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Novel *TECPR2* variant in two cases of hereditary sensory and autonomic neuropathy type 9: insights from genetic characterization and comprehensive literature review

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Abstract

Background Hereditary sensory and autonomic neuropathy type 9 (HSAN9) is a rare genetic disorder caused by genetic alterations in the *TECPR2* locus and is characterized by developmental and intellectual disability, respiratory dysfunction, gastroesophageal reflux disease (GERD), and sensory and autonomic dysfunction, which are shared among the HSAN family.

Methods Whole-exome sequencing (WES) was performed on samples from both probands, and the relevant genetic variants were confirmed in their families using Sanger sequencing. Additionally, a comprehensive literature review was conducted on previously reported cases of HSAN9, and the clinical and genetic data were assessed to provide insight into the genetic and clinical characteristics of the disease.

Results We identified two new cases of HSAN9 with a shared novel variant of *TECPR2* (NM_014844.5), c.1568del: p.Ser523PhefsTer12, classified as pathogenic according to ACMG guidelines. The probands showed characteristics of GERD, respiratory dysfunction, gait abnormalities, and developmental and speech delay, and both cases were deceased as a result of severe respiratory infection. The results of the literature review included 34 cases from 9 studies, revealing a wide range of genetic and clinical characteristics.

Conclusions Our study identified two new cases of HSAN9 with a novel variant in *TECPR2*, confirmed by WES. The clinical characteristics of the patients as well as the conduction of a comprehensive literature review are crucial in the early diagnosis and management of the disease and establishment of genotype-phenotype correlations.

Keywords *TECPR2*, Hereditary sensory and autonomic neuropathy, Hereditary sensory and autonomic neuropathy type 9, HSAN9, Whole-exome sequencing (WES)

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Introduction

Genetic alterations in the tectonin β-propeller repeat containing protein 2 (*TECPR2*) locus, a protein component of autophagy, are associated with the incidence of hereditary sensory and autonomic neuropathy type IX (HSAN9, OMIM #615031). HSANs are a heterogeneous family of genetic disorders characterized by progressive dysfunction of autonomic and sensory components of the peripheral nervous system (PNS). HSAN9, primarily known as hereditary spastic paraplegia 49 (HSP49), is an autosomal recessive disorder with intellectual disability, global developmental delay, and respiratory dysfunction in addition to the aforementioned shared characteristics of HSAN disorders [1–4]. This disease was first identified in 2012 by Oz-Levi et al. in five patients from three families with intellectual disability, gastroesophageal reflux disease (GERD), central apnea, areflexia, and facial dysmorphism [1].

Due to the heterogeneous manifestations of HSAN9 patients, as well as the limited number of confirmed cases, the identification of new cases and genetic variants is crucial in the clinical understanding of the disease and establishing genotype-phenotype correlations.

The aim of this study is to provide a comprehensive literature review on HSAN9, a rare disorder characterized by peripheral neuropathy. This review explores the clinical manifestations, genetic basis, and management strategies associated with HSAN9. Additionally, this study reports two new cases of HSAN9 in an Iranian population, characterized by a shared novel variant of *TECPR2* (c.1568del: p.Ser523PhefsTer12). By combining the literature review with the introduction of these new cases, this study aims to explore the genotype-phenotype correlation of HSAN9 and contribute to the understanding and recognition of this condition in various populations.

Case presentation

Case 1 The patient was a three-year-old girl and the result of a full-term cesarean section delivery, with a birth weight of 4 kg (z-score = 1.6, <+2SD), born to healthy, first-cousin parents. The proband had a familial history of Down syndrome in a paternal uncle, as well as history of speech delay in another paternal uncle. However, there was no family history of HSAN9 present. The disease onset occurred at birth, with a presentation of recurrent milk aspiration. The patient showed signs of failure to thrive (FTT), microcephaly, and hearing loss with no findings suggestive of vision impairment, facial dysmorphism, or tooth abnormality in the head and neck regions. She experienced swallowing difficulty resulting in recurrent hospital admissions due to aspiration, respiratory dysfunction, pneumonia, and severe GERD. However, there were no signs of impaired bowel habits. Specific cutaneous or hair abnormalities were not observed. Nevertheless, the patient experienced dermatitis lesions all over her face as well as symmetrically on her upper and lower limbs. She also experienced severe allergic reactions in response to the consumption of egg whites.

Regarding the child's developmental milestones, unassisted walking was delayed, and she never achieved running, displaying signs of ataxic-like gait. In addition, the patient had speech impairment, and despite the use of simple two-syllabic words at the age of 1, she eventually lost the ability to speak entirely. Signs of intellectual disability and reduced sensitivity to pain were also present. However, no signs of autistic features were detected.

The patient passed away at the age of three due to severe respiratory infection.

Case 2 The second case involved a seven-year-old girl, the result of a full-term pregnancy with normal vaginal delivery (NVD) and a birth weight of 4200 g (z-score = 1.9, <+2SD) from healthy parents with consanguineous marriage. The patient had no familial history of congenital developmental conditions. The first sign of the disease was manifested with failure to thrive at a young age, although the patient was diagnosed at the age of 2. She had a short stature, standing at 70 centimeters tall at the age of 7 (below the 5th percentile), and lower than normal height throughout life, as well as general muscular atrophy. However, no signs of facial dysmorphism were present. She also had mild bilateral esotropia with no vision impairment. In addition, the morphological characteristics of the front teeth underwent a transformation later in life, manifesting as a change from the typical shape to a fang-like appearance. No other signs of sensory deficit or head and neck abnormalities were present.

The patient experienced swallowing difficulty and was repeatedly admitted due to recurrent aspiration pneumonia and respiratory dysfunction. In her last two years of life, a percutaneous endoscopic gastrostomy (PEG) was provided to assist with feeding. No cutaneous lesions were present. However, she had relatively thin, scarce hair with no signs of patchy hair loss characteristic of alopecia areata. Among the developmental milestones, independent sitting was delayed until the age of 2, and she was not able to walk without assistance. Her speech was impaired and she showed behavioral abnormalities in the form of temper tantrums and self-harm tendencies. She experienced multiple episodes of seizures secondary to COVID-19 infection

and was admitted with severe respiratory dysfunction as a result of COVID-19 and passed away at the age of 7.

Methods

Blood samples were collected from the patients and both of their parents, and genomic DNA was extracted from the white blood cells using the standard salting out procedure [5]. In the process of WES, genomic DNA enrichment was conducted using the SureSelectXT V6+UTRs Kit (Agilent Technologies, Lake Forest, CA, USA), and paired-end sequencing was performed using the NovaSeq 6000 platform abiding by the manufacturer's protocol (Illumina, San Diego, CA, USA). In the next step, the sequences were aligned to the reference human genome (UCSC hg19, NCBI build 37.1) using the Burrows–Wheeler Aligner (BWA v 0.5.9) [6]. The duplicates generated by the polymerase chain reaction (PCR) were eliminated using the Picard tool (v 1.118). The test platform examined > 95% of the target regions and offered a sensitivity of > 99% and a 100X mean coverage. The Genome Analysis Toolkit (GATK v 3.7) was used to conduct variant calling [7]. Variant annotation was carried out using the ANNOVAR tool [8]. Identification of variants in the 1000 Genomes Project dbSNP 138, ESP6500 and Iranome (www.iranome.com) was defined by a minor allele frequency < 0.01. Furthermore, they were subjected to additional filtering based on pathogenicity and effect of the mutation, databases of clinically relevant variants, presence in the population, and previously established genotype-phenotype correlations as per existing literature. Variant prioritization was ultimately conducted using phenotype plausibility. Confirmation of the variants involved Sanger sequencing of the patient samples as well as targeted Sanger sequencing of the parental samples. The primers were designed by Gene Runner Software (v 3.05) specifically for exon 9 and the surrounding introns (Table 1).

Gathering Reported Cases of HSAN9 Molecularly and Clinically.

The literature review involved a systematic search of relevant databases such as PubMed, Scopus, Web of Science, and Google Scholar. The search strategy was created using a combination of keywords and Boolean operators to refine the search and capture relevant articles. Inclusion criteria were established to ensure the selection of only peer-reviewed journal articles and conference proceedings written in English, specifically focusing on *TECPR2* gene expression, function, regulation, or mechanism. Initial screening of articles was conducted based on titles and abstracts, followed by a full-text assessment for relevance by two independent reviewers, and conflicts were resolved by a third reviewer. Relevant data from the selected articles were extracted using a standardized data extraction form and thematically analyzed to identify key themes, patterns, and trends in the findings. The quality of the included studies was assessed using appropriate tools, and the findings were presented following academic writing guidelines and standards. The *TECPR2* review provided insights into the current knowledge of *TECPR2* gene expression and function, while the HSAN9 review summarized the reported cases of the condition.

Table 1 Primer pair for PCR

Primer	Sequence
Forward	5′-AACCGTGCCTTATTTTGAAT-3′
Reverse	5′-GCAGCCACTGTTCAGCACTT-3′

Results

In this study, two new cases of HSAN9 were discussed in an Iranian population with a shared novel variant identified by WES. The results of WES revealed a novel homozygous variant, c.1568del: p.Ser523PhefsTer12, located in exon 9, present in both cases. This variant has not been reported in gnomAD, the 1000 Genome Project, and Iranome and is considered pathogenic based on ACMG guidelines. There is supporting evidence of pathogenicity according to allelic data and it is considered moderately pathogenic according to population data, and strongly pathogenic according to its effect on the protein and the PM3, PM2, and PVS1 ACMG criteria are met, respectively [9]. The pedigree and results of Sanger sequencing in both cases are depicted in Figs. 1 and 2. The schematic structures of the wild-type and mutated TECPR2 proteins are illustrated in Fig. 3.

Following the conduction of the literature review, a total of 34 cases from 10 studies, with a variety of missense, nonsense, and truncating variants in the *TECPR2* genetic loci (NM_014844.5), were included (Table 2).

Discussion

In this study, we analyzed a considerably expansive cohort of individuals exhibiting damaging variations in TECPR2. This investigation encompasses a substantial number of participants, providing a strong foundation for exploring the complexities of this condition. Additionally, we have included an extensive literature review of previously reported cases of HSAN9. In total, 34 cases were reviewed, including the two new families presented here, which showcase a diverse clinical and genetic spectrum.

The two novel cases reported in this study are the first patients of HSAN9 of Iranian descent. The discussed probands in this study are two cases of HSAN9, with a shared homozygous novel variant, *TECPR2* (NM_014844.5): c.1568del: p.Ser523PhefsTer12, from two distinct families. This variant is considered

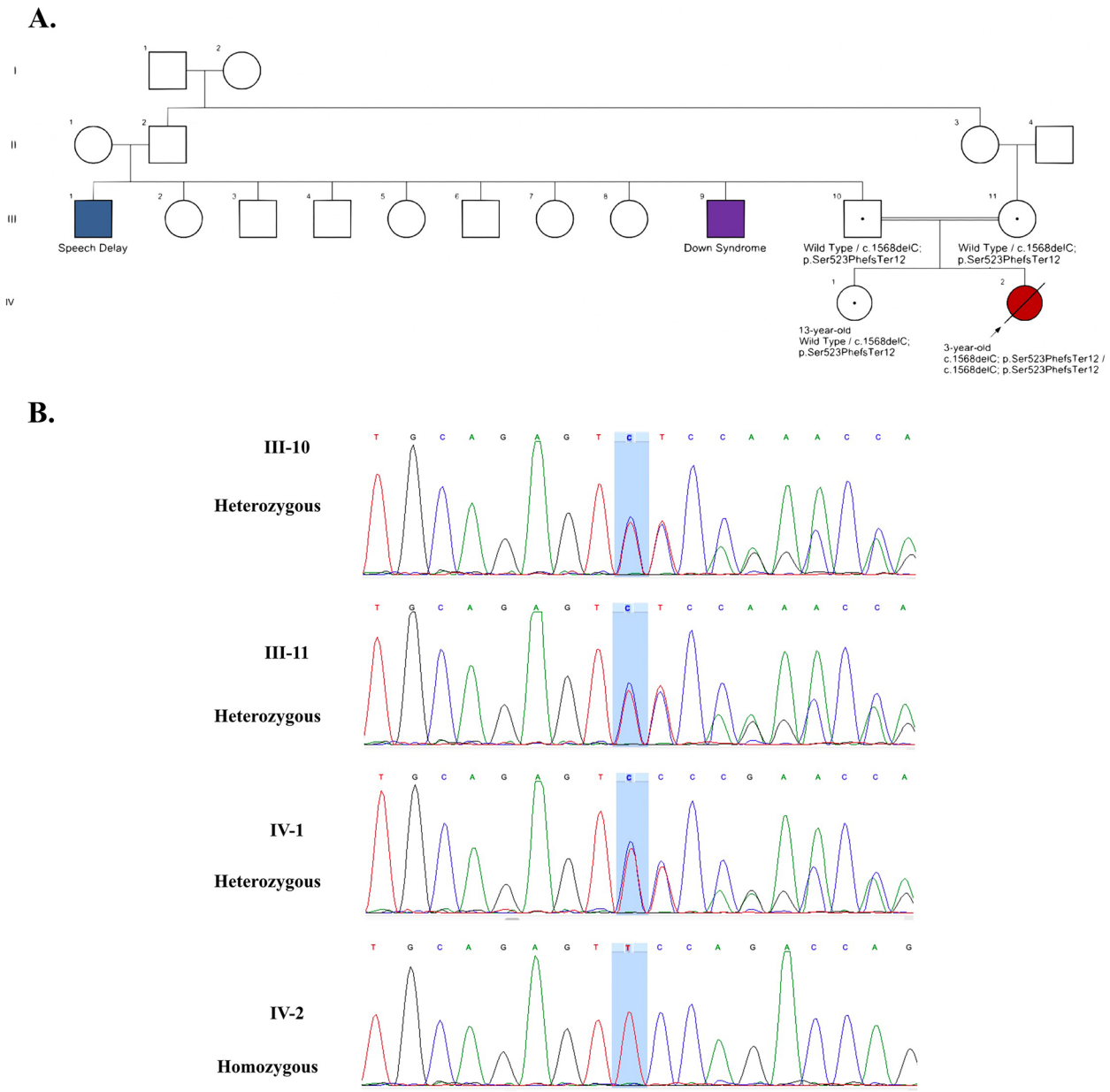

Fig. 1 Familial pedigree and electropherograms of case 1 and her parent (B). Sequencing analysis of case 1 (IV-2) identified a homozygous variant c.1568del (p.Ser523PhefsTer12) in the *TECPR2*. Segregation analysis revealed parent to be heterozygous

pathogenic according to the aforementioned ACMG criteria, and due to the resultant loss-of-function, it is implicated in clinical approaches and genetic counseling. In both cases, parents were carriers of the same variant. The patients showed symptoms such as failure to thrive, feeding difficulties, GERD, and recurrent respiratory infections, which were the primary causes of death in both cases. Gait and speech impairments were also observed in both instances. The clinical presentation in both cases aligns with the previously reported clinical features of HSAN9.

TECPR2 is an enhancer of autophagy by binding to human autophagy-related 8 (ATG8) [10]. Autophagy is a cellular process crucial for the digestion of subcellular components through the formation of autophagosomes. The formation of autophagosomes involves two major protein complexes: ULK1 and class III PI3-kinase complex I (PI3KC3-C1). Additionally, ATG9,

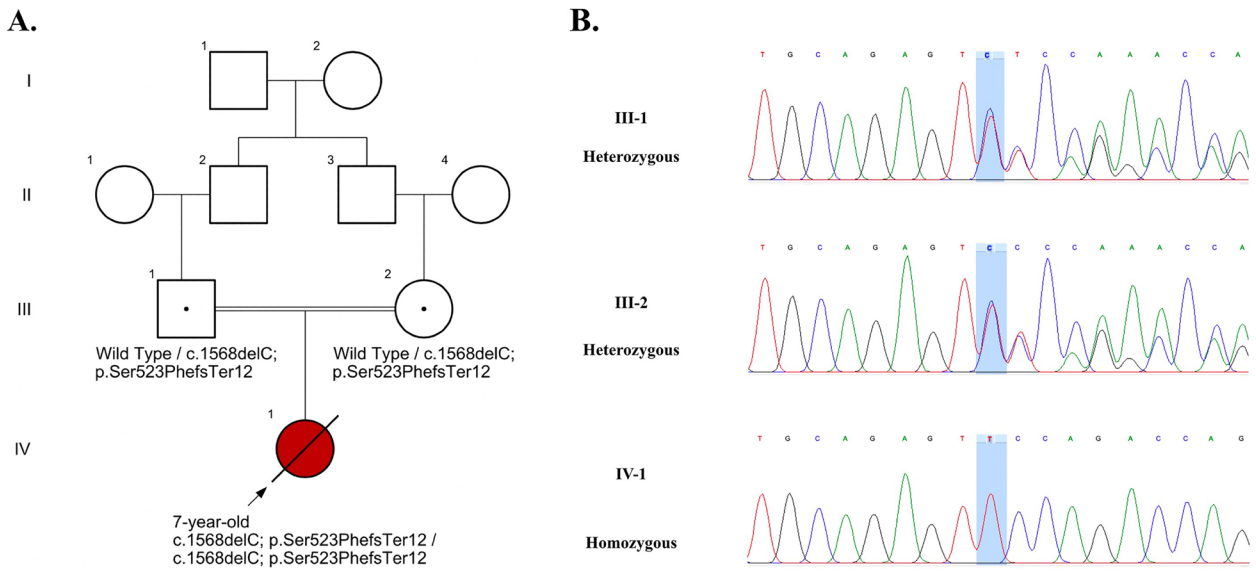

Fig. 2 Familial pedigree (A) and electropherograms of case 2 (IV-1) and her parent (B). Sequencing analysis of case 2 (III-1) identified a homozygous variant c.1568del (p.Ser523PhefsTer12) in the *TECPR2*. Segregation analysis revealed parent to be heterozygous

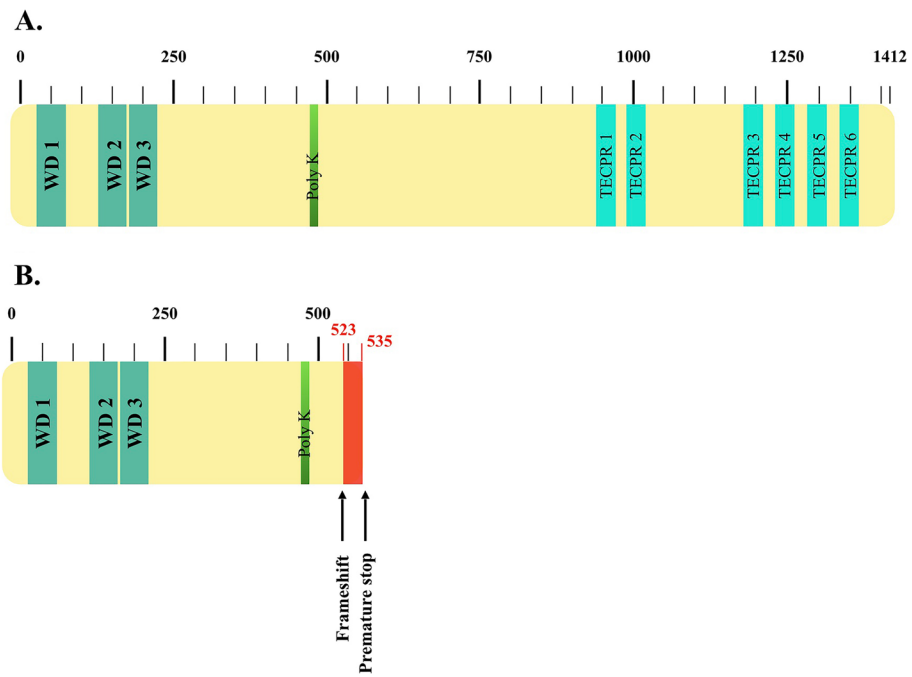

Fig. 3 Schematic illustration of (A) wild-type TECPR2 and (B) Mutant TECPR2 with c.1568del; p.Ser523PhefsTer12, resulting in a frameshift and a premature stop codon. Tryptophan-aspartate (WD) repeats, the poly-lysine tract (polyK), and TECPR domains are significant conserved domains in the structure of the wild-type TECPR2

a transmembrane protein component, plays a role in this process. Upon the activation of these components and downstream proteins of the ATG8 family, WIPI-1 to WIPI-4, and ATG12, various reactions are driven, the hallmark of which is LC3 lipidation, the process of phosphatidylethanolamine attachment to the ATG8/LC3 family. Furthermore, various vesicular trafficking proteins, including COP I, COP II, SNARE, and Rab GTPase, are also involved in autophagy [11]. TECPR2 is likely to be involved in this pathway as a scaffold protein. Its

Table 2 Summary of 34 cases with variants in the *TECPR2* genetic loci from 9 studies

No	Authors	Family	Patient (gender)	Ethnicity	Zygosity	Variant (cDNA level)	Variant (protein level)	Mutation type	ACMG classification	Family history	Parents' genotype	Consanguinity	Birthweight	Age of onset	GERD	Sensory dysfunction
-	Present study	1	1 (F)	Iranian	Homozygous	c.1568del	p.Ser523PhefsTer12	Nonsense	Pathogenic	No	Heterozygous	Yes	4000 g	1 M	Yes	Yes
-	Present study	2	2 (F)	Iranian	Homozygous	c.1568del	p.Ser523PhefsTer13	Nonsense	Pathogenic	No	Heterozygous	Yes	4200 g	1 M	No	No
1	Oz-Levi et al.	1	1 (F)	Jewish Bukharian	Homozygous	c.3416del	p.Leu1139ArgfsTer75	Nonsense	Pathogenic	No	Heterozygous	No	NA	2 Y	Yes	NA
2	Oz-Levi et al.	2	2 (M)	Jewish Bukharian	Homozygous	c.3416del	p.Leu1139ArgfsTer75	Nonsense	Pathogenic	Yes (sister)	Heterozygous	No	NA	2 Y	Yes	NA
3	Oz-Levi et al.	2	3 (F)	Jewish Bukharian	Homozygous	c.3416del	p.Leu1139ArgfsTer75	Nonsense	Pathogenic	Yes (brother)	Heterozygous	No	NA	2 Y	Yes	NA
4	Oz-Levi et al.	3	4 (M)	Jewish Bukharian	Homozygous	c.3416del	p.Leu1139ArgfsTer75	Nonsense	Pathogenic	Yes (brother)	Heterozygous	No	NA	2 Y	Yes	NA
5	Oz-Levi et al.	3	5 (M)	Jewish Bukharian	Homozygous	c.3416del	p.Leu1139ArgfsTer75	Nonsense	Pathogenic	Yes (brother)	Heterozygous	No	NA	2 Y	Yes	NA
6	Zhu et al.	1	1 (M)	Middle eastern	Homozygous	c.1319del	p.Leu440ArgfsTer19	Nonsense	Pathogenic	NA	NA	No	NA	1 Y	Yes	NA
7	Heimer et al.	1	1 (M)	Ashkenazi Jewish	Compound heterozygous	c.566C>T/ c.1319del	p.Thr189Ile/p. Leu440ArgfsTer19	Missense/ nonsense	VUS/patho-genic	NA	Heterozygous	No	3200 g	1 Y	Yes	Yes (pain)
8	Heimer et al.	2	2 (M)	Ashkenazi	Homozygous	c.1319del	p.Leu440ArgfsTer19	Nonsense	Pathogenic	No	Heterozygous	No	3180 g	First few weeks of life	Yes	Yes
9	Heimer et al.	3	3 (M)	Ashke-nazi/ Tunisian e Yamani/ Kurdish	Compound heterozygous	c.1319del/ c.3416del	p.Leu440Argfs*19/p. Leu1139Argfs*75	Nonsense/ nonsense	Pathogenic/ pathogenic	No	Heterozygous	No	3120	Since birth	Yes	Yes
10	Guan et al.	1	1 (M)	Chinese	Compound heterozygous	c.1729C>T/ c.4189G>A	p.His577Tyrosine/p. Ala1397Thr	missense/ missense	VUS/VUS	No	Heterozygous	No	3200 g	10Y	No	No
11	Covone et al.	1	1 (F)	Italian	compound heterozygous	c.2050C>G/ c.2708C>T	p.Leu684Val/p. Thr903Met	missense/ missense	Benign/VUS	No	Heterozygous	No	NA	4Y	No	No
12	Palma et al.	1	1 (F)	Ashkenazi	Homozygous	c.1319del	p.Leu440ArgfsTer19	Nonsense	Pathogenic	NA	NA	NA	NA	Birth	No	Yes (pain)
13	Palma et al.	2	2 (M)	Ashkenazi	Homozygous	c.1319del	p.Leu440ArgfsTer20	Nonsense	Pathogenic	NA	NA	NA	NA	Birth	No	Yes (pain)
14	Patwari et al.	1	1 (F)	NA	Compound heterozygous	c.774del/ c.1028_1032del	p.Asp259MetfsTer44/p. Lys343ArgfsTer2	Nonsense/ nonsense	Pathogenic/ pathogenic	No	NA	NA	NA	6M	No	Yes (pain)
15	Ramsey et al.	1	1 (F)	Caucasian	Compound heterozygous	c.1318_1319del/ c.3072G>A	p.Leu440ValfsTer13/p. Trp1024Ter	Missense/ nonsense	Pathogenic/ pathogenic	NA	NA	NA	NA	Birth	Yes (history of Nis-sen fun-doplica-tion)	NA

Table 2 (continued)

No	Authors	Family	Patient (gender)	Ethnicity	Zygosity	Variant (cDNA level)	Variant (protein level)	Mutation type	ACMG classification	Family history	Parents' genotype	Consanguinity	Birthweight	Age of onset	GERD	Sensory dysfunction
16-32	Neuser et al.	1-15	1-17(11 M, 6 F)	5 Ashkenazi Jewish, 2 Bukharian Jewish	Homozygous/ compound heterozygous	c.3416del (2), c.1319del (4), c.571C>T, c.694dup, c.2829del, c.3830del/ c.1319del, c.4103G>A	p.Leu1139ArgfsTer76 (2), p.Leu440ArgfsTer19 (4), p.Gln191Ter, p.Thr232AsnfsTer15, p.Asn944ThrfsTer7, p.Asn1277ThrfsTer43/p. Leu1139ArgfsTer19, p.Trp1368Ter	Nonsense	Pathogenic, likely pathogenic (c.4103G>A)	NA	NA	In 7 families	NA	NA	Yes (9)	Yes (pain (4))
33	Khalaf-Nazzal et al.	1	1 (M)	Palestinian	Homozygous	c.745G>A	p.Gly249Arg	missense	VUS	No	Heterozygous	Yes	3400g	9M	No	No
34	Khalaf-Nazzal et al.	1	2 (F)	Palestinian	Homozygous	c.745G>A	p.Gly249Arg	missense	VUS	No	Heterozygous	Yes	3300g	6 M	Yes	Yes (pain)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
-	Present study	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	NA	FTT, microcephaly, hearing loss, dermatitis, severe allergic reaction to egg whites	Normal	3 Y	Severe respiratory infection	Present study
-	Present study	No	Yes	NA	Yes	Yes	NA	Yes	Yes	NA	FTT, short stature, muscle atrophy, strabismus, teeth abnormalities, thin scarce hair, temper tantrums and self-mutilation behavior	NA	7 Y	Severe respiratory infection	Present study

Table 2 (continued)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
1	Oz-Levi et al.	Yes (encephalopathic event)	Yes (spastic, ataxic)	Absent	Yes	Yes (dysarthric)	Yes	Yes (central apnea)	Yes	Yes	Short stature, mild brachycephalic microcephaly, round face, low anterior hairline, dental crowding, short broad neck, chubby appearance, hypo mimic face, dysmetric, acute detereoration episodes, recurrent ankle pressure ulcers	Thin corpus callosum, cerebral atrophy, cerebellar atrophy	NA	NA	23176824
2	Oz-Levi et al.	Yes (encephalopathic event)	Yes (spastic, ataxic)	Absent	Yes	Yes (dysarthric)	Yes	Yes (central apnea)	Yes	Yes	Short stature, mild brachycephalic microcephaly, round face, low anterior hairline, dental crowding, short broad neck, chubby appearance, hypo mimic face, dysmetric, acute detereoration episodes, generalized tonic-clonic seizures, transient severe encephalopathy with intermittent rise in levels of transaminases	NA	5.5 Y	Aspiration	23176824

Table 2 (continued)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
3	Oz-Levi et al.	Yes (encephalopathic event)	Yes (spastic, ataxic)	Absent	Yes	Yes (dysarthric)	Yes	Yes (central apnea)	Yes	Yes	Short stature, mild brachycephalic microcephaly, round face, low anterior hairline, dental crowding, short broad neck, chubby appearance, hypo mimic face, dysmetric, acute detereoration episodes, generalized tonic-clonic seizures	NA	NA	NA	23176824
4	Oz-Levi et al.	Yes (encephalopathic event)	Yes (spastic, ataxic)	Absent	Yes	Yes (dysarthric)	Yes	Yes (central apnea)	Yes	Yes	Short stature, mild brachycephalic microcephaly, round face, low anterior hairline, dental crowding, short broad neck, chubby appearance, hypo mimic face, dysmetric, acute detereoration episodes	NA	NA	NA	23176824
5	Oz-Levi et al.	Yes (encephalopathic event)	No	Absent	Yes	Yes (dysarthric)	Yes	Yes (central apnea)	Yes	Yes	Short stature, mild brachycephalic microcephaly, round face, low anterior hairline, dental crowding, short broad neck, chubby appearance, hypo mimic face, dysmetric,	Thin corpus callosum, cerebral atrophy, cerebellar atrophy	NA	NA	23176824

Table 2 (continued)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
6	Zhu et al.	Yes (with encephalopathy)	NA	Absent	NA	NA	NA	Yes	NA	Yes	NA	NA	NA	NA	25590979
7	Heimer et al.	NA	Yes (unstable and clumsy)	Brisk	Yes	Yes	Yes	Yes (severe bilateral lung disease, unilateral emphysema and suspected bronchiectasis, sleep apnea)	Yes	Yes	Neurogenic sensory-motor swallowing defect, hyperactivity, impulsivity, quick mood changes, microcephaly, short stature, chubby appearance, mild coarse face, short neck with retrocollis, arched palate, pectus carinatum, extensor plantar response present, astigmatism, myopia, mild bilateral neurosensory hearing defect, episodes of loss of consciousness/awake apnea following deep breath, crying, or laughing	NA	6 Y	Severe pulmonary infection and septic shock	26542466

Table 2 (continued)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
8	Heimer et al.	Yes (encephalopathic event)	Yes (ataxic)	Absent	Yes	Yes	Yes	Yes (chronic lung disease with bacterial secretions and need for nocturnal ventilation, sleep apnea)	Yes	Yes	Sleepy and floppy, repeated coughing and vomiting, disturbed sleep due to apnea, episodes of fever or hypothermia, bradycardia and hypertension, cold extremities, dehydration, sweating, and pallor, restlessness, violent mood swings, episodes of encephalopathic head-drop and somnolence, facial dysmorphism, microcephaly, chubby appearance, short stature, retrocollis, scoliosis, small feet, hypotonia, esotropia, open tented mouth, high-arched palate, sialorrhea, extensor plantar response, truncal tituba-tion, decreased hearing	mild cerebral and vermian atrophy	NA	NA	26542466

Table 2 (continued)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
9	Heimer et al.	Yes	NA	Absent	Yes	Yes	NA	Yes (central apnea,	Yes	Yes	Recurrent vomiting, recurrent episodes of dehydration, cold extremities, postural hypotension and unexplained fevers with hypertension, sleep disturbances, episodes of apathy, restlessness, hyperactivity, chubby appearance, short stature, low hairline, mild coarse face, short neck, retrocollis, microcephaly	mild ventricular enlargement and thinning of corpus callosum	NA	NA	26542466
10	Guan et al.	Yes (episodes of suddenly increased body temperature)	Yes	Positive and symmetric	No	Yes (secondary aphasia)	No	No	No	Yes	Severe cognitive impairment, personality change, seizures	Widened cerebellar sulci and severe cerebellar atrophy, thin corpus callosum, and mild enlargement of lateral ventricle	NA	NA	35130874

Table 2 (continued)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
11	Covone et al.	No	Yes (instability, spastic)	Brisk	No	Yes (dysarthria at age 10)	No	Yes (ventilation through tracheostomy after an episode of severe respiratory infection at the age of 13)	No	Yes	Recurrent vomiting, weekness, scoliosis, strabismus, positive Gowers maneuver, ankle clonus, musiclar atrophy, ocular apraxia, positive Babinski sign, joint retraction, equinos-varus feet, tongue hypotrophy, tongue fasciculation	Global corpus callous thinning	NA	NA	27406698
12	Palma et al.	Yes (reduced basal tearing)	Yes (proprioceptive ataxia)	Brisk	Yes	NA	NA	Yes (central sleep apnea, stridor)	NA	Yes	Neurogenic dysphagia, constipation, strabismus, sensorineural hearing loss	NA	NA	NA	33884296
13	Palma et al.	Yes (reduced basal tearing)	Yes (proprioceptive ataxia)	Brisk	Yes	NA	NA	Yes (central sleep apnea, stridor)	NA	Yes	Neurogenic dysphagia, constipation, strabismus	Thin corpus callous	NA	NA	33884296
14	Patwari et al.	Yes (photophobia, chronic constipation)	Yes (poorly coordinated)	Normal	Yes	Yes	NA	Yes (central apnea, Biot's breathing)	No	Yes	Strabismus, dysphagia, hand flapping, fifth percentile height and weight, excessively friendly, hyperactive, motor coordination immaturity, circadian disturbance with advanced sleep phase	peri-atrial and subcortical white matter T2 hyperintensity	NA	NA	32209221

Table 2 (continued)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
15	Ramsey et al.	NA	Yes (ataxic)	Absent	NA	Yes (slurred)	NA	Yes (central sleep apnea)	Yes	Yes	Frequent vomiting, tremor while standing, progressive hearing loss, fatigue, vision impairment, facial weakness, myopathic shape of mouth, mid face hypoplasia, combative, aggressive, hurting herself and others, epicodes of posturing and arm stiffness	Cerebellar vermis, olive, and pons atrophy, diffuse white matter T2/FLAIR hyperintensity	5Y	Central apnea	34994087
16-32	Neuser et al.	Yes (temperature instability (3), hyperhydrosis (2))	Yes (11)	Brisk (13)	Yes (All)	Yes (all)	Yes (All)	Yes (central nocturnal (8) or daytime (5) hypoventilation)	Yes (14)	Yes (all)	Small for gestational age (3), below average height (11), below -2SD height (7), brachycephaly (7), microcephaly (4), microbrachycephaly (3), distinct facial characteristics (11), skeletal abnormalities (5), behavioral dysregulation (6), ASD (2), dysarthria (6), febrile seizure (2), refractory epilepsy (3), hearing impairment (3), visual impairment (5), dysphagia (9), airway malformation (4), constipation (5)	delayed myelination, mild ventriculomegaly, periventricular gliosis, corpus callosum thinning, cerebral and cerebellar atrophy	NA	NA	33847017

Table 2 (continued)

No	Authors	Autonomic dysfunction	Abnormal gait	Deep tendon reflexes	Developmental delay	Speech impairment	Intellectual disability	Respiratory dysfunction	Recurrent respiratory infection	Hypotonia	Others	Imaging	Age of death	Cause of death	PMID
33	Khalaf-Nazzal et al.	Yes (chronic constipation)	Yes (wide-based gait)	Brisk	Yes	Yes	Yes	Yes (intubation and ICU admission secondary to severe viral gastritis at age of 3 years)	No	Yes	Bilateral sensorineural hearing impairment, strabismus, behavioral abnormality including self-mutilation, hyperactivity, aggression, and sleep disturbances, history of GTC seizure, craniofacial dysmorphism, muscle atrophy, cold extremities	Corpus callous thinning (posterior body and splenium), dysmorphic ventricles, mild loss of frontal volume	5.5 Y	Encephalopathy and multi-organ failure	38436550
34	Khalaf-Nazzal et al.	NA	Yes (unable to walk)	Absent	Yes	Yes	NA	Yes (intubation and ICU admission at ages of 22 months and 2 years)	Yes	Yes	Sensorineural hearing loss, history of GTC seizure, craniofacial dysmorphism, lower limb spasticity, muscular atrophy	Corpus callosum thinning, prominent cortical sulci, enlarged ventricles, reduction of cerebral volume	NA	NA	38436550

binding to LC3C, a member of the ATG8 family, enables localization to the endomembrane, enhancing its ability to bind to and stabilize the levels of COPII subunit, SEC24D, a cellular trafficking agent, assisting in the formation of SEC24D/SEC23A heterodimer at the assembly site of COP II. Formation of COPII-coated vesicles is involved in membrane exchange between the endoplasmic reticulum and the phagophore [10, 11]. Fig. 4 illustrates the cellular mechanism of autophagy.

Studies have suggested a role for TECPR2 in autophagosome targeting/fusion based on evidence of autophagosome accumulation linked to *TECPR2* variants. Additionally, TECPR2 has been associated with homotypic fusion and protein sorting complex (HOPS) and the biogenesis of lysosome-related organelle complex 1 (BLOC-1). TECPR2, in cooperation with lipidated LC3, is also involved in the stabilization of SEC24D, a component of COP II, which is involved in endoplasmic reticulum (ER)-Golgi trafficking at the ER exit site (ERES) [10, 12].

TECPR2 is a relatively large multidomain protein with 1411 residues, containing an amino-terminal domain, a carboxy terminal domain, and an LC3-interacting region (LIR) motif at the carboxy terminal. The N- and C-termini contain a WD (tryptophane-aspartic acid) domain and a TECPR domain, respectively (Fig. 3) [1].

Hereditary sensory and autonomic neuropathies (HSANs) are a group of diverse neurodevelopmental and neurodegenerative conditions with characteristic peripheral sensory and autonomic dysfunction [12]. To date, 16 subtypes have been identified, with HSAN9 being the most recently recognized subtype, an autosomal recessive neurodevelopmental disorder caused by variants in the *TECPR2* genetic locus [12].

To date, fewer than 40 cases have been documented, displaying a broad range of phenotypic variations. The clinical and genetic characteristics of the identified cases are summarized in Table 2. The first variant of HSAN was reported by Oz-Levi et al. in 2012 in five patients of Jewish Bukharian heritage and was initially classified as hereditary spastic paraplegia 49 (HSP49). The patients were members of three distinct families and had a homozygous shared variant, c.3416delT, in exon 16 of *TECPR2*. The clinical manifestations of the disease included spastic paraparesis, intellectual disability, respiratory dysfunction, GERD, dysmorphism, and absent reflexes, as well as signs of progressive brain atrophy in multiple sites in MRI findings [1].

In 2015, Zhu et al. conducted whole exome sequencing analysis on 119 trios of patients with suspected genetic disorders and identified a trio with a homozygous frameshift variant in TECPR2 (c.1319delT). The male patient in this

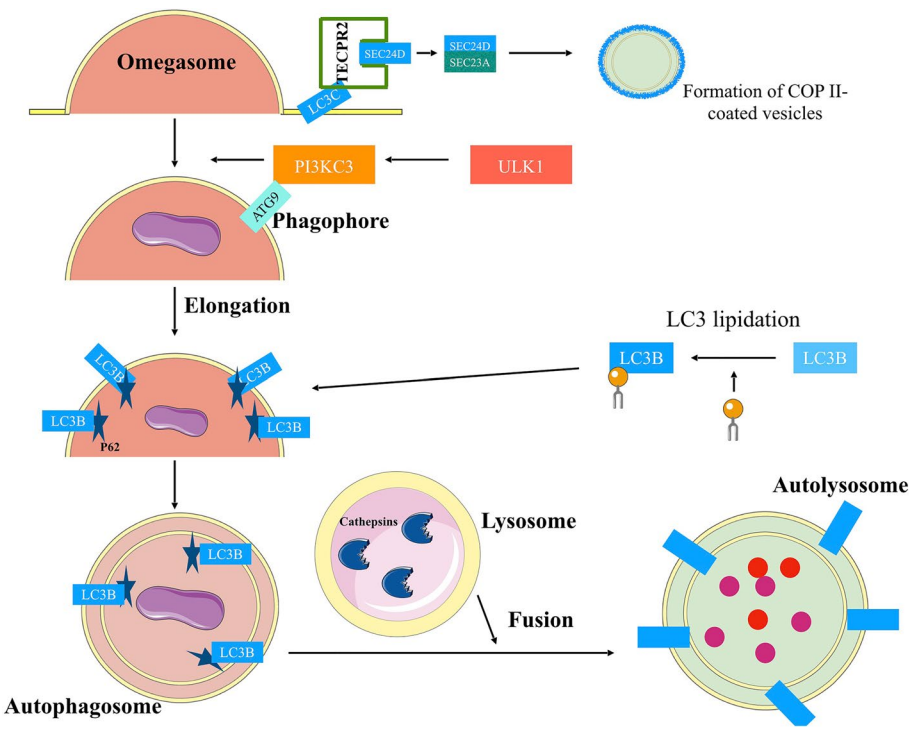

Fig. 4 The cellular mechanism of autophagy. This figure was created using the Servier Medical Art Commons Attribution 3.0 Unported License (http://smart.servier.com (accessed 18 August 2023))

trio, born to parents without a consanguineous marriage history, displayed clinical symptoms such as hypotonia, GERD, respiratory problems, absent reflexes, intellectual disability, encephalopathy, and autonomic dysfunction from infancy [13]. Heimer et al. reported three patients with two novel variants, c.1319delT and c. 566 C>T in *TECPR2*. In addition to the previously reported disease characteristics, these patients showed significant signs of sensory autonomic neuropathy, such as insensitivity to specific stimuli, hypotonia, absent reflexes, vasomotor dysfunction, temperature abnormality, and episodic reduced arousal. Based on the sensory autonomic findings, Heimer et al. proposed reclassifying such cases as an HSAN subtype in contrast to the previous classification as HSP49 [2]. Two additional patients with similar genotypic and phenotypic characteristics were also identified by Palma et al. in 2021 [14]. Neuser et al. identified 17 patients from 15 distinct families with biallelic variants in *TECPR2*. The patients showed patterns of intellectual disability, developmental delay, hypotonia, ataxia, brisk reflexes, and respiratory dysfunction [4].

Covone et al. reported a 16-year-old case of motor neuron disease with a compound heterozygote missense variant genotype and classical HSAN9 phenotype as previously mentioned, with normal intellectual abilities. The patient was also positive for a heterozygote missense variant in the *SPG7* genetic locus, potentially contributing to the observed phenotype [3]. In addition to the aforementioned studies, several patients with compound heterozygous genotype and clinical presentations of HSAN9 have been reported to date [15–17]. The latest reported cases of are two Palestinian siblings with a shared novel homozygous variant, c.745G>A, displaying classical HSAN9 traits, including developmental delay and sensorimotor dysfunction, facial dysmorphism, as well as history of hospitalization due to exacerbation of symptoms and respiratory distress [18].

The patients discussed in this study are both female cases of HSAN9 with a shared homozygous variant, c.1568del: p.Ser523PhefsTer12, located in exon 9 of the *TECPR2* genetic locus. Both patients were born from consanguineous marriages between carriers of the same variant. Both probands showed characteristic signs of HSAN9, such as recurrent respiratory infections, gait abnormalities, and developmental delays. The second case displayed strabismus, along with behavioral abnormalities in the form of temper tantrums and self-mutilation. When compared to the known clinical spectrum of previously identified cases, both probands showed both similarities and differences. Similar to most reported cases, the age of onset was early in life. However, some reported cases with a compound heterozygous genotype had a relatively delayed disease onset. Notably, both probands had a relatively high birthweight. While birthweight has not been consistently reported in most previous cases, the cases where it is included in the data do not exhibit such characteristics.

GERD is a frequently observed finding in most cases of HSAN9. Patient 1 in our study showed signs of severe GERD, while patient 2 did not. Patient 2 showed sensory dysfunction in the form of reduced sensitivity to pain, a common trait among HSAN9 cases. Abnormal gait, developmental delay, recurrent aspiration pneumonia, and severe respiratory failure were also among the frequently observed clinical characteristics both in the literature and our cohort. FTT, microcephaly, short stature, hearing loss, strabismus, behavioral signs, and hair and teeth abnormalities were also noted in our study's probands, consistent with previously reported cases. In addition, the first case showed signs of immunological hypersensitivity reactions, including dermatitis and a severe allergic reaction to egg white.

Conclusion

In this study, we reported two new cases of HSAN9 with a shared novel variant of *TECPR2.* The comprehensive literature review on the previously reported cases and description of the clinical and genetic characteristics of our probands provides valuable insight into the genetic and clinical landscape of this rare disease. This information can play a crucial role in enhancing our understanding of the genotype-phenotype correlation, aiding in the early detection of suspected cases, and confirming diagnoses through molecular methodologies.

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We do not have any financial disclosures to make.

Authors' contributions

AM wrote the main manuscript text. STF was involved in the in-silico analysis and prepared the figures. PK was involved in neurological evaluation and physical examination. MM was involved in genetic counseling. M-RG contributed to the study conception, design and coordination. Sample preparation, data collection, and genetic analysis were performed by EG, and MR. HS and FH-G provided intellectual input and contributed to the revision process. All authors reviewed the manuscript. All the authors have read and approved the final manuscript.

Data availability

The primer sequences for PCR are provided in Table 1. The datasets generated and/or analyzed during the current study are available in the ClinVar repository (Accession number SCV000784534.2), https://www.ncbi.nlm.nih.gov/clinvar/variation/548608/.

Declarations

Ethics approval and consent to participate

This study is in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethical Committee at the Shahid Beheshti University of Medical Sciences. Informed consent was obtained from adult participants to participate in the study. Written informed consent was obtained from parents of kin next of kin for all participants aged under 18.

Consent for publication
Written informed consent for publication of identifying images or other personal or clinical details was obtained from the parents or legal guardians of any participant under the age of 18.

Competing interests
The authors declare no competing interests.

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References

1. Oz-Levi D, Ben-Zeev B, Ruzzo EK, Hitomi Y, Gelman A, Pelak K, et al. Mutation in TECPR2 reveals a role for autophagy in hereditary spastic paraparesis. Am J Hum Genet. 2012;91(6):1065–72.
2. Heimer G, Oz-Levi D, Eyal E, Edvardson S, Nissenkorn A, Ruzzo EK, et al. TECPR2 mutations cause a new subtype of familial dysautonomia like hereditary sensory autonomic neuropathy with intellectual disability. Eur J Paediatr Neurol. 2016;20(1):69–79.
3. Covone AE, Fiorillo C, Acquaviva M, Trucco F, Morana G, Ravazzolo R, et al. WES in a family trio suggests involvement of TECPR2 in a complex form of progressive motor neuron disease. Clin Genet. 2016;90(2):182–5.
4. Neuser S, Brechmann B, Heimer G, Brösse I, Schubert S, O'Grady L, et al. Clinical, neuroimaging, and molecular spectrum of TECPR2-associated hereditary sensory and autonomic neuropathy with intellectual disability. Hum Mutat. 2021;42(6):762–76.
5. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988;16(3):1215.
6. Zimmermann M, Deininger N, Willikens S, Haack TB, Grundmann-Hauser K, Streubel B, et al. Tetraparesis and sensorimotor axonal polyneuropathy due to co-occurrence of pompe disease and hereditary ATTR amyloidosis. Neurol Sci. 2021;42(4):1523–5.
7. McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kernytsky A, et al. The genome analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res. 2010;20(9):1297–303.
8. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res. 2010;38(16):e164.
9. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24.
10. Stadel D, Millarte V, Tillmann KD, Huber J, Tamin-Yecheskel BC, Akutsu M, et al. TECPR2 cooperates with LC3C to regulate COPII-Dependent ER export. Mol Cell. 2015;60(1):89–104.
11. Hurley JH, Young LN. Mechanisms of autophagy initiation. Annu Rev Biochem. 2017;86:225–44.
12. Nalbach K, Schifferer M, Bhattacharya D, Ho-Xuan H, Tseng W, Williams LA, et al. Spatial proteomics reveals secretory pathway disturbances caused by neuropathy-associated TECPR2. Nat Commun. 2023;14(1):870.
13. Zhu X, Petrovski S, Xie P, Ruzzo EK, Lu YF, McSweeney KM, et al. Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios. Genet Med. 2015;17(10):774–81.
14. Palma JA, Yadav R, Gao D, Norcliffe-Kaufmann L, Slaugenhaupt S, Kaufmann H. Expanding the genotypic spectrum of congenital sensory and autonomic neuropathies using whole-exome sequencing. Neurol Genet. 2021;7(2):e568.
15. Patwari PP, Wolfe LF, Sharma GD, Berry-Kravis E. TECPR2 mutation-associated respiratory dysregulation: more than central apnea. J Clin Sleep Med. 2020;16(6):977–82.
16. Ramsey K, Belnap N, Bonfitto A, Jepsen W, Naymik M, Sanchez-Castillo M, et al. Progressive cerebellar atrophy caused by heterozygous TECPR2 mutations. Mol Genet Genomic Med. 2022;10(2):e1857.
17. Guan Y, Lu H, Zuo W, Wang X, Wang S, Wang X, et al. Novel detection of mutation in the TECPR2 gene in a Chinese hereditary spastic paraplegia 49 patient: a case report. BMC Neurol. 2022;22(1):47.
18. Khalaf-Nazzal R, Dweikat I, Ubeyratna N, Fasham J, Alawneh M, Leslie J, et al. TECPR2-related hereditary sensory and autonomic neuropathy in two siblings from Palestine. Am J Med Genet A. 2024;194(7):e63579.

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