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NLM Citation: Heimer G, Neuser S, Ben-Zeev B, et al. *TECPR2*-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability. 2022 Sep 22. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

TECPR2-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability

Synonyms: Hereditary Sensory and Autonomic Neuropathy Type IX with Developmental Delay (HSAN9), Hereditary Spastic Paraplegia Type 49 (SPG49)

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Created: September 22, 2022.

Summary

Clinical characteristics

TECPR2-related hereditary sensory and autonomic neuropathy with intellectual disability (*TECPR2*-HSAN with ID) is characterized by developmental delay and subsequent intellectual disability, behavioral abnormalities, neurologic manifestations (muscular hypotonia, sensory neuropathy with lower-limb hypo- or areflexia and ataxic gait), and autonomic dysfunction (including central hypoventilation and apnea, gastrointestinal dysmotility, dysphagia, and gastroesophageal reflux disease with recurrent aspiration). To date, more than 30 individuals with *TECPR2*-HSAN with ID have been identified.

Diagnosis/testing

The diagnosis of *TECPR2*-HSAN with ID is established in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TECPR2* identified by molecular genetic testing.

Management

Treatment of manifestations: Currently there are no specific disease-modifying treatments for *TECPR2*-HSAN with ID. Supportive care is recommended to improve quality of life, maximize function, reduce complications, and minimize risk for apnea and asphyxia, the two most common causes of death. Supportive care can include multidisciplinary care by pediatric specialists in neurology, development, behavior, feeding, pulmonology, gastroenterology, orthopedics, ethics, and medical genetics.

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Surveillance: Routinely monitor existing manifestations, response to supportive care, and emergence of new manifestations.

Agents/circumstances to avoid: Avoid drugs that cause decreased consciousness, hypopnea, and CO_2 retention such as benzodiazepines or antihistamines; or if necessary, use at low doses with close monitoring.

Genetic counseling

TECPR2-HSAN with ID is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *TECPR2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *TECPR2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *TECPR2*-related hereditary sensory and autonomic neuropathy with intellectual disability (*TECPR2*-HSAN with ID) have been published.

Suggestive Findings

TECPR2-HSAN with ID **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings

- Developmental delay / intellectual disability (mainly in the moderate to severe range)
- Neurologic findings
  - Muscular hypotonia
  - Gait ataxia
  - Hyporeflexia / areflexia of the lower limbs
  - Impaired pain sensitivity
  - Dysarthria
- Autonomic dysfunction
  - Impaired temperature regulation
  - Impaired blood pressure regulation
  - Central nocturnal and/or daytime hypoventilation
  - Dysphagia
  - Abnormal gastrointestinal mobility resulting in gastroesophageal reflux and/or constipation
- Recurrent respiratory infections resulting from aspiration as a result of gastroesophageal reflux and dysphagia
- Behavioral abnormalities (hyperactivity, aggressiveness, autism spectrum disorder)
- Distinctive facial features that may include brachycephaly, synophrys, thick eyebrows, hypotelorism, epicanthus, round or triangular-shaped face, and dental crowding [Heimer et al 2016, Neuser et al 2021]

Brain imaging

- Thin or dysplastic corpus callosum
- Mild ventriculomegaly (often asymmetric)
- Delayed myelination (i.e., delayed appearance of signal changes related to final myelination of white matter pathways in affected children)
- Mild cerebral atrophy or mild atrophy of the cerebellar hemispheres or vermis

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity) and/or a Bukharian or Ashkenazi Jewish background. Absence of a known family history and/or of Bukharian or Ashkenazi Jewish background does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *TECPR2*-HSAN with ID **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TECPR2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *TECPR2* variants of uncertain significance (or of one known *TECPR2* pathogenic variant and one *TECPR2* variant of uncertain significance) does not establish or rule out a diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (targeted analysis for founder variants, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (Option 1), whereas genomic testing does not (Option 2).

Option 1

Targeted analysis for founder variants can be performed first in individuals of Bukharian or Ashkenazi Jewish ancestry (see Table 7).

A **hereditary spastic paraplegia**, **neuropathy**, **cerebral palsy**, or **intellectual disability multigene panel** that includes *TECPR2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Limitations of exome sequencing may include limited detection of intragenic deletions/insertions and whole-gene deletions or duplications.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *TECPR2*-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
TECPR2	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Oz-Levi et al [2012], Zhu et al [2015], Heimer et al [2016], Anazi et al [2017], Patwari et al [2020], Neuser et al [2021], Palma et al [2021], Ramsey et al [2022]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

TECPR2-related hereditary sensory and autonomic neuropathy with intellectual disability (*TECPR2*-HSAN with ID) is characterized by developmental delay and subsequent intellectual disability, behavioral abnormalities, neurologic manifestations (muscular hypotonia, sensory neuropathy with lower-limb hypo- or areflexia and ataxic gait), and autonomic dysfunction (including central hypoventilation and apnea, gastrointestinal dysmotility, dysphagia, and gastroesophageal reflux disease with recurrent aspiration).

To date, more than 30 individuals with biallelic pathogenic variants in *TECPR2* have been identified [Oz-Levi et al 2012, Zhu et al 2015, Heimer et al 2016, Anazi et al 2017, Patwari et al 2020, Neuser et al 2021, Palma et al 2021, Ramsey et al 2022]. The following description of the phenotypic features associated with *TECPR2*-HSAN with ID is based on these reports and the authors' personal experience with additional unpublished cases.

Table 2. *TECPR2*-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability: Frequency of Select Features

Feature		% of Persons w/Feature [1]
Abnormal development	DD/ID	100% (33/33)
	Speech impairment	92% (24/26)
Behavioral abnormalities		62.5% (15/24)
Neurologic	Muscular hypotonia	100% (34/34)
	Gait ataxia	100% (23/23)
	Dysarthria	87.5% (14/16)
Sensory neuropathy	Hypo- or areflexia	85% (29/34)
	Decreased pain sensitivity	50% (13/26)
Autonomic neuropathy	Central hypoventilation / Apnea	82% (27/33)
	Dysphagia	53% (18/34)
	GERD	94% (31/33)
Recurrent pneumonia		74% (20/27)

Table 2. continued from previous page.

Feature		% of Persons w/Feature [1]
Recurrent aspiration		71% (22/31)
Dysmorphic features	Microcephaly	59% (16/27)
	Short stature	58% (15/26)
	Short neck or retrocollis	52% (15/29)

DD/ID = developmental delay / intellectual disability; GERD = gastroesophageal reflux disease
1. Denominator reflects the number of persons assessed for the feature.

Developmental delay is usually noted in infancy with motor and later speech delay. Independent walking is delayed and the gait is often apraxic-ataxic. Most individuals achieve independent walking.

Intellectual disability is typically in the moderate to severe range; however, individuals with milder cognitive impairment have been described [Neuser et al 2021].

Speech impairment. Speech delay is universal; speech remains markedly impaired, with a subset of individuals remaining nonverbal.

Neurologic manifestations. Motor manifestations are axial and appendicular hypotonia. Lower-limb spasticity, dystonia, dyskinesia, and Parkinsonian features (especially rigidity) can develop in late childhood/adolescence.

Gait is mostly ataxic; however, crouched gait can develop at later stages. Although most individuals achieve independent walking, regression in the second decade of life with loss of independent walking is possible.

Findings suggestive of a sensory neuropathy typically include hypo- or areflexia in the lower limbs and decreased pain sensitivity.

Epilepsy is uncommon, but a few individuals experienced febrile or unprovoked seizures. EEG findings of nonspecific background slowing and epileptiform discharges may be seen in a minority of individuals.

Autonomic neuropathy, a prominent feature, significantly affects morbidity and mortality. Autonomic dysfunction presents with central daytime and nocturnal hypopnea and apnea, hypercarbia, dysphagia with recurrent aspiration, gastroesophageal reflux, and constipation. The dysphagia can lead to both recurrent aspiration and asphyxia.

Other features of the autonomic neuropathy are temperature and blood pressure instability, hyperhidrosis, and electrolyte disturbances. Anecdotally, disproportionally decreased consciousness can develop in response to intercurrent illness or mild central nervous system depressants such as antihistamines.

Recurrent respiratory infections are common and can occur as early as the first year of life. These are likely a result of recurrent aspiration due to dysphagia and gastroesophageal reflux and can be precipitated by laryngeal clefts or laryngomalacia seen in a subset of individuals with *TECPR2*-HSAN with ID. Over time, recurrent respiratory infections can result in chronic lung disease complicated by bronchiectasis.

Behavioral dysregulation is common and often significantly affects quality of life. Manifestations range from hyperactivity and restlessness to psychomotor slowing and apathy. There is a tendency for shouting and grabbing objects and, sometimes, aggressive behaviors. Some individuals display features of autism spectrum disorder.

Other findings include the following:

- Microcephaly (usually mild or in the low ranges of normal)
- Short stature (usually mild or in the low ranges of normal)
- Short neck with a retrocollis hyperextension posture

- Kyphosis, scoliosis, and a barrel-shaped chest, usually developing in the second decade of life
- Sensorineural hearing impairment may develop; however, data are insufficient to estimate severity or typical age of onset.
- Various ophthalmologic findings including refractive errors (astigmatism, myopia), strabismus, and abnormal ocular movement (periodic upward gaze deviation, oculomotor apraxia, and nystagmus)

Prognosis. *TECPR2*-HSAN with ID, a progressive disorder, is associated with reduced life expectancy. Several individuals died in the first or second decade of life [Authors, unpublished data]. The oldest individual known to the authors lived until age 19 years. The leading causes of death are asphyxia from aspiration of solid foods, nocturnal central apnea, and complications of chronic progressive lung disease.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified [Neuser et al 2021].

Nomenclature

TECPR2-HSAN with ID was originally described as a form of hereditary spastic paraplegia (SPG49) when the first affected individuals were diagnosed at a relatively late age and showed lower-limb spasticity and a crouched gate. However, with the characterization of additional affected individuals, it became clear that the hallmark feature associated with biallelic *TECPR2* pathogenic variants is sensory and autonomic neuropathy. Hence, the *TECPR2*-related phenotype was reclassified as a subtype of hereditary sensory and autonomic neuropathy (HSAN9).

Prevalence

TECPR2-HSAN with ID is an ultra-rare disease. A little more than 30 cases have been reported. The calculated incidence ranges from 1:22,500 (Bukharian population) to 1:5,961,640 newborns (general population, based on gnomAD).

About half of affected individuals are born to consanguineous parents.

Two populations with founder variants are identified:

- Individuals of Jewish Bukharian background: c.3416delT; p.Leu1139ArgfsTer75 [Oz-Levi et al 2012]
- Individuals of Jewish Ashkenazi background: c.1319delT; p.Leu440ArgfsTer19 [Heimer et al 2016]

The carrier frequency for the Bukharian Jewish population is 1.33% [Oz Levi et al 2012].

The carrier frequency for the Ashkenazi Jewish population is at least 0.65% [Neuser et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TECPR2*.

Differential Diagnosis

Table 3. Sensory and Autonomic Neuropathies in the Differential Diagnosis of *TECPR2*-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability

Gene	Disorder [1]	Key Features	Comment
DST	HSAN6 (OMIM 614653)	Sensory & autonomic neuropathy, profound ID w/absent milestones, joint contractures	Unlike *TECPR2*-HSAN w/ID, HSAN6 is assoc w/poor feeding, joint contractures, ↓ tongue papilla, alacrima, & absent flair in response to histamine test.
ELP1 (formerly *IKBKAP*)	HSAN3 (See Familial Dysautonomia.)	Sensory & autonomic neuropathy, mild ID, mood lability	Similar to *TECPR2*-HSAN w/ID, HSAN3 is assoc w/ hypotonia, areflexia, & autonomic manifestations w/ resulting respiratory disease. However, in HSAN3, ID is usually borderline or mild, & there is poor feeding & nephropathy as well as the unique features of alacrima, ↓ tongue papilla, & absent flair in response to histamine test.
KIF1A	HSAN2C (See HSAN2.)	Sensory neuropathy, ± ID, ± autonomic dysfunction	Similar to *TECPR2*-HSAN w/ID, HSAN2C is assoc w/ short stature & hypo-/areflexia. However, in HSAN2C, ID is uncommon, onset is not congenital, & there are frequent painless deformities & muscular atrophy.
NGF	HSAN5 (See Congenital Insensitivity to Pain Overview.)	Sensory & autonomic neuropathy	HSAN5 is assoc w/painless deformities (due to sensory neuropathy) & anhidrosis w/episodic fevers (due to autonomic neuropathy). ID is usually borderline or mild.
NTRK1	HSAN4 (See *NTRK1* Congenital Insensitivity to Pain with Anhidrosis.)	Sensory & autonomic neuropathy, ID, mood lability, hyperactivity	HSAN4 is assoc w/painless deformities (due to sensory neuropathy), postural hypotension, anhidrosis w/ episodic fevers (due to autonomic neuropathy), & absent flair in response to histamine test.

HSAN = hereditary sensory and autonomic neuropathy; ID = intellectual disability
1. The disorders listed in Table 3 are inherited in an autosomal recessive manner.

Note: Children with *TECPR2*-related hereditary sensory and autonomic neuropathy with intellectual disability (*TECPR2*-HSAN with ID) may be initially misdiagnosed with cerebral palsy. The absence of characteristic findings for cerebral palsy (such as ante- or perinatal risk factors) and the presence of consanguinity and clinical findings such as marked hypotonia and hypo-/areflexia with autonomic neuropathy and suggestive dysmorphic features can help differentiate *TECPR2*-HSAN with ID from cerebral palsy. Additionally, *TECPR2*-HSAN with ID shows a progressive course, whereas manifestations of cerebral palsy remain stable.

Management

Recommendations for clinical management of *TECPR2*-related hereditary sensory and autonomic neuropathy with intellectual disability (*TECPR2*-HSAN with ID), including symptomatic treatment and surveillance, have been published [Neuser et al 2021].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *TECPR2*-HSAN with ID, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *TECPR2*-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability

System/Concern	Evaluation	Comment
Neurologic	Thorough neurologic exam w/attn to muscle tone, gait ataxia, hypo-/areflexia, ↓ sensitivity to pain	• Perform EEG if history suggests seizures. • Brain MRI may be considered (after careful eval of risks of sedation/anesthesia in this patient population). [1]
Developmental	Perform developmental eval; assess for behavioral dysregulation & features of ASD.	Refer for appropriate developmental support, special education, & ABA therapy if indicated.
Speech impairment	Speech-language pathologist	
Activities of daily living	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastroenterology	Evaluate for swallowing difficulties, gastroesophageal reflux, & constipation.	• Consider swallow study for assessing dysphagia. • If dysphagia or aspiration are present, consider aspiration precautions (i.e., avoidance of certain food consistencies or nothing by mouth).
Respiratory	Investigate for obstructive or central apneas, respiratory infections, &/or aspiration.	• Baseline chest x-ray • Polysomnography
ENT	Consider audiogram to assess for sensorineural impairment.	
Ocular	Assess for strabismus, eye movement abnormalities, & refractive errors.	
Orthopedic	Assess for scoliosis or kyphosis & evaluate need for supportive devices.	
Cardiac	Consider blood pressure monitoring & echocardiography in case of signs of pulmonary hypertension.	
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *TECPR2*-HSAN w/ID to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ABA = applied behavioral analysis; ADL = activities of daily living; ASD = autism spectrum disorder; HSAN = hereditary sensory and autonomic neuropathy; ID = intellectual disability; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. It is possible that the imaging spectrum in *TECPR2*-HSAN with ID is not fully appreciated at this time and that clinically relevant findings could be missed (e.g., there could be individuals with developmental brain malformations and seizures that are amenable to epilepsy surgery).

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Currently there are no specific disease-modifying treatments for *TECPR2*-HSAN with ID.

Supportive care to improve quality of life, maximize function, reduce complications, and minimize risk for apnea and asphyxia, which are the two most prevalent causes of death, is recommended. Supportive care can include multidisciplinary care by pediatric specialists in the disciplines of neurology, development, behavior, feeding, pulmonology, gastroenterology, orthopedics, ethics, and medical genetics (see Table 5).

Table 5. Treatment of Manifestations in Individuals with *TECPR2*-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability

Manifestation/Concern	Treatment	Considerations/Other
Developmental	Developmental support incl PT, OT, & speech therapy	Consider ABA therapy in cases of ASD.
Motor & orthopedic abnormalities	Consider ankle-foot orthoses & other braces.	
Gastroesophageal reflux	Antacids, H2 blockers, or proton pump inhibitors	
Aspiration	Gastrostomy tube w/or w/o fundoplication	If dysphagia or aspiration are present, consider aspiration precautions (i.e., avoidance of certain food consistencies or nothing by mouth).
Asphyxia	Avoid solid foods that can lodge in trachea & cause asphyxia.	
Chronic lung disease	Routine chest physiotherapy & cough assist devices	
Nocturnal central hypo-/apnea	Consider continuous nighttime pulse oximetry &/or nighttime noninvasive ventilation.	
Nocturnal obstructive hypo-/apnea	Consider adenoidectomy / tonsillectomy if obstructive sleep apnea is present.	
Ocular	Adjust glasses to correct refraction errors & strabismus.	In some cases, surgical repair of strabismus may also be considered.
Seizures	Anti-seizure medication	

ABA = applied behavioral analysis; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary and an instruction of nothing per os (NPO) should be considered.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider

cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one-on-one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations and response to supportive care and to detect new manifestations, see Table 6.

Table 6. Recommended Surveillance for Individuals with *TECPR2*-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability

System/Concern	Evaluation	Frequency
Neurologic	• Neurologic exam for response to treatments & evidence of progression of existing findings or emergence of new findings • Perform EEG if indicated.	Every 6 mos
Development	Monitor developmental progress & educational needs.	
Respiratory	• Pulmonary eval • Consider venous blood gases.	
	• Consider chest x-ray & sputum cultures. • Consider echocardiography to monitor for pulmonary hypertension. • Consider arterial blood gases.	Every 12 mos
Gastroenterology	Gastroenterology eval & consultation w/dietician	Every 6 mos
	Consider swallow study (unless fed by gastrostomy).	Every 12 mos
	Perform electrolytes & liver function tests.	Every 12 mos & also during intercurrent illnesses
Orthopedic	Orthopedic eval to assess for need for supportive devices (such as orthoses) & monitor for potential complications such as hip dislocation & scoliosis	Every 6 mos
	Consider spine x-ray.	Every 12 mos
Sleep	Polysomnography study	
ENT	ENT eval	In case of snoring or consistent tonsillar enlargement
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Agents/Circumstances to Avoid

Avoid drugs that cause decreased consciousness, hypopnea, and CO_2 retention such as benzodiazepines or antihistamines; if necessary, use at low doses with close monitoring.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

TECPR2-related hereditary sensory and autonomic neuropathy with intellectual disability (*TECPR2*-HSAN with ID) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *TECPR2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *TECPR2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *TECPR2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with *TECPR2*-HSAN with ID are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TECPR2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *TECPR2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers and to the parents of affected children.
- Carrier testing for reproductive partners of known carriers should be considered, particularly if consanguinity is likely and/or the reproductive partner is of Bukharian or Ashkenazi Jewish background, as these population groups have higher carrier frequencies as a result of founder variants (see Prevalence).

Prenatal Testing and Preimplantation Genetic Testing

Once the *TECPR2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Spastic paraplegia type 49

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. TECPR2-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability : Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
TECPR2	14q32.31	Tectonin beta-propeller repeat-containing protein 2	TECPR2	TECPR2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for TECPR2-Related Hereditary Sensory and Autonomic Neuropathy with Intellectual Disability (View All in OMIM)

615000	TECTONIN BETA-PROPELLER REPEAT-CONTAINING PROTEIN 2; TECPR2
615031	NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, TYPE IX, WITH DEVELOPMENTAL DELAY; HSAN9

Molecular Pathogenesis

TECPR2 (tectonin beta-propeller repeat containing 2) is a large, multidomain protein comprising an amino-terminal tryptophan-aspartic-acid dipeptide (WD) domain, a middle unstructured region, and a carboxy-terminal TEPCR domain containing six TECPR repeats followed by a functional LC3 interacting region (LIR) motif at the extreme carboxy terminus [Stadel et al 2015]. TECPR2 was identified as an interactor of the ATG8 family proteins, which play key roles in autophagy [Oz Levi et al 2012]. TECPR2 regulates targeting of autophagosomes to lysosomes, a process primarily mediated by its carboxy-terminal TECPR domain. In fibroblasts of individuals with homozygous stop codon *TECPR2* variants, formation of mature autophagosome was consistent with the notion that TECPR2 plays an important role in late stages of autophagosome targeting to lysosomes [Fraiberg et al 2021]. Ectopic expression of either full-length TECPR2 or the TECPR domain rescued autophagy in fibroblasts of individuals with *TECPR2*-HSAN with ID in an LIR-dependent manner.

Animal models supporting a defect in autophagy include:

- Accumulation of autophagosomes in a *Tecpr2* knockout mouse [Tamim-Yecheskel et al 2021]. These mice exhibited neuroaxonal dystrophy with development of axonal spheroids in a progressive age-dependent manner in the dorsal column pathway of the brain stem and spinal cord accompanied by sensory pathway defects on behavioral tests, consistent with the hereditary sensory and autonomic neuropathy observed in individuals with TECPR2 deficiency [Heimer et al 2016].
- Observation of similar findings in Spanish water dogs with a homozygous missense variant (p.Arg1337Trp) in a highly conserved position in the *TECPR2* C-terminal region [Hahn et al 2015]. Neuronal loss and spheroid formation were accentuated in the gray matter of the cerebral hemispheres, cerebellum, and brain stem; sporadic spheroids were also found in white matter. Interestingly, in the spinal cord this histopathologic process was restricted to sensory pathways.

Mechanism of disease causation. Loss of function; evidence for missense variants is still not sufficient.

***TECPR2*-specific laboratory technical considerations.** The lack of functional data has prevented classification of several novel *TECPR2* variants [Neuser et al 2021].

Table 7. Notable *TECPR2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_014844.5 NP_055659.2	c.3416delT	p.Leu1139ArgfsTer75	Founder variant in persons of Bukharian Jewish background [Oz-Levi et al 2012]
	c.1319delT	p.Leu440ArgfsTer19	Founder variant in persons of Ashkenazi Jewish background [Heimer et al 2016]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Readers are encouraged to contact the authors for questions about research on *TECPR2*-related hereditary sensory and autonomic neuropathy with intellectual disability.

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Acknowledgments

The authors thank all families for their participation in research.

Revision History

- 22 September 2022 (bp) Review posted live
- 13 June 2022 (sn) Original submission

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