HHS Public Access

Author manuscript

J Neurol Sci. Author manuscript; available in PMC 2022 August 15.

Published in final edited form as:

J Neurol Sci. 2021 August 15; 427: 117498. doi:10.1016/j.jns.2021.117498.

RARE MUTATIONS IN *ATL3*, *SPTLC2* AND *SCN9A* EXPLAINING HEREDITARY SENSORY NEUROPATHY AND CONGENITAL INSENSITIVITY TO PAIN IN A BRAZILIAN COHORT

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Abstract

Hereditary sensory neuropathies (HSN) are a group of rare neurological disorders with heterogeneous clinical and genetic characteristics. Although at least 17 different genes have already been associated with HSN, the epidemiology of the disorder in Brazil is still unknown. Performing whole genome sequencing (WGS) in 23 unrelated Brazilian families diagnosed with HSN, we detected pathogenic variants in *ATL3*, *SPTLC2*, and *SCN9A* in 12 patients belonging to five unrelated families. Clinical features associated with heterozygous mutations in *ATL3* (c.575A>G; p.(Tyr192Cys)) and *SPTLC2* (c.529A>G; p.(Asn177Asp)) were sensory deficits, neuropathic pain, and recurrent ulcerations. Presenting as congenital insensitivity to pain, three unrelated probands carried biallelic loss-of-function mutations in *SCN9A*. The so far undescribed stop mutation c.2106G>A (p.(Trp702Ter)) and the likewise novel splicing variant c.3319–1G>A were found in compound-heterozygosity with, respectively, the known pathogenic variants c.2908G>T (p.Trp970Ter) and c.2690G>A (p.Glu897Ter). In total, we identified pathogenic mutations in 21.7% of our families, which suggests that most of the cases could be explained by yet to be discovered genes or unusual alleles. Our study represents the first mutational screen in a Brazilian HSN cohort, enabling additional insights for genotype-phenotype correlations, reducing misdiagnoses, and providing early treatment considerations.

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Keywords

hereditary sensory neuropathy; congenital insensitivity to pain; autonomic disturbances; next generation sequencing; mutation

1. INTRODUCTION

Hereditary sensory neuropathies (HSN) constitute a heterogenous group of disorders characterized by axonal degeneration, exclusively or predominantly affecting the sensory neurons (1). They are mainly characterized by slowly progressive loss of multimodal sensation, frequently accompanied by chronic ulcerations in feet and hands, and complicated by severe infections, osteomyelitis, and amputations (2). In some, but not all cases, neuropathic pain and autonomic symptoms can also be present as a main feature (1).

To date, mutations in 15 genes have been associated with HSN, six in the autosomal dominant (*SPTLC1*, *SPTLC2*, *ATL1, DNMT1*, *ATL3*, and *SCN11A*) and nine in the autosomal recessive forms (*HSN2/WNK1*, *FAM134B*, *KIF1A*, *SCN9A*, *IKBKAP*, *NTRK1*, *NGF*-β, *DST*, *PRDM12*) (OMIM # 162400). With new, upcoming treatment options, such as L-serine supplementation for *SPTLC1*- or *SPTLC2*-associated HSAN1A and C (3), an early and precise genetic diagnosis is essential. In Brazil, the relative frequency of HSN is still unknown, since a systematic study has not been conducted yet. We herein performed whole genome sequencing (WGS) in 23 unrelated Brazilian HSN families diagnosed, thereby describing 2 novel and 4 known pathogenic variants in *ATL3*, *SPTLC2* and *SCN9A* in five unrelated families.

2. MATERIALS AND METHODS

2.1 Patient Cohort

We collected DNA samples from 23 unrelated families clinically characterized by predominant sensory polyneuropathy, with or without signals of dysautonomia, followed up at the Department of Neurology of the University Hospital, School of Medicine of Ribeirão Preto, University of São Paulo, (HCFMRP/USP). All procedures were approved by the HCFMRP University Ethics Committee, and informed consent was obtained from all participants or their parents before sample collection.

2.2 Whole genome sequencing and variant filtering

Genomic DNA was isolated from peripheral blood leukocytes using *DNeasy Blood & Tissue Kit* (Qiagen®), and WGS was performed in 23 index individuals through BGISEQ-500. DNA nanoball and combinational probe anchor synthesis were developed from Complete Genomics™ sequencing technologies. Library preparation, hybridization and sequencing were performed according to the manufacturer's standard procedure provided by BGI (BGI-Shenzhen). On average, 91.7% of the target region was successfully covered by sequencing data at more than 27 reads.

WGS data were analyzed by and uploaded into the GENESIS platform (4) and variants were filtered based on their functional impact predicted based on bioinformatic tools (Mutation Assessor, LOFTEE, MutationTaster, MetaLR, CADD, FATHMM, PolyPhen-2, SIFT, VEST3, PROVEAN, LRT and MetaSVM), allele frequencies less than 0.01 (ExAC and gnomAD), number of supporting reads for the variant site more than 10, and evidence for evolutionary conservation. Sanger sequencing, performed by Eurofins, was used to validate the variants, confirm compound-heterozygosity, and perform co-segregation analyses.

2.3 Variants classification

The following criteria were used to classify a variant as pathogenic: 1) variant is present in a known gene associated with the individual's phenotype; 2) variant fits the mode of inheritance of the known gene; 3) variant is classified as pathogenic or likely pathogenic in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines (5) or with ClinVar variant classification, and/or have been published in the literature with enough evidence of pathogenicity, like supportive functional studies.

3. RESULTS

We identified disease-causing variants in *ATL3*, *SCN9A*, and *SPTLC2* in 12 patients from five unrelated families. These results yielded a genetic diagnosis in 21.7% (5/23) of our families. Detailed information on the genotypes and phenotypes is provided in tables 1 and 2.

At the age of 10 years, the female proband of family 1 developed a progressive sensory loss together with neuropathic pain and recurrent ulcerations at both feet. Temperature and pinprick perception were diminished, reflecting a pronounced small fiber dysfunction. In the clinical course, she developed neuropathic joints. As a sign of large fiber involvement, the vibration perception decreased distally, whereas muscle strength, deep tendon reflexes, and nerve conduction studies (NCS) remained normal. The proband's father, brother, and daughter all developed similar symptoms, the brother accompanied by mild autonomic disturbances (erectile dysfunction). In all affected family members, we detected the heterozygous missense variant c.575A>G (p.(Tyr192Cys)) in *ATL3* that had previously been described in the context of HSAN, without being identified in healthy controls (GnomAD).

Proband 2 developed an unsteady gait and recurrent ulcerations at the age of 19 years. With ascending muscle weakness, neuropathic pain, and sensory deficits, she had pronounced walking difficulties and impaired motor skills at the age of 38 years. Clinical examinations were indicative for both large and small fiber damage, and lower limb tendon reflexes were abolished. Two further of the patient's sisters presented with the same phenotype, while the parents' affection status is unknown. The most severe clinical picture was observed in the proband, including proximal muscle weakness in the course. In contrast to other affected family members, she additionally suffered from diabetes mellitus. We identified the co-segregating heterozygous missense mutation c.529A>G (p.(Asn177Asp)) in *SPTLC2* that has previously been described to cause HSAN1 and does not occur in healthy controls (GnomAD).

In families 3, 4, and 5, all probands were sporadic cases presenting with self-injuring behavior that became manifest during the first six months of life and eventually led to severe burn or bite injuries at the tongue, lips, and hands. Injections did not seem to be considered painful, and infections were not noticed. At the age of six years, proband 3 further showed signs of anosmia and autonomic dysfunction (hypohydrosis and urinary incontinence). Consanguinity was reported in one (family 4) out of three families. In all three probands, we found biallelic loss-of-function variants in *SCN9A*. The stop variant c.2690C>A (p.(Trp897Ter)) was found in homozygosity in family 4, as well as in a compound-heterozygous state with the splice variant c.3319–1G>A in family 5. Proband 3 showed two stop variants in exons 14 and 17 (c.2106G>A p.(Trp702Ter); c.2908G>T p.(Trp970Ter)) in compound-heterozygosity. All variants are absent in healthy controls (GnomAD).

4. DISCUSSION

Using WGS, we herein identified disease-causing mutations in 21.7% of our 23 HSN patients that were all of Brazilian descent. Thereby, the overall diagnostic yield ranged in a similar spectrum than previously described by Davidson et al (14.3%) (6) and Rotthier et al. (19%) (2), suggesting that most of the cases could be explained by novel genes that remain to be discovered.

It is for the first time that a Brazilian HSN cohort, representing one specialized center, has been systematically screened and published in this context. Compared to other inherited neuropathies like Charcot-Marie-Tooth disease, HSN is especially rare and the accurate worldwide prevalence is unknown. The disorder frequently remains undiagnosed or misdiagnosed, making it difficult to determine the true frequency in the general population. As demonstrated by our and other cohorts, however, its major impact on the patients' quality of life still merits a precise diagnosis and early treatment considerations.

We identified pathogenic variants most frequently in *SCN9A*, accounting for 60% of the genetic identified cases. *SCN9A* encodes for the α-subunit of the voltage-gated sodium channel Nav1.7, which is strongly expressed in nociceptive neurons (7). The four identified *SCN9A* variants of our study correspond to biallelic null mutations, which suggest loss-of-function of the Nav1.7 protein, resulting in congenital insensitivity to pain. Two of these variants (p.(Trp897Ter); p.(Glu970Ter)) have been previously described in families from various ethnic origins (7–9). The other stop variant, p.(Trp702Ter), has not been reported in the literature or public databases. It is a predicted null variant not found in 207,574 chromosomes and is classified as pathogenic according to the ACMG guidelines. Considering the specific, compatible phenotype, the matching pathomechanism, and the proven compound-heterozygosity with a known disease-causing variant, we herein evaluate it as pathogenic, which is in accordance with the ACMG criteria.

The novel splice site variant c.3319–1G>A in *SCN9A* is absent from gnomAD (278,252 chromosomes), is predicted to disrupt the original acceptor splice site of exon 18, has a pathogenic computational verdict (4 pathogenic predictions from DANN, EIGEN, FATHMM-MKL and MutationTaster vs no benign predictions) and is classified as pathogenic according to the ACMG criteria. Three splicing mutations have been reported so

far (IVS17+3delA, c.901+5G>C, and IVS8–2A>G), leading to loss-of-function of the sodium channel and consequent insensitivity to pain (10–12). Since proband 5 has a well-known disease-causing nonsense mutation at exon 16 and a compound-heterozygous splicing variant at the acceptor consensus site at the intron 17/exon 18 junction, we hypothesize that this novel variant is pathogenic.

In family 1, we identified the known pathogenic mutation c.575A>G (p.(Tyr192Cys)) in *ATL3*. Worldwide, only four families have been reported with an *ATL3*-associated HSN so far, one from German, Spanish, Bosnian, and Chinese origin, each (13–15). With a dominant negative effect, this alteration causes mislocalization of an endoplasmic reticulum (ER)-shaping GTPase, which results in axon growth deficits in cultivated primary neurons (16). It has also been reported that increased ER–mitochondria contact and crosstalk may have a negative impact on mitochondrial trafficking (17). In our Brazilian family, the mutation co-segregated in four affected family members, matching the expected autosomal dominant mode of inheritance.

The *SPTLC2* mutation c.529A>G (p.Asn177Asp) identified in family 2 has previously been described in a German HSN1 family with five affected individuals (18). Pathogenic variants in *SPTLC2* reduce the substrate specificity of the serine-palmitoylCoA-transferase (SPT), leading to an increased synthesis of neurotoxic1-deoxysphingolipids (1-deoxySL) (18). Affected family members with the p.(Asn177Asp) mutation showed elevated 1-deoxySL plasma levels, confirming the underlying gain-of-function pathomechanism that is associated with the most frequent subtype of autosomal dominant HSN (18). In our Brazilian family, the variant co-segregated in three affected family members. The most severely affected individual was patient 13936, who had an additional diabetes mellitus. Interestingly, abundance of the main gluconeogenic amino acid L-alanine can additionally shift the substrate specificity of the SPT, resulting in increased 1-deoxySL levels in patients with diabetes mellitus (19) and diabetic neuropathy as well (20). These additive effects might therefore explain why individual 13936 was at a higher risk for a more severe disease course, despite carrying the same variant as the other affected family members. Importantly, high-dose oral L-serine supplementation has been shown to be beneficial in a recent phase 2 clinical trial (3) and should therefore be considered as a pathomechanism-based treatment option.

In summary, we herein described two novel and four known pathogenic, HSN-related gene mutations in a Brazilian cohort of mixed HSN subtypes. WGS is an efficient way to approach ultra-rare hereditary diseases in order to identify the underlying genetic cause and explore further treatment options.

ACKNOWLEDGEMENTS

The authors are grateful to all study participants for their cooperation and support. This work was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, process: POS-DOC - 88881.172252/2018–01), NIH grants (5R01NS105755 and 5U54NS065712) and grants from the German Research Foundation (Deutsche Forschungsgemeinschaft, DGF) and the Interdisciplinary Centre for Clinical Research within the faculty of Medicine at the RWTH Aachen University (IZKF TN1–9, 532009).

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Highlights

- Whole genome sequencing in the first cohort of Brazilian patients with HSN
- Enrichment of the genetic variant spectrum of HSN
- Pathogenic variants in *ATL3*, *SPTLC2*, and *SCN9A*
- Novel pathogenic variants in *SCN9A*

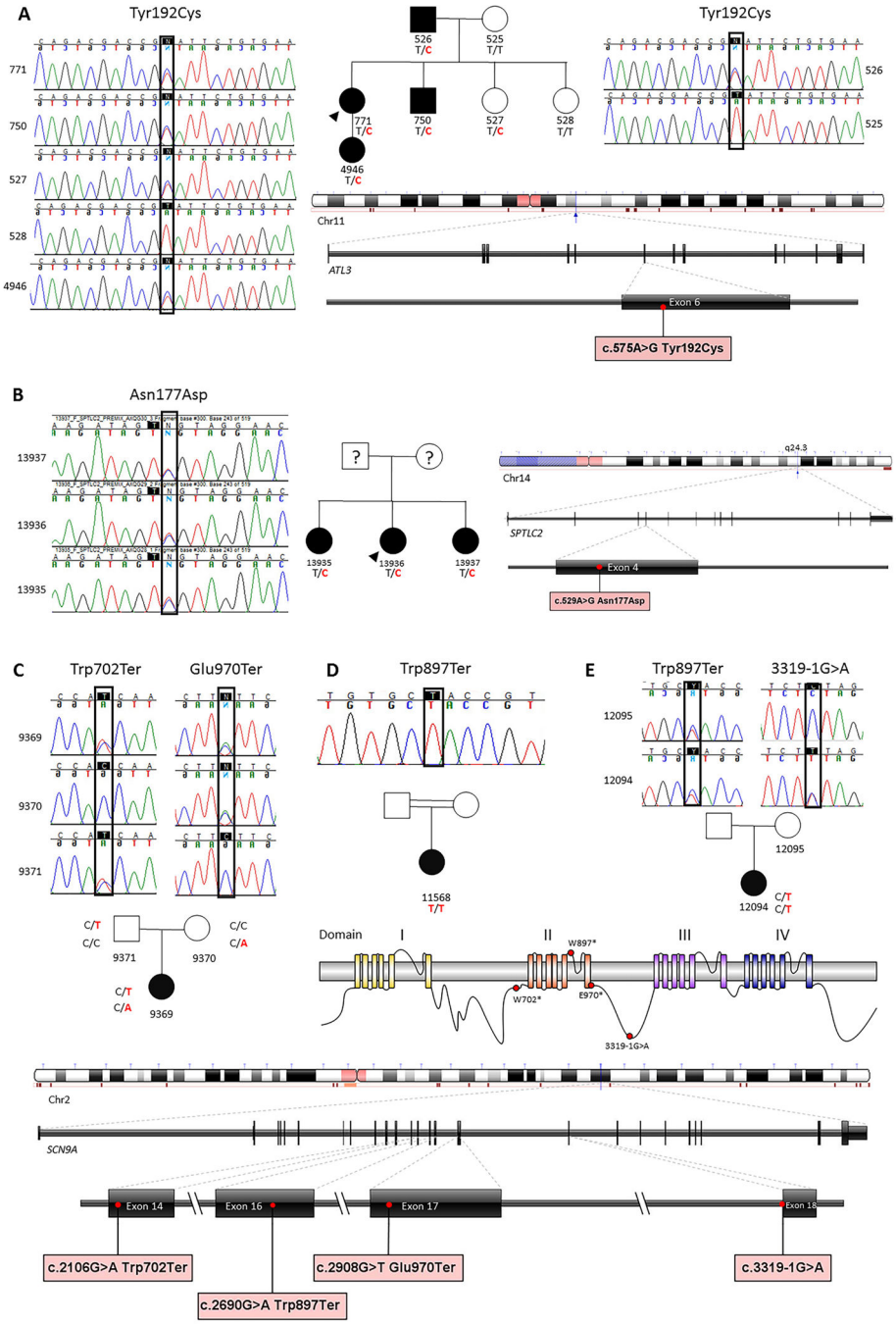

Figure 1.

Five Brazilian kindreds with HSN pathogenic variants. The boxes highlight the position of the variants in each sequence. Diagrams show cDNA position of the *ATL3, SPTLC2* and *SCN9A* mutations. Segregation of the heterozygous missense variants Tyr192Cys in *ATL3* **(A)** and Asn177Asp in *SPTLC2* **(B)**. Biallelic loss-of-function *SCN9A* variants are show in the compound-heterozygous states (Trp702Ter; Glu970Ter) **(C)**, (Trp897Ter; c.3319–1G>A) **(E)** and in the homozygosis (Trp897Ter) in the consanguineous family **(D)**. The relatives *SCN9A* mutations positions in the Nav1.7 protein are shown in the bottom. Square = male,

circle = female, black filled symbol = affected, empty symbol = unaffected; arrowhead = proband.

Table 1.

Variants found in HSN patients classified according to ACMG and ClinVar criteria

HSN type (OMIM number)	Mode of Inheritance	Gene	Chromosome Position (GRCh37/hg19)	Variant		Functional Consequence	
				cDNA level	Protein level	ACMG classification	ClinVar classification
1F (615632)	AD	*ATL3*	Chr11: 63414022	c.575A>G	p.(Tyr192Cys)	Likely pathogenic	Pathogenic
1C (613640)	AD	*SPTLC2*	Chr14: 78043212	c.529A>G	p.(Asn177Asp)	Uncertain significance	Uncertain significance
2D (243000) CIP	AR	*SCN9A*	Chr2: 167137072	c.2106G>A	p.(Trp702Ter)	Pathogenic	Not available
			Chr2: 167129319	c.2908G>T	p.(Glu970Ter)	Pathogenic	Not available
2D (243000) CIP	AR	*SCN9A*	Chr2:167133644	c.2690G>A	p.(Trp897Ter)	Pathogenic	Pathogenic
2D (243000) CIP	AR	*SCN9A*	Chr2:167133644	c.2690G>A	p.(Trp897Ter)	Pathogenic	Pathogenic
			Chr2:167108396	c.3319–1G>A		Pathogenic	Not available

AD: autosomal dominant; AR: autosomal recessive; CIP: congenital insensitivity to pain

Table 2:

Clinical information of the patients with HSN mutation

ID/Sex/Age (y)	Family/ relationship	Age at onset (y)	First symptoms	Neuropathic pain	Autonomic dysfunction	Disturbed wound healing		Anosmia	Gait	Sensory assessment			Deep tendon reflexes UL/LL	Muscle strength UL/LL	Nerve conduction studies	
						Ulcers UL/LL	Amputations			Pin prick UL/LL (level)	Temperature UL/LL (level)	Vibration UL/LL (level)			SNAP UL/LL	CMAP UL/LL
771/F/48	family 1, proband	10	sensory loss in feet and recurrent ulcers	yes	no	no/yes	no	no	normal	normal/ ankles	normal/ ankles	normal/ feet	normal/ decreased	normal/ normal	normal/ normal	normal/ normal
526//M/69	family 1, father	16	sensory loss in feet and recurrent ulcers	yes	no	no/yes	yes, both legs	no	wheelchair	wrist/ above knees	normal/ knees *	elbows/not tested *	normal/not tested *	normal/ not tested *	MD	MD
750/M/45	family 1, brother	16	sensory loss in feet and recurrent ulcers	yes	erectile dysfunction, urinary retention	no/yes	yes, left thumb	no	normal	wrist/ above knees	normal/mid feet	normal/ normal	normal/ normal	normal/ normal	normal/ normal	normal/ normal
4946/F/24	family 1, daughter	not known	sensory loss in hands and feet	yes	no	no/yes	no	no	normal	2 cm above wrist/mid leg	wrist/ankles	normal/ ankles	brisk/ normal	normal/ normal	normal/ normal	normal/ normal
13936/F/38	family 2, proband	19	recurrent ulcers, walking difficulties	yes	no	yes/yes	no	no	abnormal (muscle weakness)	5 cm above elbow/mid thigh	elbow/knees	normal/ costal margin	reduced/ absent	reduced/ reduced	MD/MD	normal/MD
13935/F/46	family 2, sister	20	recurrent ulcers, sensory loss, walking difficulties	yes	no	yes/yes	no	no	abnormal (muscle weakness, afferent ataxia)	mid forearm/mid thigh	normal/knees	normal/ knees	normal/ absent at ankle	normal/ reduced	reduced/ MD	normal/MD
13937/F/47	family 2, sister	19	walking difficulties	yes	no	yes/yes	no	no	abnormal (muscle weakness, afferent ataxia)	elbow/mid thigh	normal/knees	normal/ knees	normal/ normal	normal/ reduced	reduced/ reduced	normal/MD
9369/F/10	family 3, proband	<1	insensitivity to pain, automutilation	no	urinary incontinence, hypohydrosis	no/yes	no	yes	normal	decreased, generalized	MD	normal	normal/ normal	normal/ normal	normal/ normal	MD
11568/F/21	family 4, proband	<1	insensitivity to pain, automutilation	no	no	no	no	no	normal	absent, generalized	normal/ normal	normal/ feet	normal/ normal	normal/ normal	normal/ normal	borderline/ reduced
12094/F/8	family 5, proband	<1	insensitivity to pain	no	no	no	no	no	normal	absent, generalized	MD	MD	reduced/ reduced	normal/ normal	normal/ normal	borderline/ reduced

Abbreviations (alphabetical order): CMAP, compound motor action potential; F: female; LL: lower limb; M: male; MD, missing data; SNAP, sensory action potential; UL: upper limb; y, years; * amputation

The given age refers to the age at examination. In the sensory testing, the level of abnormal is given if applicable.