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Familial Dysautonomia

Synonyms: Hereditary Sensory and Autonomic Neuropathy Type III (HSAN III), Riley-Day Syndrome

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Summary

Clinical characteristics

Familial dysautonomia, which affects the development and survival of sensory, sympathetic, and parasympathetic neurons, is a debilitating disorder present from birth. Neuronal degeneration progresses throughout life. Affected individuals have gastrointestinal dysfunction, autonomic crises (i.e., hypertensive vomiting attacks), recurrent pneumonia, altered pain sensitivity, altered temperature perception, and blood pressure instability. Hypotonia contributes to delay in acquisition of motor milestones. Optic neuropathy results in progressive vision loss. Older individuals often have a broad-based and ataxic gait that deteriorates over time. Developmental delay / intellectual disability occur in about 21% of individuals. Life expectancy is decreased.

Diagnosis/testing

The diagnosis of familial dysautonomia is established in a proband with suggestive findings and biallelic pathogenic variants in *ELP1* (formerly *IKBKAP*) identified by molecular genetic testing.

Management

Treatment of manifestations: Affected individuals are often managed by multidisciplinary specialists that include neurologists, physiatrists, orthopedic surgeons, physical and occupational therapists, speech-language pathologists, pulmonologists, cardiologists, nephrologists, ophthalmologists, dentists and dental hygienists, and social workers. Feeding teams manage neurogenic dysphagia; mental health professionals treat anxiety.

Surveillance: Routine monitoring of the following: weight, nutrition, safety of oral feeding, developmental/educational progress, mental status, pulmonary function, sleep-disordered breathing, frequency and severity of dysautonomic crises, blood pressure lability, vision and low vision needs, ataxia and activities of daily living, spine for scoliosis, dental care and needs; assessment of caregiver needs.

Agents/circumstances to avoid: The following can exacerbate symptoms: hot or humid weather; full bladder.

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Pregnancy management: Pregnancies in women with FD are considered high risk because of blood pressure lability. Visceral pain related to contractions during labor is perceived normally; therefore, analgesia should be provided.

Genetic counseling

Familial dysautonomia is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ELP1* 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 being unaffected and not a carrier. Once the *ELP1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible. Carrier screening is available on a population basis for individuals of Ashkenazi Jewish heritage.

Diagnosis

The five cardinal clinical diagnostic criteria for familial dysautonomia are absence of fungiform papillae on the tongue, absence of flare after injection of intradermal histamine, decreased or absent deep-tendon reflexes, absence of overflow emotional tears, and Ashkenazi Jewish descent [Axelrod & Pearson 1984]. This last criterion, however, was rebutted after the discovery of three rare non-Jewish *ELP1* variants [Leyne et al 2003].

Suggestive Findings

Clinical findings

- Gastrointestinal dysfunction with vomiting crises
- Recurrent aspiration pneumonia
- Altered sensitivity to pain and temperature
- Extreme blood pressure variability with postural hypotension
- Hypotonia
- Decreased or absent deep tendon reflexes
- Decreased taste and absence of fungiform papillae of the tongue, giving it a smooth, pale appearance
- Absence of overflow tears with emotional crying (alacrima) determined either by history in infants older than age three months or the Schirmer test (See **Specialized testing**.)

Specialized testing

- **Schirmer test.** As newborns do not cry tears, the Schirmer test must be performed after age six months. In the Schirmer test, the end of a filter paper, 5 mm wide and 35 mm long, is placed in the lateral portion of a lower eyelid. Less than 10 mm of wetting of the filter paper after five minutes indicates diminished baseline and reflex tear secretion.
- **Absence of axon flare response** after intradermal histamine injection
- **Pupillary hypersensitivity to parasympathomimetic agents**. Topical administration of methacholine 2.5% or pilocarpine 0.0625% has no observable effect on the normal pupil but causes miosis after approximately 20 minutes in almost all individuals with FD.

Heritage. Infant is of Ashkenazi Jewish heritage. (Absence of known Ashkenazi Jewish heritage does not exclude the diagnosis.)

Establishing the Diagnosis

The diagnosis of familial dysautonomia is established in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *ELP1* (formerly *IKBKAP*) identified by molecular genetic testing.

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 *ELP1* variants of uncertain significance (or identification of one known *ELP1* pathogenic variant and one *ELP1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are more likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of familial dysautonomia has not been considered may be more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ELP1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Typically, if only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

In individuals of Ashkenazi Jewish heritage, targeted analysis for the *ELP1* variant c.2204+6T>C (formerly IVS20+6T>C) can be performed first. This founder variant accounts for more than 99% of pathogenic variants among Ashkenazi Jewish individuals with FD.

A hereditary neuropathy multigene panel that includes *ELP1* 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

When the diagnosis of familial dysautonomia has not been considered because an individual has atypical phenotypic features and/or is not known to have Ashkenazi Jewish heritage, **comprehensive genomic testing,** which does not require the clinician to determine which gene is likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 Familial Dysautonomia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ELP1 (*IKBKAP*)	Targeted analysis for pathogenic variants [3]	>99% (Ashkenazi Jewish population) [4]
	Sequence analysis [5]	>99% [4]
	Deletion/duplication analysis [6]	None detected to date

1. See Table A. Genes and Databases for chromosome locus and protein name.
2. See Molecular Genetics for information on variants detected in this gene.
3. For pathogenic variants c.2204+6T>C and/or p.Arg696Pro [Dong et al 2002]
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Familial dysautonomia (FD) affects the development and survival of sensory, sympathetic, and parasympathetic neurons. It is a debilitating disease present from birth. Neuronal degeneration progresses throughout life. Affected individuals have gastrointestinal dysfunction, autonomic crises (I.e., hypertensive vomiting attacks), recurrent pneumonia, altered pain sensitivity, altered temperature perception, and cardiovascular instability. Hypotonia contributes to delay in acquisition of motor milestones. Older individuals often have a broad-based and ataxic gait that deteriorates over time. Developmental delay / intellectual disability occur in about 21% of individuals. Life expectancy is decreased [Welton et al 1979].

Table 2. Clinical Manifestations of Familial Dysautonomia

System Involved	Clinical Manifestations
Autonomic system	• Oropharyngeal incoordination (60% of neonates) • Esophageal dysmotility, GERD [1] • Insensitivity to hypercapnia and hypoxia [2] • Breath holding • Orthostatic hypotension w/o compensatory tachycardia [1, 3] • Supine hypertension [1] • Autonomic crises (i.e., hypertensive vomiting attacks) (40%)
Sensory system	• Insensitivity to pain (sparing hands, soles of feet, neck, & genital areas) [1] • Abnormal temperature perception on trunk & lower extremities [1] • Depressed patellar reflexes
Motor system	• Hypotonia • Mild/moderate motor DD • Broad-based or mildly ataxic gait [1] • Spinal curvature (95%; esp kyphosis) [1]

Table 2. continued from previous page.

System Involved	Clinical Manifestations
Cranial nerves	• Absence of overflow tears • Depressed corneal reflexes • Optic nerve atrophy [1] • Strabismus • Deficient taste, esp sweet • Dysarthric, nasal speech
Respiratory [4]	• Chronic aspiration & recurrent aspiration pneumonia • Suppurative lung disease & bronchiectasis • Restrictive lung disease • Upper-airway obstruction due to cranial dimorphism & ↓ muscle tone of pharyngeal muscles, → obstructive sleep apnea • Obstructive lung disease & airway hyperreactivity • Sleep-disordered breathing (obstructive & central sleep apnea) • Daytime hypoventilation
Renal [5]	• CKD w/histopathologic features of chronic hypertensive nephrosclerosis • Tubular atrophy • Lack of sympathetic innervation of renal vasculature • ↑ incidence of rare kidney malformations & hydronephrosis
Cognitive ability / Personality	• Usually normal intellect (verbal skills better than motor) • Concrete or literal thinking • Skin picking (esp fingers & nose) • Resistance to change (phobias) [1]

Adapted from Axelrod [1996]
CKD = chronic kidney disease; DD = developmental delay; GERD = gastroesophageal reflux disease
1. Progressive neurologic abnormalities
2. Bernardi et al [2003]
3. Brown et al [2003]
4. Kazachkov et al [2018]
5. Norcliffe-Kaufmann et al [2013b]

Most infants with familial dysautonomia are born after an uncomplicated term pregnancy. However, there is an increased rate of polyhydramnios and breech presentation.

Autonomic dysfunction. Neonates (i.e., infants age ≤28 days) typically have impaired oropharyngeal incoordination (i.e., neurogenic dysphagia) manifest as poor initiation of sucking and poor swallowing mechanisms. Protective airway reflexes (including cough) are decreased or lacking; the risk of aspiration and aspiration pneumonia shortly after birth is extremely high. Additional gastrointestinal problems that can interfere with eating and weight gain include esophageal dysmotility and GERD.

Infants with FD may have difficulties maintaining normal body temperature and may be indifferent to pain stimuli.

Sympathetic nervous system involvement results in orthostatic hypotension that is exacerbated by exercise and warm environments. Syncope is surprisingly infrequent, and usually indicates volume depletion, anemia, or hypoxia.

Urinary stress incontinence is common in adolescent and adult women [Saini et al 2003].

Episodic somnolence has been reported.

Autonomic crises, also described as hypertensive vomiting attacks, occur in about 40% of individuals. Attacks occur when stimuli increase sympathetic outflow causing an uncontrolled release of catecholamines

(neurotransmitters such as epinephrine and dopamine) into the circulation. Common triggers include emotion, illness, abdominal discomfort, and bladder distension; however, sometimes the crises are unpredictable and without obvious cause. Dopamine, which is believed to activate receptors in the chemoreceptor trigger zone of the area postrema (located in the medulla oblongata), cause cyclic vomiting (or retching in persons who have undergone fundoplication). These dopaminergic crises can also be associated with tachycardia, hyperhidrosis, irritability, and personality changes. Crises may last several days.

Sensory disturbances are significant. Pain and temperature thresholds are greatly elevated; affected individuals report a relative indifference to pain. The risk for decubitus ulcers, burns, and other minor injuries to become infected is increased. Failure to recognize fractures has also been described.

Motor development. Infants and young children have varying degrees of hypotonia that contribute to delay in motor milestones. Although some infants may acquire motor skills in the usual timeframe, most infants demonstrate some degree of delay in acquisition of motor skills. Sitting without support is usually achieved around age 12-18 months, standing alone around age one to two years, and walking independently around age two to three years [Sheba Medical Center Familial Dysautonomia Database, unpublished data].

Older individuals often have a broad-based, ataxic gait that progressively deteriorates over time. Individuals with FD have difficulty performing rapid movements and maintaining their balance while changing direction or turning. By age 20 years 3% of affected individuals require assistance walking; this percentage increases linearly to 14% by age 30 years, 27% by age 40 years, and 49% by age 50 years [Macefield et al 2011].

Ophthalmologic. Recurrent corneal ulcers and occasionally permanent opacities result from alacrima and corneal hypoesthesia.

The major cause of visual loss in FD is optic neuropathy affecting mostly the P-type retinal ganglion cells. Beginning early in life, all individuals with FD experience progressive loss of retinal ganglion cell axons. The temporal retinal nerve fiber layer (RNFL) is the most affected. The less energy-dependent ganglion cells are relatively spared, whereas the more energy-dependent maculopapillary ganglion cells are selectively damaged [Mendoza-Santiesteban et al 2014]. The accelerated retinal damage continues until the third decade of life and then plateaus [Kfir et al 2021]. Visual impairment frequently begins at an early age and can progress to blindness usually after the third decade of life.

Eye movement disorders such as strabismus are very common.

Respiratory illness is common. According to the New York University Familial Dysautonomia Patient Registry [Kazachkov et al 2018], upper-airway obstruction is present in 83%, lower-airway disease in 85%, and restrictive lung disease in 94% [Palma et al 2019].

Although most individuals undergo gastrostomy with Nissen fundoplication upon diagnosis, recurrent lower-airway infections remain common. Most individuals with FD develop chronic lung disease secondary to recurrent aspiration. CT imaging of the lungs shows bronchiectasis in 26% of affected individuals.

Lack of input from the peripheral chemoreceptors results in almost absent ventilatory responses to hypoxemia; the chemoreceptor ventilatory responses to hypercapnia are also reduced, but to a lesser extent.

The majority of children and adults with FD have some degree of sleep-disordered breathing. Central apnea is more frequent in children; obstructive apnea is more frequent in adults.

The increased incidence of sudden death during sleep can be attributed to the following risk factors: treatment with fludrocortisone, plasma potassium concentrations <4 mEq/L, and untreated sleep apnea [Palma et al 2017].

Kyphoscoliosis, a common finding, develops during the first two decades. By age 20 years, 80% of affected individuals have some degree of spinal deformity, possibly due to abnormal posture of the trunk as needed to maintain balance.

Renal. Chronic kidney disease is common. Renal function tends to deteriorate with advancing age. Almost all persons with FD who reach their fourth decade have a markedly decreased estimated glomerular filtration rate (eGFR) [Elkayam et al 2006].

Baroreflex failure, manifest as excessive increases or decreases in blood pressure with wide fluctuations, is associated with a faster progression of renal disease. Some individuals progress to end-stage renal disease and may require dialysis. A few renal transplants have been performed.

Renal tubular acidosis, requiring treatment, is common. Hyperkalemia, which is also common, is not always explained by the degree of renal insufficiency.

There is also an increased incidence of congenital renal defects, including a single kidney, horseshoe kidney, and crossed renal ectopia (i.e., a kidney that has crossed from its side to the other side such that the kidneys are both located on one side of the body) [Norcliffe-Kaufmann et al 2013a].

Cognitive function differs widely among affected individuals. Both learning difficulties and poor concentration are common. Although acquisition of verbal skills is delayed during the first nine years, verbal skills subsequently improve to within the normal range for age [Palma et al 2014].

Personality issues. Anxiety is the most common psychiatric problem. Skin or nail picking and trichotillomania occur in around 10% of individuals [Palma et al 2014].

Other

- **Craniofacial findings** include small jaw, mandibular retrognathia, malocclusion, dental crowding, and smaller tooth size [Mass 2016].
- **Dental trauma** occurs in 60% of individuals (often from frequent falling due to ataxia and balance issues); 32% have orodental self-mutilation (i.e., chewing the gums without noticing).
- **Sexual maturation** is frequently delayed; however, sexual development is normal in both sexes. Women with FD have delivered normal infants following uncomplicated pregnancies. Fertility in males has been reported; one male has fathered six children.
- **Growth.** Neonates with FD are usually born appropriate for gestational age with head circumference within the normal range. Individuals with FD often fall severely below their projected midparental adjusted height; the reported average adult height for males is 158 centimeters and for females is 150 centimeters.

  Although poor linear growth velocity, low-to-normal insulin-like growth factor-I (IGFI) levels, and delayed skeletal age are reported in FD, challenge tests for growth hormone deficiency have been inconclusive. Growth hormone treatment in individuals in an open-label study resulted in growth velocity that exceeded pre-treatment rates in 12 of the 13 treated individuals [Kamboj et al 2004].

Quality of life. Using a questionnaire to evaluate the quality of life in persons with FD, Sands et al [2006] determined that FD imposed a greater physical than psychosocial burden on children, whereas young adults reported both mental and physical quality of life within the average range. Self-esteem was problematic and improved with age. Both age groups reported decreasing physical quality of life with age, with worsening general health that limited their roles at school or work.

Prognosis. FD has always been recognized as a potentially life-threatening disorder with a high mortality rate and a high incidence of sudden death. Causes of death are primarily pulmonary (26%) and unexplained (38%); the latter may result from unopposed vagal stimulation. Sepsis is also a significant cause of death (11%) [Axelrod et al 2002].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed [Blumenfeld et al 1999].

The p.Arg696Pro pathogenic variant is extremely rare in the Ashkenazi Jewish population and has never been detected in the homozygous state; therefore, the phenotype associated with p.Arg696Pro homozygosity is unknown.

Prevalence

The incidence of FD among the Ashkenazim is 1:3,700 live births, which corresponds to a carrier frequency of 1:36 [Slaugenhaupt et al 2001].

A study by Lehavi et al [2003] from Israel identified 34 carriers among 1100 individuals of full Ashkenazi Jewish parentage (carrier rate 1:32). Further analysis revealed different carrier frequencies among a subset of Polish Ashkenazi Jews: Among the 195 individuals of full Polish background, 11 carriers were detected (1:18), in contrast to only three of the 298 of full non-Polish background (1:99).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ELP1* (*IKBKAP*).

Differential Diagnosis

Table 3. Genes and Disorders of Interest in the Differential Diagnosis

Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
ATL1	HSN1D (See Spastic Paraplegia 3A.)	AD	Loss of pain & temperature sensation; osteomyelitis; lancinating pain; distal motor involvement (variable); facultative deafness; no visceral signs of autonomic involvement
ATL3	HSN1F (OMIM 615632)	AD	• Loss of pain & temperature sensation; osteomyelitis; lancinating pain; distal motor involvement (variable); facultative deafness; no visceral signs of autonomic involvement • Similar to HSN1D [1]
CLTCL1 *NGF* *NTRK1* *PRDM12* *SCN9A* *SCN11A* *ZFHX2*	Congenital insensitivity to pain (See also *NTRK1* Congenital Insensitivity to Pain with Anhidrosis.)	AR AD	• Inability to perceive pain from birth from any noxious stimuli leading to repeated injuries & prevention of normal healing. Painless fractures & joint damage frequently occur & can lead to permanent damage; corneal injuries; anhidrosis that disturbs thermoregulation & can lead to recurrent episodes of unexplained fever (Note: marked hyperhidrosis is observed in assoc w/ *SCN11A* c.2432T>C [p.Leu811Pro].) • Self-mutilating injuries of the fingers (biting off fingertips) & oral cavity (incl loss of the tongue tip, injuries to the inside of the teeth/gums, & avulsion of teeth) are common.
DNMT1	HSN1E	AD	• Loss of pain & temperature sensation; osteomyelitis; lancinating pain; distal motor involvement (variable); facultative deafness; no visceral signs of autonomic involvement • Distinguished by hearing loss, dementia, & narcolepsy

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics / Comment
DST	HSAN6 (OMIM 614653)	AR	Dysautonomic symptoms; absent tearing, feeding difficulties, absent deep tendon reflexes, abnormal histamine test w/no axon flare, distal contractures, motionless open-mouthed facies, severe ID/DD, early death [-2]
KIF1A *RETREG1* *SCN9A* *WNK1*	HSAN2	AR	Progressively ↓ sensation to pain, temperature, & touch. Onset can be at birth & is often before puberty. Sensory deficit is predominantly distal (lower limbs more severely affected than upper limbs). Over time sensory function becomes severely ↓. Unnoticed injuries & neuropathic skin promote ulcerations & infections → spontaneous amputation of digits or need for surgical amputation. Osteomyelitis is common. Painless fractures can complicate the disease. Autonomic disturbances are variable.
LIFR	Stüve-Wiedemann syndrome (OMIM 601559)	AR	Combination of autonomic nervous system manifestations resembling FD & characteristic bony changes (bowing of long bones, camptodactyly) [3]
MPZ	CMT2IJ (See CMT Overview.)	AD	p.Thr124Met is assoc w/severe sensory loss, shooting pains, & occasional pseudo-Argyl-Robertson pupils but no ulcerations.
RAB7A	CMT2B (See CMT Overview.)	AD	• Acral ulcero-mutilating sensory neuropathy; sensory loss of all modalities w/a high frequency of foot ulcers necessitating amputations • Motor features are common; distal muscle weakness & wasting are often the 1st & most prominent features.[4]
SPTLC1	HSAN1A	AD	Prominent early sensory loss & later positive sensory phenomena (e.g., dysesthesia & characteristic "lightning" or "shooting" pains); painless injuries, which, if unrecognized, result in slow wound healing & subsequent osteomyelitis requiring distal amputations; motor involvement is present in all advanced cases & can be severe; SNHL is variable; onset ranges from teens to 6th decade.
SPTLC2	HSAN1C	AD	Phenotypically similar to HSAN1A
TECPR2	*TECPR2*-related HSAN with ID	AR	DD/ID, muscular hypotonia, ataxia, hyporeflexia, respiratory infections, & central/nocturnal hypopnea

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; FD = familial dysautonomia; HSAN = hereditary sensory and autonomic neuropathy; ID = intellectual disability; MOI = mode of inheritance; SNHL = sensorineural hearing loss; XL = X-linked

1. Fischer et al [2014], Kornak et al [2014]
2. Only one affected family has been reported to date [Edvardson et al 2012].
3. Di Rocco et al [2003]
4. Verhoeven et al [2003]

HSAN1B (OMIM 608088), a disorder of unknown genetic cause, can also be considered in the differential diagnosis. HSAN1B is characterized by cough and gastroesophageal reflux; loss of pain & temperature sensation; osteomyelitis; lancinating pain; distal motor involvement (variable); and facultative deafness. There are no visceral signs of autonomic involvement.

Management

Clinical practice guidelines have been published [Kazachkov et al 2018] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with familial dysautonomia, 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 Familial Dysautonomia

System/Concern		Evaluation	Comment
Growth		Measure height, weight, head circumference	
Neurologic involvement		By pediatric neurologist	• Comprehensive neurologic exam w/attn to sensory ataxia, abnormalities in proprioception • Positive Romberg sign; ↓ or absent deep tendon & H-reflexes • Consider: (1) MRI if concerns re worsening gait ataxia &/or balance; (2) EEG if concerns re seizures.
Development		Developmental assessment for infants/young children	• To incl motor, adaptive, & cognitive eval • Eval by speech-language pathologist • Eval for early childhood intervention programs / special education
Cognitive abilities		Standardized testing	
Psychiatric/behavioral issues		Assessment by mental health professional as needed	Anxiety is the most common psychiatric problem.
Neurogenic dysphagia		Multidisciplinary incl pulmonologist, neurologist, nutritionist, gastroenterologist, speech-language pathologist, chest physiotherapist, & caregivers	Baseline eval by multidisciplinary team w/video fluoroscopic swallow study to define safe consistencies of food & best oral hygiene
Blood pressure instability		24-hr blood pressure monitoring & orthostatic challenge	
Decreased sensitivity to pain		Skin exam	For decubitus ulcers & pressure sores (e.g., from shoes & devices such as back brace)
Sleep-disordered breathing		Full (in-laboratory) polysomnography incl end-tidal CO_2 measurements	Perform even if no clinical manifestations. Transcutaneous CO_2 measurements may be unreliable.
Airway disease	**Upper-airway obstruction**	Laryngoscopy, sleep endoscopy	Perform awake flexible laryngoscopy when breathing is noisy. If no anatomic obstruction is found, consider sleep laryngoscopy.
	Lower-airway disease	Pulmonary function tests, sputum cultures, bronchoscopy, & bronchoalveolar lavage	• Spirometry & response to bronchodilators may help assess airway obstruction. • Obtain culture from lower airways when clinical evidence suggests suppurative lung disease.
	Restrictive lung disease	Lung volume measurements via plethysmography or nitrogen washout	Secondary to hyperkyphotic (usually upper thoracic) scoliosis, mostly during 2nd decade
	Acute respiratory exacerbation	Respiratory exam & chest x-ray	• Acute respiratory exacerbation may present w/minimal symptoms despite significant hypoxemia & hypercarbia; because respiratory drive remains depressed even during acute respiratory exacerbations, patients do not appear dyspneic or tachypneic. • Dysautonomic crises may occur during acute respiratory exacerbations & are often the presenting manifestation.
Dysautonomic crises		As determined by medical history	Hyperadrenergic vomiting attacks may continue for several days.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Ophthalmologic involvement	Ophthalmologic exam	• Incl assessment of best corrected visual acuity, cornea for possible injury due to ↓ corneal sensation, fundoscopic exam for evidence of optic atrophy. • Assessment of retina to incl OCT w/measurements of mean RNFL & macular GCIPL thickness
Musculoskeletal	Physical medicine & rehab / PT / OT eval	To incl assessment of: • Gross motor & fine motor skills & need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Need for AFOs, specialized shoes • Mobility, activities of daily living, & need for adaptive devices/durable equipment
	Eval by pediatric orthopedist	Assess amount & progression of spinal curvature & extent of foot deformities.
Dental	Eval by dental hygienist	• ↑ saliva flow may ↓ incidence of dental caries, but changes in composition of saliva → more plaque & ↑ in periodontal disease. • Evaluate for dental, gingival, & tongue trauma (usually due to self-mutilation).
	General dental eval	Evaluate for dental, gingival, & tongue trauma (usually due to self-mutilation).
	Eval by orthodontists & maxillofacial professionals	To assess abnormalities of bite & dental spacing
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of FD in order to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support.	

AFO = ankle/foot orthoses; FD = familial dysautonomia; GCIPL = ganglion cell and inner plexiform layer; MOI = mode of inheritance; OCT = optic coherence tomography; RNFL = retinal nerve fiber layer
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no curative therapy for familial dysautonomia. Treatment is supportive.

Affected individuals are often managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, physical and occupational therapists, speech-language pathologists, pulmonologists, and social workers (see Table 5).

Table 5. Treatment of Manifestations in Individuals with Familial Dysautonomia

Manifestation/Concern		Treatment	Considerations/Other
Short stature		Growth hormone treatment may be effective & should be considered based on guidelines re height, growth velocity, & bone maturation. [1]	• GH stimulation testing may not be reliable. • Monitor spinal curvature, as it tends to worsen during accelerated growth.
Neurogenic dysphagia		Per feeding team; for infants, thickened formula & different-shaped nipples to manage oropharyngeal incoordination	Low threshold for gastrostomy tube & Nissen fundoplication to maintain nutritional status & ↓ risk of aspiration
GERD		Upright positioning w/feeds, prokinetic agents, H_2 antagonists, proton pump inhibitors, & gastrostomy w/or w/o fundoplication are appropriate.	A diagnosis of GERD should be confirmed w/ esophageal impedance & manometry.
DD / Educational issues		See Developmental Delay / Intellectual Disability Management Issues.	
Psychiatric/behavioral issues		By mental health professional	Selective serotonin reuptake inhibitors are sometimes effective in treating anxiety; psychotherapy & behavioral techniques may also help.
Blood pressure instability		Carbidopa is effective in reducing blood pressure variability. [2]	
Decreased sensitivity to pain		Close attn to decubitus ulcers, burns, & other minor injuries, joint swelling & bone deformity. Signs of local or systemic infection should be monitored & treated w/antibiotics.	
Sleep-disordered breathing		CPAP or BiPAP	Due to chemoreflex failure, begin noninvasive ventilation even when sleep-disordered breathing is mild to ↓ risk of sudden unexpected death during sleep. [3]
Airway disease	**Upper-airway obstruction**	Tonsillectomy & adenoidectomy.	If upper-airway obstruction is not resolved, refer to airway mgmt specialist.
	Lower-airway disease	Treat suppurative lung disease/bronchiectasis w/daily chest physiotherapy.	• Cough augmentation is most effective in clearing airway mucus & best achieved by mechanical insufflation/exsufflation methods. • Inhaled hypertonic saline may be beneficial. • Treat acute exacerbation promptly w/ antibiotics.
	Restrictive lung disease	Airway mucus clearance w/manually assisted coughing or mechanical insufflation/exsufflation methods	Consider surgical correction of scoliosis on a case-by-case basis. Surgical complications can be severe; data re respiratory function pre- & post-surgery are lacking.
	Acute respiratory exacerbation	Start antibiotics covering aspiration flora promptly, preferably after obtaining sputum culture.	• Oral antibiotics for 14 days • Initiation of IV antibiotics depends on baseline respiratory status; consider when no improvement after oral antibiotics.
	Chronic lung disease	Daily chest physiotherapy (nebulization, bronchodilators, cough augmentation, incentive spirometry, & postural drainage)	• Early diagnosis & treatment of pneumonia & infections (secondary to aspiration) • Treatment w/oseltamivir is indicated for influenza virus infections. [4]

Table 5. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Dysautonomic crises		• Instructions to manage crises at home w/fluids & medications via gastrostomy • Guidance re when to visit ER for more extensive eval & treatment	Careful attn to dehydration & electrolyte imbalance; investigate underlying cause when crises are refractory to treatment or other symptoms are present.
		Benzodiazepines ↓ retching/vomiting. As ventilation may be suppressed, noninvasive ventilation is recommended as a precaution.	IV benzodiazepine may cause prolonged apnea & should only be administered in ER or ICU settings.
		Clonidine (centrally acting α2-adrenergic agonist) may ↓ sympathetic activity.	May be given via gastrostomy, sublingually, or transdermally
		Intranasal dexmedetomidine may be a feasible & safe acute treatment for adrenergic crisis. [5]	In severe cases IV dexmedetomidine may be used, but only in ICU settings. [6]
		Carbidopa (dopa-decarboxylase inhibitor) given daily may ↓ frequency & severity of hypertensive vomiting attacks. [7]	
Bradyarrhythmia		Pacemaker	For those w/history of syncope &/or cardiac arrest
Orthostatic hypotension		• Physical countermaneuvers to ↑ venous return & PT to ↑ muscle strength in legs help prevent orthostatic hypotension. • Treatment w/midodrine may be effective for short periods; use as needed prior to physical activity that may cause orthostatic hypotension. • Hydration is useful only for short periods due to impaired osmopressor response (most likely due to ↓ function of peripheral osmosensory pathway).	Treatment of orthostatic hypotension w/high doses of fludrocortisone aggravates renal damage.
Hypertension		Attn to factors precipitating hypertension (rather than use of antihypertensive agents) as blood pressure is labile	Sleeping w/20°-40° elevation of head of bed ↓s supine hypertension & nocturnal pressure-diuresis & ↑s intravascular volume in the AM.
		Standard treatment of hypertension in persons w/CKD	
Kidney		• Adequate control of blood pressure • Treat renal tubular acidosis w/bicarbonate. • Low-potassium diet for hyperkalemia	
Ophthal-mologic	**Optic neuropathy**	Low vision aids	Per low vision clinic
	Corneal ulceration	Artificial tear solutions (w/methylcellulose) 3-6x/day, maintenance of normal body hydration, & moisture chamber spectacle attachments	• Soft contact lenses can promote healing. • Tarsorrhaphy only for corneal injury unresponsive to routine measures • Corneal transplantation offers limited success.
	Chronic blepharitis	Combined topical antibiotic/corticosteroid ointment	
	Strabismus	Early surgical correction may help.	
Sensory ataxia		OT/PT	Many adults use walkers or wheelchairs when outside the home.

Table 5. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Musculo-skeletal	**Foot deformity**	PT to preserve flexibility; special shoes w/good ankle support &/or AFOs to correct foot drop & aid walking	Excellent ongoing foot care to avoid development of ulcers at pressure points
	Spine deformities	PT to preserve flexibility	Bracing is not effective & may cause pressure ulcers; spinal fusion may be necessary.
Dental	**Sialorrhea**	Botulinum toxin injections in major salivary glands	Surgical approaches & anticholinergic drugs were used in the past.
	Excessive plaque & calculus accumulation	Dental cleaning & preventive care	Biannually by dental hygienist
	Periodontal disease, dental trauma, & self-mutilation	Dental eval & care	Assess for occult biting of oral mucosa & establish plan for tooth extraction when needed.
	Small jaw	Care by maxillofacial professionals	As needed for dental crowding & moderate/severe malocclusion
Family support & resources		Address caregiver needs (e.g., respite care, home nursing, coordination of multiple subspecialty appointments, equipment, medications, & supplies).	

AFOs = ankle/foot orthoses; BiPAP = bi-level positive airway pressure; CKD = chronic kidney disease; CPAP = continuous positive airway pressure; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

1. Kamboj et al [2004]
2. Norcliffe-Kaufmann et al [2020]
3. Palma et al [2017]
4. Palma et al [2014]
5. Spalink et al [2017]
6. Dillon et al [2017]
7. Norcliffe-Kaufmann et al [2013b]

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:

- Individualized education plan (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.

Surveillance

Table 6. Recommended Surveillance for Individuals with Familial Dysautonomia

System/Concern	Evaluation	Frequency
Constitutional	Assess height & weight, head circumference.	Routinely in growing children
Neurogenic dysphagia	Assess weight, nutrition, safety of oral feeding.	• In growing children: routinely • In adults: when respiratory function ↓s or respiratory infections ↑
DD / Educational issues	Assess developmental/educational progress.	At least annually
Behavior	Evaluate mental status.	Routinely during interim visits
Respiratory	Pulmonary function tests: • Spirometry before & after bronchodilator challenge to diagnose reversible obstructive disease • Quantitative measure of MIP & MEP to document disease progression & inform mgmt	Annually in all capable persons regardless of respiratory status; more frequently in those w/ significant respiratory involvement
Sleep-disordered breathing	Full laboratory polysomnography incl end-tidal CO_2 measurements	• Annually regardless of previous normal studies • Before & 6-8 weeks after starting growth hormone therapy
Dysautonomic crises	Frequency & severity of hyperadrenergic crises	Annually
Bradyarrhythmia	24-48-hr Holter monitoring regardless of previous normal studies	

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Orthostatic hypotension	Eval of symptoms & orthostatic challenge tests	Perform during interim visits.
Blood pressure	Monitor BP to assure optimal mgmt of BP lability to help limit neurologic progression w/age (which can be assoc w/ compromised cerebral perfusion)	Annual 24-hr BP monitoring
Kidney	Assess kidney function to assure early detection of renal disease	• Persons w/normal kidney function: annually • Persons w/CKD: per treating nephrologist
	Monitor existing kidney disease.	Per treating physician
Ophthalmologic	Monitor eye movements, visual acuity, strabismus, corneal issues.	Per treating ophthalmologist
	Optic coherence tomography	Repeat annually due to accelerated & significant loss of RNFL & GCIPL.
	Low vision needs	Per treating low vision clinic
Sensory ataxia	OT/PT assessment re activities of daily living, durable equipment needs, safety of the home/living environment	At each visit
Musculoskeletal	Spine exam	Annually during growth period; less frequently thereafter
Dental	Dental cleaning	Biannually
	General dental exam for evidence of occult biting (e.g., of buccal mucosa, tongue) & possible need for preventive dental extraction	Annually
	Orthodontists & maxillofacial professionals re abnormal bite & dental crowding	Per treating dental professionals
Family support & resources	Assessment of caregiver needs (e.g., respite care, home nursing, coordination of multiple subspecialty appointments, equipment, medications, & supplies)	At each visit

BP = blood pressure; GCIPL = ganglion cell and inner plexiform layer; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; OT = occupational therapist; PT = physical therapist; RNFL = retinal nerve fiber layer

Agents/Circumstances to Avoid

Symptoms tend to be worse in hot or humid weather; affected individuals should try to avoid being outdoors in such conditions as much as possible.

Other situations that can exacerbate disease manifestations include a full bladder; frequent visits to the lavatory are recommended [Axelrod & Gold-von Simson 2007].

Since long car rides, coming out of a movie theater, or fatigue can also worsen symptoms, such situations should be avoided as much as possible [Axelrod & Gold-von Simson 2007].

Episodic hypertension can occur in response to emotional stress or visceral pain, and therefore should be avoided when possible [Axelrod & Gold-von Simson 2007].

Environmental situations associated with hypobaric hypoxia (e.g., aircraft flight or ascent to high altitude) pose a potential risk to individuals with daytime hypercapnia [Palma et al 2014].

Evaluation of Relatives at Risk

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

Pregnancy Management

Pregnancies in women with FD are considered high risk because of abrupt changes in blood pressure.

High blood pressure secondary to FD is difficult to differentiate from toxemia or other causes of pregnancy-related high blood pressure.

Awareness of volume loss and low blood pressure is important because of the absence of reflex tachycardia to low blood pressure.

Visceral pain related to contractions during labor is perceived normally; therefore, analgesia should be provided. Epidural anesthesia is preferable due to blood pressure lability during general anesthesia or spinal block [Maayan et al 2000].

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

Familial dysautonomia (FD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *ELP1* [*IKBKAP*] pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ELP1* 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, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ELP1* 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 being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- All offspring of an individual with FD inherit a pathogenic variant in *ELP1* from their affected parent.
- The risk that the Ashkenazi Jewish reproductive partner of an individual with FD is heterozygous for an *ELP1* disease-causing allele is 1:32 (see Prevalence). Thus, the risk to the offspring of an affected individual and an Ashkenazi Jewish partner of having FD is approximately 1.5%. (The risk that a person of non-Ashkenazi Jewish ancestry is a carrier of FD is <1:150. For offspring of an individual with FD and a non-Ashkenazi Jewish reproductive partner, the risk of having FD is <1:300.)
- It is appropriate to offer molecular genetic testing of *ELP1* to the reproductive partner of an individual with FD (see Related Genetic Counseling Issues, **Population screening**).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ELP1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ELP1* pathogenic variants in the family.

See Related Genetic Counseling Issues, **Population screening** for information about carrier testing in individuals who do not have a family history of FD.

Related Genetic Counseling Issues

Population screening

- Because of the increased carrier rate for FD in individuals of Ashkenazi Jewish heritage (see Prevalence), the American College of Obstetricians and Gynecologists recommends offering carrier screening for FD to individuals of Jewish descent [ACOG 2017] (full text). Targeted analysis for pathogenic variants in *ELP1* is often included in panels of "Ashkenazi Jewish pathogenic variants" offered to individuals interested in preconception or prenatal risk assessment modification.
- If an individual has FD or is known to be a carrier of an *ELP1* pathogenic variant, it is appropriate to offer molecular genetic testing of *ELP1* to the individual's reproductive partner regardless of the reproductive partner's heritage.

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 affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ELP1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for FD 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.

- **Autonomic Disorders Consortium**
  Autonomic Disorders Consortium
- **Familial Dysautonomia Foundation, Inc.**
  315 West 39th Street
  Suite 701
  New York NY 10018
  Phone: 212-279-1066
  Email: info@famdys.org
  www.familialdysautonomia.org
- **Familial Dysautonomia Now Foundation**
  Phone: 847-913-0455
  Email: info@fdnow.org
  www.fdnow.org
- **MedlinePlus**
  Familial dysautonomia
- **Norton & Elaine Sarnoff Center for Jewish Genetics**
  Phone: 312-357-4718
  Email: jewishgenetics@juf.org
  www.juf.org/cjg

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. Familial Dysautonomia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ELP1	9q31.3	Elongator complex protein 1	IKBKAP homepage - Leiden Muscular Dystrophy pages	ELP1	ELP1

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 Familial Dysautonomia (View All in OMIM)

223900	NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, TYPE III; HSAN3
603722	ELONGATOR COMPLEX PROTEIN 1; ELP1

Molecular Pathogenesis

ELP1 protein is one of the six subunits of the Elongator complex, which facilitates transcriptional elongation, and is required for efficient translation of proteins. During embryogenesis, ELP1 is expressed first in the central and peripheral nervous systems and in the gastrointestinal tract. It is then expressed in secretory tissues and cartilage, and finally in muscle. Once the organs are formed, ELP1 expression appears in the skin and mucosal tissue. Overall, expression is more prominent in the nervous system and retina, and to a lesser extent in other organs. The complete absence of ELP1 leads to embryonic lethality with failure of vasculogenesis and neurulation [Norcliffe-Kaufmann et al 2017]. Individuals with biallelic *ELP1* pathogenic variants have at birth multiple lesions affecting mostly sensory (afferent) nerve fibers.

Mechanism of disease causation. The c.2204+6T>C founder variant affects the intronic splice donor site in *ELP1* exon 20. The skipping of exon 20 leads to a frameshift and generation of a premature termination codon in exon 21 of *ELP1* mRNA. The aberrant skipping of exon 20 is tissue specific, mostly in neurons.

***ELP1*-specific laboratory technical considerations.** Information on two other rare variants that have not yet been published is available in the NYU Center for Dysautonomia's 2020-2021 Year in Review (pdf).

Table 7. Notable *ELP1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_003640.5 NP_003631.2	c.2087G>C	p.Arg696Pro	A rare variant identified in Ashkenazi Jews [Dong et al 2002]
NM_003640.5	c.2204+6T>C (IVS20+6T>C)	--	Founder variant that accounts for >99.5% of pathogenic variants in Ashkenazi Jews [Dong et al 2002]

Variants listed in the table have been provided by the author. *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.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

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