Journal of Neurology (2019) 266:735–744
https://doi.org/10.1007/s00415-019-09196-1

ORIGINAL COMMUNICATION

Peripheral neuropathy in hereditary spastic paraplegia caused by *REEP1* variants

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Received: 16 November 2018 / Revised: 7 January 2019 / Accepted: 8 January 2019 / Published online: 12 January 2019

Abstract

SPG31 is a hereditary spastic paraplegia (HSP) caused by pathogenic variants in the *REEP1* gene. The phenotype (SPG31) has occasionally been described with peripheral nervous system involvement, in additional to the gradually progressing lower limb spasticity that characterizes HSP. The objective of this study was to characterize patients with pathogenic *REEP1* variants and neurophysiologically assess the extent of peripheral nerve involvement in this patient group. Thirty-eight index cases were molecular-genetically tested, yielding two previously reported pathogenic *REEP1* variants and a novel missense variant, in a total of four index patients. Three of four probands and five additional family members underwent nerve conduction studies, electromyography, quantitative sensory testing, and examination of the autonomic nervous system. None of the examined patients had completely unremarkable results of peripheral nerve studies. Most showed electrophysiological signs of carpal tunnel syndrome, and one patient demonstrated a multifocal compression neuropathy. Autonomic testing revealed no severe dysfunction, and findings were limited to adrenergic function. HSP caused by pathogenic *REEP1* variants may be accompanied by a generally mild and subclinical polyneuropathy with a predisposition to compression neuropathy, and should be considered in such cases.

Keywords Hereditary spastic paraplegia · REEP1 · SPG31 · Nerve conduction studies · Polyneuropathy · Carpal tunnel syndrome

Introduction

Hereditary spastic paraplegia (HSP) comprises a group of neurodegenerative disorders characterized by slowly progressive, lower limb spasticity and weakness in its pure form and additional neurological signs and symptoms in the complex form [1]. The pattern of inheritance can be autosomal dominant, autosomal recessive, or X-linked. The three most frequent forms of autosomal dominant HSP are SPG4, SPG3A, and SPG31 caused by pathogenic variants in the *SPAST, ATL1*, and *REEP1* genes, respectively [2, 3].

SPG31 is found in 7.5% of patients with a pure phenotype and a family history of autosomal dominant inheritance without pathogenic variants in *SPAST* and *ATL1* [4]. Age of onset is bimodal with a peak in the second and fourth decades of life [4]. At present, 56 pathogenic *REEP1* variants have been reported. Disease-causing variants in *REEP1* are predominantly truncating mutations suspected to trigger the nonsense-mediated mRNA decay, and the pathogenic mechanism is generally thought

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09196-1) contains supplementary material, which is available to authorized users.

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to be haploinsufficiency [3–5]. A few pathogenic missense variants affecting highly conserved amino acids of *REEP1* have been identified, as well, and 3′-UTR variants are speculated to be pathogenic by affecting a miRNA-binding site [4, 6, 7].

The SPG31 phenotype was initially described as pure [4], but complex phenotypes with amyotrophy, neuropathy, ataxia, and cognitive impairment have been identified [7]. Neuropathy in particular is a frequent complicating feature in patients with HSP due to pathogenic *REEP1* variants. In general, however, data on the extent of peripheral nerve involvement in SPG31 are scarce. The aim of the present study is to characterize HSP patients with disease-causing variants in *REEP1* and to further examine the function of the peripheral nervous system to describe the clinical and neurophysiological consequences of variants in this gene.

Methods

Patients

The study was approved by the local ethics committee and informed consent was obtained from 38 patients with HSP referred to the Neurogenetics Clinic [(KF) 01-142/94 and (KF) 01-232/96]. Pathogenic variants in the *SPAST* and *ATL1* genes had previously been excluded in all patients by direct sequencing. Twenty-three index patients were from families with an autosomal dominant pattern of inheritance and 15 were isolated cases. The patients underwent clinical examination and an EDTA blood sample was drawn. After a pathogenic variant was identified, additional family members were investigated. Clinical and molecular-genetic assessment was performed in a total of 15 and 18 family members, respectively. One family member did not want to participate in molecular-genetic testing. Neurophysiological testing was accepted and performed in three of four index patients (family A, B, and C) and five additional family members.

Detection of genetic variants

DNA was extracted from EDTA blood using the standard methods and sent to Centogene GmbH (Rostock, Germany). Coding regions of *REEP1* were directly sequenced. Multiplex ligation-dependent probe amplification (MLPA) of *REEP1* was performed to identify exon deletions or duplications. The identified variants were confirmed in the DNA samples from patients and their family members in our own laboratory by Sanger sequencing. NM_022912.2 was used as reference sequence.

Electrophysiology

Nerve conduction studies (NCS) and electromyography (EMG)

NCS and EMG were carried out using the standard techniques and reference values of our lab. The right and left median, ulnar, sural, and tibial nerves—and, in some cases, the right peroneal nerve—were examined using surface electrodes for recording and stimulation. In addition, the left sural nerve was studied in five patients orthodromically using the near-nerve technique [8]. EMG in the right abductor digiti minimi muscle (ADM) was performed recording spontaneous activity, interference pattern at maximal contraction, and mean duration and amplitude of at least 20 motor unit potentials using a concentric needle electrode. All recordings were performed using Keypoint® hardware and software (Dantec, Medical, Denmark). Recorded values were compared to the normal values obtained in our lab [8, 9] and Z scores outside 95% confidence intervals ($Z > |2|$) were considered abnormal.

Quantitative sensory testing (QST)

QST was performed on the limbs of the most affected side.

Vibration thresholds (Vibrameter©, Somedic, Sweden) were measured as the mean of three trials from the first metacarpal and the first metatarsal bone using the method of limits [10] and reported as Z scores.

Thermal thresholds for warm detection (WDT) and cold detection (CDT) were examined (Medoc TSA-2001; Medoc Ltd., Israel) on the thenar eminence and on the dorsum of the foot and compared to upper or lower limits [11].

Autonomic function

Autonomic functions were examined using a standard battery.

Sympathetic nervous system function

Sympathetic function was examined from the blood-pressure response to tilt table testing and the Valsalva's maneuver. Continuous pressure measurement (Finometer©, FMS, The Netherlands) from the right index finger and repeated brachial sphygomanometrical blood-pressure measurements (Dinmap Criticon, GE Healthcare, Germany) were recorded during the tests. Patients were in a horizontal position at least 8 min before commencing the tilt. Patients were then tilted to 70° and remained there

for 20 min. Symptoms were recorded during the entire tilt phase. After termination of the tilt phase, the recording proceeded for at least 5 min.

Changes in mean blood pressure as well as pulse pressure during (phase 2; early and late) and after (phase 4) the Valsalva maneuver were analyzed, and changes in systolic and diastolic blood pressure were analyzed during the tilt test [12, 13].

Peripheral sympathetic sudomotor responses (QSWEAT, WR Medical, USA) were recorded at the standard positions and compared to the normal values [14].

Parasympathetic nervous system function

Parasympathetic function was examined from the heart rate variability during paced deep breathing (five cycles per min) and from the heart rate response during Valsalva's maneuver and compared to limits of the normal range (unpublished values of the lab and [12], respectively). The overall autonomic function was reported using the Composite Autonomic Scoring Scale [15] with indices for sudomotor (0–3), adrenergic (0–4), and cardiovascular heart rate (0–3). The scores were compared to the reported scores [15, 16].

Results

Detected variants

A previously reported nonsense variant, c.337C>T, p.(Arg113*) [6], leading to a premature stop codon, was found in two index patients (A II-2 and C II-2) (Table 1). A previously reported frame shift variant, c.512delC, p.(Pro171Hisfs*52) [3], was detected in one index patient (B II-2). Finally, a previously unreported, missense variant, c.230T>C, p.(Leu77Pro), was found in one index patient (D III-3).

Patients

The four patients with *REEP1* variants reported a total of 17 affected family members (Fig. 1a). Thirteen of the family members were molecular-genetically tested and an *REEP1* mutation was identified in 11 of them. The index patient of family A (A II-2) presented with the symptoms of early onset, pure HSP. He had slow progression and was able to walk independently at the age of 65 years, although with a severely spastic gait. All of his four children had pure HSP with childhood or early adult onset. The pathogenic variant was also identified in a blood sample from the patient's mother, who did not exhibit symptoms or signs at examination at age 85. The index patient from family B (B II-2) was 71 years at the time of examination. He had a phenotype with spastic paraplegia and bilateral weakness and atrophy of hand muscles (Fig. 1b). The patient's affected son (III-1) also presented with spastic paraplegia, weakness, and atrophy of the hand muscles, along with a percussion myotonia of the left thenar eminence. The index patient in family C (C II-2) was referred, because his twin boys had developed spastic paraplegia. Upon examination at age 38, a mild spastic paraparesis was found and an *REEP1* variant (c.337C>T) was identified in the patient, his children, and in his mother—who exhibited symptoms, as well. This was the same variant that was detected in family A. The two families were apparently unrelated but may share a common ancestor. The index patient of family D (D III-3) was referred with the early onset gait problems and progressive pure HSP. His 45-year-old father (D II-1) had at examination a mild, not disabling spasticity, and one of the sisters (D III-1) had had problems with sports in school and had a mild lower limb spasticity at examination at the age of 17 years.

Electrophysiology

Focal mononeuropathies

All examined patients had neurophysiological signs of at least one focal mononeuropathy.

Median nerve: seven of the eight patients (13 of 16 hands) showed the signs of carpal tunnel syndrome (CTS) with prolonged distal motor latency (DLM) and slowing of orthodromic sensory conduction velocity after stimulation of interdigital nerves at the palm or digit II. In addition, four of those patients and six hands had an abnormally increased difference in distal motor latency recorded at the second lumbrical or second volar interosseus after stimulating the ulnar and median nerves (range 0.7–1.0 ms, upper limit of normal 0.4 ms) [17]. In most patients, the changes were subtle, but one patient (B II-2) had pronounced changes with marked asymmetry and probable motor fiber loss in the right hand. Three patients (A III-1, B II-2, and C I-2) reported clinical symptoms of CTS, and C I-2 was referred to surgery at the time of examination. Upon clinical evaluation using QST, the WDTs were below the lower limit of normal (LLN) suggesting warm hyperalgesia in five of the seven patients with CTS.

Ulnar nerve: of the eight patients, four had a slowing in the cubital segment, but only one patient (C II-2) had a focal slowing at the elbow complying with the American Association of Electrodiagnostic Medicine (AAEM) criteria [18]. The patient presented no clinical symptoms thereof.

Quantitative EMG of the ADM was performed in five patients and demonstrated no clear abnormalities.

Peroneal nerve: study of one peroneal nerve was performed in two of the eight patients. No focal neuropathy was found.

Table 1 Patient characteristics

Family/patient	(A) II-2	(A) III-1	(A) III-2	(A) III-3	(A) III-4	(B) II-2	(B) III-1	(C) I-2	(C) II-2	(D) II-2	(D) III-1	(D) III-3
REEP1 variant	c.337C>T p.Arg113*	c.337C>T p.Arg113*	c.337C>T p.Arg113*	c.337C>T p.Arg113*	c.337C>T p.Arg113*	c.512delC p.Pro171Hisfs*52	c.512delC p.Pro171Hisfs*52	c.337C>T p.Arg113*	c.337C>T p.Arg113*	.230T>C p.(Leu77Pro)	.230T>C p.(Leu77Pro)	c.230T>C p.(Leu77Pro)
Gender	Male	Male	Female	Male	Female	Male	Male	Female	Male	Male	Female	Male
Age at onset (years)	Early childhood	22	Early childhood	Early childhood	Early childhood	20	25	Early adulthood	Childhood	Probably early	Early childhood	Early childhood
Age at examination (years)	63	40	35	24	19	71	49	63	38	45	18	7
Est. disease duration (years)	60	18	30	20	15	51	24	40	30	35	15	4
Motor disability stage	Walking without aid, unable to run	Walking without aid, able to run	Walking without aid, able to run	Walking without aid, unable to run	Walking without aid, unable to run	Walking without aid, unable to run	Walking without aid, unable to run	Walking without aid, able to run	Walking without aid, able to run	Walking without aid, able to run	Walking without aid, able to run	Walking without aid, able to run
Phenotype	Pure	Pure	Pure	Pure	Pure	Complex	Complex	Pure	Pure	Pure	Pure	Pure
Lower limb												
Spasticity	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present
Hyperreflexia	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present
Paraparesis	4+/4+	4+/4+	5/5	4+/4+	4+/4+	4+/4+	4/4	5 −/5 −	5 −/5 −	5 −/5	5/5	4+/4+
Atrophy	None	Distal bilateral atrophy	None	Diffuse bilateral crural atrophy	Slight diffuse bilateral crural thinning	None	None	Slight crural atrophy bilaterally	Slight bilateral intertarsal atrophy	None	None	None
Plantar response	Extensor	Extensor	Extensor	Extensor	Flexor	Flexor	Indifferent	Extensor	Flexor	Extensor	Extensor	Extensor
Pes cavus	None	None	None	Slight tendency	None	Present	None	Present	Slight tendency, most pronounced on the left side	Present	Present	Present

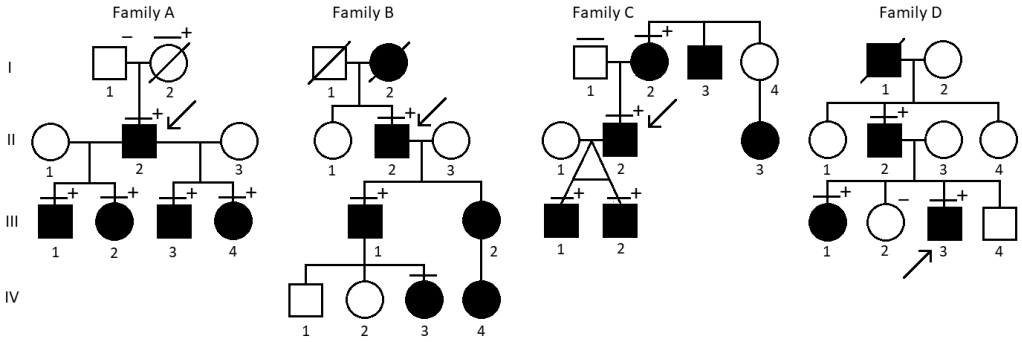
Table 1 (continued)

Family/patient	(A) II-2	(A) III-1	(A) III-2	(A) III-3	(A) III-4	(B) II-2	(B) III-1	(C) I-2	(C) II-2	(D) II-2	(D) III-1	(D) III-3
Ataxia (heel to shin)	None	None	None	None	None	None	None	None	None	None	None	None
Distal sensory deficits	Impaired vibration sense	None	None	None	Bilateral crural decreased sensation Impaired vibration sense	Impaired vibration sense	Impaired vibration sense	Impaired vibration sense	Impaired vibration sense	None	None	None
Upper limb												
Spasticity	None	None	None	None	None	None	None	Discrete hypertonia	None	None	None	None
Hyperreflexia	None	None	Present	None	None	None	None	Present	None	None	Present	None
Paresis	None	None	None	None	None	Decreased abduction of left thumb and opposition of both thumbs	Decreased abduction of thumbs	None	None	None	None	None
Atrophy	None	None	None	None	None	Atrophy of thenar and interosseous muscles	Atrophy of left thenar and interosseous muscles	None	Slight bilateral atrophy of first dorsal interosseous muscle	None	None	None
Distal sensory deficits	None	None (reports numbness and tingling of digits I–III of his right hand during manual labor)	None	None	None	None (reports numbness and tingling of digits I–III of his right hand when driving)	None	None (reports occasional numbness and tingling of digits I–III on both hands)	None	None	None	None

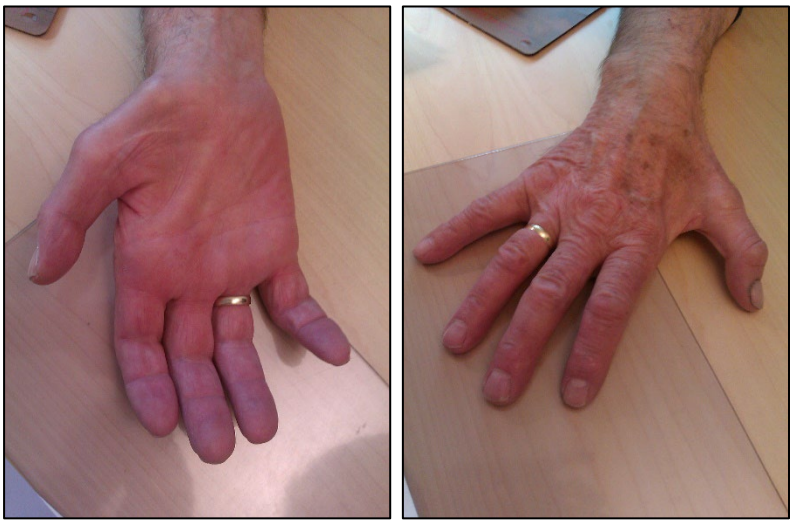
Table 1 (continued)

Family/patient	(A) II-2	(A) III-1	(A) III-2	(A) III-3	(A) III-4	(B) II-2	(B) III-1	(C) I-2	(C) II-2	(D) II-2	(D) III-1	(D) III-3
Gait	Spastic	Spastic	Slightly spastic	Spastic, Trendelenburg sign	Marked by contractures, spasticity, and slight foot drop. Impaired toe and heel walking	Spastic, wide-based	Spastic	Tendency to hyperextend knees slightly, otherwise normal	Slightly spastic, but without hyperextension of the knees	Slightly spastic	Slightly spastic	Spastic
Romberg's test	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Additional neurological symptoms	None	None	None	None	None	None	Discrete resting tremor of both hands. Percussion myotonia of right thenar muscles	Diffuse neuropathic pain in both upper limbs, radiating distally from shoulder level	None	None	None	None
Urinary symptoms	None	Urgency	Urgency	None	None	None	None	None	None	None	None	None

Muscle strength grading—5: muscle activation against examiner's full resistance, full range of motion. 4: muscle activation against some resistance, full range of motion. "+" and "−" indicate intermediate levels of muscle activation



a *Pedigrees of the 4 included SPG31 families. Black symbols indicate affected individuals. Horizontal bars indicate clinically examined subjects. "+" and "-" indicate molecular-genetically tested subjects with and without REEP1 mutation, respectively. Arrows indicate probands.*



b *Pronounced atrophy of the thenar and 1st dorsal interosseus muscles in patient II-2, family B.*

Fig. 1 Patient pedigrees and clinical images

Polyneuropathy

With the finding of focal neuropathies in all the examined patients, the diagnosis of polyneuropathy relies on nerve conduction studies in nerves without focal pathology.

A reduction in motor nerve action potential amplitude was found in two patients affecting one nerve in two limbs (upper limbs of A II-2 and lower limbs of B II-2). In addition, four other patients (A III-1, A III-2, A III-4, and C II-2) had a slightly reduced motor nerve conduction velocity in one nerve in one limb.

Sensory nerve action potential amplitudes were reduced in five patients, but only affecting one limb in each. Sural nerve test results were abnormal in four of these patients.

Using minimal criteria for the diagnosis of polyneuropathy [19], one sural and one additional nerve abnormality was found in only two patients (B II-2 and A III-1).

Clinical examination using QST revealed abnormal vibration thresholds in three patients, but with involvement of the hands in only the patient with severe polyneuropathy (B II-2), while the thresholds in the two others were normal in the hands and only marginally abnormal in the feet (Table S1).

QST for temperature in the feet was found abnormal in only two patients, one of whom had significant abnormalities in the NCS (B II-2), and the other (A III-1) had minor NCS abnormalities.

Central nervous system function

Three patients had VEP, SSEP, or MEP performed prior to genetic diagnosis. VEPs and SSEPs were normal. Two of three patients had abnormal central conduction velocities to both legs on MEP (A II-2 and A III-3). One patient had

a normal MEP despite clear clinical upper motor neuron signs (C II-2).

Autonomic function testing

Sudomotor adrenergic function was slightly abnormal in only three patients, which were all among the elderly family members (A II-2, B II-2, and C I-2) (Table S2). The abnormality was slight with sweat volumes all above 50% of LLN.

The sympathetic measures from the Valsalva's maneuver and tilt table test were normal in three patients, while the remaining five had different aspects of abnormalities. One patient (A III-1) had a significant reduction in mean blood pressure (BP) during early phase II (− 42.1 mmHg) and a lack of recovery during late phase II. This patient had retained the ability to increase in BP during phase IV. A slight fall in BP during the early phase II was found I two patients (A III-4 and B II-2). None of the patients had abnormal BP responses to the tilt table testing.

The heart rate responses to deep breathing were normal in all except one patient with minor abnormalities, while all had normal Valsalva's ratios.

The Composite Autonomic Scoring Scale (CASS) revealed the signs of minor autonomic disturbance (score 1–2) in seven of the patients.

Discussion

Four families with pathogenic variants in *REEP1* were identified: two harbored the same previously described truncating variant, c.337C>T [6], whereas the previously described truncating c.512delC variant [3] was found in one family, and a novel, likely pathogenic missense variant, c.230T>C, was detected in one family. This variant changes a highly conserved leucine at position 77 to proline (p.Leu77Pro). Although both residues are hydrophobic, the physiochemical difference is significant, expressed by a Grantham distance of 93. The variant is absent from the gnomAD and ExAC database, and several in silico analyses predicted the variant to have pathogenic potential. The variant segregated with the phenotype and was thus classified a likely pathogenic.

Seven of the eight patients tested electrophysiologically had a pure HSP phenotype upon clinical examination and one (B II-2) presented with the signs of peripheral nerve affection involving weakness and atrophy of hand muscles bilaterally (Fig. 1b). This was observed in the patient's son, as well (B III-1). Of note, occasional numbness and tingling in median nerve innervated digits of one or both hands were reported by three patients.

To further characterize symptoms and findings indicative of peripheral nerve dysfunction, a comprehensive study of peripheral and central nerve function was carried out in three index patients and five family members to characterize the neurophysiological consequences of the identified *REEP1* variants. None of the patients examined had completely unremarkable studies of peripheral nerves, but, in general findings, were minor (Tables S1 and S2). Signs of autonomic dysfunction were predominantly restricted to adrenergic function tests and we found no signs of severe dysfunction with orthostatic hypotension. All abnormal CASS scores were comparable to findings in patients with polyneuropathy without autonomic symptoms [15].

Overall, the abnormalities were more pronounced in the upper extremities, and some degree of asymmetry was observed. Most patients had electrophysiological evidence of CTS, three of these symptomatic. One patient (B II-2) demonstrated a quite different picture with a possible multifocal pattern: the right median nerve being more affected than the left, and the median nerves being more affected than the ulnar nerves. In the lower extremities, the tibial nerve CMAP amplitudes were markedly abnormal, while the sural nerve SNAP amplitudes were only slightly reduced. This pattern could not be explained by any known comorbidity in this patient or by duration of the disease as several other patients had disease courses over 30 years, but only subtle changes.

The observed phenotypes and neurophysiological findings correspond to those described elsewhere, as most SPG31 patients demonstrate a pure phenotype and occasionally show signs of peripheral nervous system involvement, although electrophysiological data on SPG31 patients are limited. Reported findings include: motor or sensorimotor, axonal peripheral polyneuropathies (not described in detail) in 5 of 11 patients with SPG31, one of whom exhibited moderate amyotrophy of the hands [7]; a sensorimotor peripheral neuropathy in the upper limbs of a patients with asymmetric distal amyotrophy of the first dorsal interosseus muscle [4]; neurophysiological signs of chronic denervation of the peroneal and quadriceps muscles, consistent with a motor neuropathy, in an index patient with profound lower limb muscle wasting [6]. A single family has been described with distal hereditary motor axonal neuropathy (dHMN), without signs of spasticity, due to an *REEP1* splice site variant [20], and a pathogenic heterozygous single-nucleotide *REEP1* variant has been identified in one family and an unrelated sporadic patient with Charcot-Marie-Tooth disease type 2 [21, 22]. Finally, one study detected homozygous REEP1 splice site variants, evaluated as pathogenic, in an index patient with unaffected heterozygous parents and siblings. The phenotype involved axonal sensorimotor polyneuropathy, hyperreflexia, diaphragmatic palsy, and distal arthrogryposis [23].

The c.337C>T variant was initially identified in a family of three affected individuals with complex HSP characterized by early onset, severe gait disturbance, pes cavus, pronounced lower limb amyotrophy, and a motor

neuropathy in the proband [6]. Interestingly, it has been proposed that peripheral neuropathy is a consequence of certain *REEP1* alterations conferring a toxic gain-of-function through aggregation of mutant protein, as opposed to the established loss-of-function following nonsense-mediated decay [20, 21]. Hence, the cellular pathogenic mechanism leading to lower motor neuron involvement in SPG31 may differ from the one causing an upper motor neuron phenotype. Beetz et al. suspected that variants such as the c.337C>T—affecting exon 5 of the *REEP1* gene and thus not triggering complete nonsense-mediated decay—may confer both a loss- and toxic gain-of-function, resulting in a mixed HSP-dHMN phenotype [20]. Whether this applies in our series is not known, however, the only patient with objective signs of a distal neuropathy and pes cavus (B II-2) did not carry the c.337C>T variant, but a frame shift variant in exon 6 (c.512delC). Conversely, in one study of a Korean family with pure, autosomal dominant HSP electrophysiological studies were unremarkable in three family members carrying the c.337C>T variant [24].

The phenotypical spectrum of HSP caused by pathogenic *REEP1* variants is continuously expanding and encompasses both distal hereditary motor neuropathy and other hereditary sensory and motor neuropathies. Based on the present study findings, *REEP1* should be considered in clinical presentations involving HSP and compression neuropathies, and might possibly be found in patients with a neurophysiologic pattern of pressure palsies where a pathogenic variant in *PMP22* is not found. In conclusion, our data suggest that SPG31 HSP is associated with a generally mild and asymptomatic polyneuropathy, with a predisposition to CTS and possibly other compression neuropathies.

Acknowledgements The study was supported by Ludvig and Sara Elsass Foundation and the Novo Nordisk Foundation.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

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