L + I739V variants)

Abbreviations: GoF (Gain-of-function), UK (unknown).