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VPS13D Movement Disorder

Synonyms: Spinocerebellar Ataxia, Recessive, Type 4 (SCAR4); Spinocerebellar Ataxia with Saccadic Intrusion (SCASI); *VPS13D* Hyperkinetic Movement Disorder

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Summary

Clinical characteristics

VPS13D movement disorder is a hyperkinetic movement disorder (dystonia, chorea, and/or ataxia) of variable age of onset that can be associated with developmental delay. Onset ranges from birth to adulthood. Individuals can present in childhood with motor delays and gait instability. Cognitive impairment ranging from mild intellectual disability to developmental delay has been reported, and several individuals have normal cognitive function. Individuals have also presented as young adults with gait difficulties caused by spastic ataxia or ataxia. In addition to gait ataxia, affected individuals had limb ataxia, dysarthria, and eye movement abnormalities (macro-saccadic oscillations, nystagmus, and saccadic pursuit). Additional features reported in some individuals include peripheral neuropathy and/or seizures. The disorder progresses to spastic ataxia or generalized dystonia, which can lead to loss of independent ambulation.

Diagnosis

The diagnosis of *VPS13D* movement disorder is established in a proband by identification of biallelic pathogenic variants in *VPS13D* on molecular genetic testing.

Management

Treatment of manifestations: Standard treatment for seizures; spasticity treatments include baclofen, tizanidine, benzodiazepines, dantrolene sodium, gabapentin, botulinum toxin injections, and intrathecal baclofen; treatment options for dystonia include trihexyphenidyl, botulinum toxin injections, benzodiazepines, baclofen, and levodopa. A multidisciplinary team including occupational and physical therapists and a physiatrist is important; supportive developmental therapies should be provided as needed.

Surveillance: Monitor for urinary urgency, contractures, and seizures; evaluate fall risk and gait stability; monitor developmental progress and educational needs.

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Genetic counseling

VPS13D movement disorder is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the *VPS13D* pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

VPS13D movement disorder **should be suspected** in individuals with the following clinical, laboratory, and imaging findings.

Clinical presentation

- Infantile-onset hypotonia and severe developmental delay or motor delay that progresses to severe generalized dystonia or spastic ataxia
- Childhood-onset chorea or dystonia
- Early-adulthood-onset progressive spastic ataxia, dystonia, and myoclonus

Additional clinical features

- Macro-saccadic intrusions; these large abnormal back-and-forth eye movements with stationary inter-saccadic intervals are often triggered by saccades.
- Pyramidal signs (e.g., hyperreflexia, Babinski signs)
- Peripheral axonal neuropathy
- Seizures

Laboratory findings

- Elevated CSF lactate (in 1 individual) [Gauthier et al 2018]
- Enlarged mitochondria with altered morphology on muscle biopsy; identified in the only individual evaluated by muscle biopsy [Gauthier et al 2018, Seong et al 2018]

Brain MRI findings

- Symmetric T_2-weighted and FLAIR hyperintensities in the caudate and putamen
- Hyperintense T_2-weighted and FLAIR signal abnormalities of periventricular and subcortical regions
- Hypointense basal ganglia (globus pallidus)
- Thin corpus callosum [Gauthier et al 2018]
- Mild cerebellar atrophy, often involving the vermis [Seong et al 2018]

Note: Brain MRI findings can be striking, but imaging results vary among individuals with *VPS13D* movement disorder. Imaging findings can resemble those seen in Leigh syndrome. Some individuals with *VPS13D* movement disorder have had normal brain MRI examinations.

Establishing the Diagnosis

The diagnosis of *VPS13D* movement disorder **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *VPS13D* on 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 *VPS13D* variants of uncertain significance (or of one known *VPS13D* pathogenic variant and one *VPS13D* variant of uncertain significance) does not establish or rule out a diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, 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. Because the phenotype of *VPS13D* movement disorder is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with developmental delay and/or movement disorder are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *VPS13D* movement disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *VPS13D* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *VPS13D* 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 over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the relatively recent description of *VPS13D* movement disorder, some panels for developmental delay and/or movement disorder may not yet include this gene. (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 phenotype is indistinguishable from many other inherited disorders characterized by developmental delay and/or movement disorder, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are 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 *VPS13D* Movement Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
VPS13D	Sequence analysis [3]	23/24 [4]
	Gene-targeted deletion/duplication analysis [5]	1/24 [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Gauthier et al [2018], Seong et al [2018]
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. Partial duplication of *VPS13D* exons 24 to 30 was reported in one family [Gauthier et al 2018].

Clinical Characteristics

Clinical Description

To date, 19 individuals from 12 families have been identified with *VPS13D* movement disorder. This disorder is characterized by hyperkinetic movement (dystonia, chorea, or ataxia) of variable onset that can be associated with developmental delay. Onset ranging from birth to age 39 years has been reported. Eleven individuals presented in childhood with mainly motor delays and gait instability. Of those, two individuals had arm tremor, one had chorea, and one had torticollis at presentation. Eight individuals presented as young adults with gait difficulties caused by spastic ataxia or ataxia. In addition to gait ataxia, those presenting in young adulthood also had limb ataxia, dysarthria, and eye movement abnormalities (macro-saccadic oscillations, nystagmus, and saccadic pursuit). The disorder progresses to spastic ataxia or generalized dystonia, which can lead to loss of independent ambulation.

Developmental delay. Eleven individuals presented as children with mainly motor delay. However, four individuals have mild intellectual disability and two have developmental delay.

Movement disorder. Dystonia in reported individuals has included generalized dystonia, cervical dystonia, laryngeal dystonia, and bibrachial dystonia with tremor. Other movement disorders reported include chorea and, more rarely, stereotypies and myoclonus.

Pyramidal signs. Most individuals had hyperreflexia, extensor cutaneous plantar signs, and lower-limb (more than upper-limb) spasticity.

Peripheral neuropathy has been reported and is characterized by decreased or absent ankle reflexes (in 2 families) and abnormal deep sensory function. EMG and nerve conduction studies in a few individuals showed sensorimotor axonal neuropathy. *Pes cavus* is described in one individual. Several adults also had muscle atrophy and lower-limb weakness.

Oculomotor findings have included horizontal macro-saccadic pursuits and square wave jerks. These two entities are often confused and macro-saccadic oscillations are more typical of a cerebellar involvement. In addition, individuals presented with jerky pursuit, hypermetric saccades, and gaze-evoked nystagmus.

Seizures. Three individuals were reported to have childhood-onset seizures. No further details about seizure type or EEG findings were available. One individual was treated with phenobarbital and diazepam.

Brain MRI findings can be striking, but imaging results vary among individuals with *VPS13D* movement disorder. Reported findings include symmetric T_2-weighted and FLAIR hyperintensities in the caudate and putamen, hyperintense T_2-weighted and FLAIR signal abnormalities of periventricular and subcortical regions, hypointense basal ganglia (globus pallidus), thin corpus callosum [Gauthier et al 2018], and mild cerebellar atrophy, often involving the vermis [Seong et al 2018]. Imaging findings can resemble those seen in Leigh syndrome. Some individuals with *VPS13D* movement disorder have had normal brain MRI.

Muscle biopsy in one individual showed abnormal subsarcolemmal mitochondrial accumulation and mild lipidosis suggestive of mitochondrial disease. However, enzymatic analysis for respiratory chain function was normal [Gauthier et al 2018].

Other

- **Male infertility** associated with azoospermia or oligospermia was reported in two individuals.
- **Abnormal head size.** Both microcephaly (in 2 individuals) and macrocephaly (1 individual) have been described; no further details were available.
- **Hearing loss.** One individual was reported to have progressive hearing loss; no further details were available.

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations are known.

Nomenclature

VPS13D movement disorder was initially described as spinocerebellar ataxia with saccadic intrusions (SCASI) associated with the spinocerebellar ataxia, recessive type 4 (SCAR4) locus [Swartz et al 2002].

Prevalence

VPS13D movement disorder is rare and has been described in 19 individuals from 12 families. The families are mainly of European descent (French Canadian, German, Dutch, Slovenian, Italian) [Gauthier et al 2018, Seong et al 2018]. One Indonesian and one Egyptian family have also been described [Gauthier et al 2018, Seong et al 2018].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *VPS13D*.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of *VPS13D* Movement Disorder

DiffDx Disorder	Gene(s)	MOI	Clinical Features of the DiffDx Disorder	
			Overlapping w/*VPS13D* movement disorder	Distinguishing from *VPS13D* movement disorder
Spastic ataxia 1 [1]	*VAMP1*	AD	Spastic ataxic gait	• Adult onset • No dystonia • Normal brain MRI
Spastic ataxia 2 [1]	*KIF1C*	AR	Pediatric-onset spastic ataxic gait	No extrapyramidal involvement
Spastic ataxia 3 [1]	*MARS2*	AR	• Spastic ataxic gait • White matter abnormalities	Hearing impairment

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of the DiffDx Disorder	
			Overlapping w/*VPS13D* movement disorder	Distinguishing from *VPS13D* movement disorder
Spastic ataxia 4 [1]	*MTPAP*	AR	Spastic ataxia	Neuropathy w/loss of reflexes
Spastic ataxia 5 [1]	*AFG3L2*	AR	• Pediatric-onset spastic ataxia • Dystonia	• Myoclonic epilepsy • Oculomotor apraxia
Leigh syndrome [2]	Many	AR XL mt	Bilateral basal ganglia lesions	Cardiac or skeletal muscle involvement
HSP (incl SPG3A, SPG4, SPG7, SPG11) [3]	*ATL1* *SPAST* *SPG7* *SPG11*	AD AR	Pediatric-onset spastic gait	No cerebellar features
SCAR2 [1]	*PMPCA*	AR	Pediatric-onset ataxic gait	Cerebellar atrophy
SCAR7 [1]	*TPP1*	AR	Pediatric-onset ataxic gait	Posterior column involvement

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; HSP = hereditary spastic paraplegia; MOI = mode of inheritance; mt = mitochondrial
SCAR = spinocerebellar ataxia, autosomal recessive; XL = X-linked
1. See Hereditary Ataxia Overview.
2. See Mitochondrial DNA-Associated Leigh Syndrome and NARP.
3. These are the more common subtypes of hereditary spastic paraplegia with onset in childhood.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *VPS13D* movement disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *VPS13D* Movement Disorder

System/Concern	Evaluation	Comment
Musculoskeletal	Physiatry & PT eval	To ensure proper bracing & walking aids
Neurologic	Neurologic eval	EEG, EMG/NCS if clinically indicated
Eyes	Ophthalmologic eval	Eval for macrosaccadic intrusions
Endocrine	Fertility eval in males of reproductive age	Eval for male infertility, oligospermia
Miscellaneous/ Other	Developmental assessment	Incl eval of motor, speech/language, general cognitive, & vocational skills
	Consultation w/clinical geneticist &/or genetic counselor	

EEG = electroencephalogram; EMG = electromyogram; NCS = nerve conduction study; PT = physical therapy

Treatment of Manifestations

Seizures. Standardized treatment with anti-seizure medication (ASM) by an experienced neurologist. Many different ASMs may be effective; none has been demonstrated to be effective specifically for this disorder.

Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Spasticity. Recommendations for spasticity treatment include baclofen, tizanidine, benzodiazepines, dantrolene sodium, gabapentin, botulinum toxin injections, and intrathecal baclofen, which are established treatments in a similar condition, Friedreich ataxia [Corben et al 2014].

Dystonia. Treatment options for dystonia include trihexyphenidyl, botulinum toxin injections, benzodiazepines, baclofen, and levodopa [Jinnah & Factor 2015]. Deep brain stimulation has not been reported as a treatment for *VPS13D* hyperkinetic movement disorder.

Ataxia. No specific pharmacologic treatments for ataxia have been approved. Riluzole is probably effective in reducing ataxia symptoms (European Federation of Neurological Societies [EFNS] – level B rating) and varenicline is probably effective in improving gait and stance in individuals with spinocerebellar ataxia type 3 (SCA3) (EFNS – level B rating) [van de Warrenburg et al 2014]. Neither of these medications has been tested in individuals with *VPS13D* spastic ataxia.

A multidisciplinary team including occupational and physical therapists as well as a physiatrist is important in the care of individuals with this complex movement disorder.

Developmental Delay / Intellectual Disability Educational Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States (US); 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. In the US, early intervention is a federally funded program available in all states.

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.

Ages 5-21 years. In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21. Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

Gross motor dysfunction. Physical therapy is recommended to maximize mobility. Consider use of durable medical equipment 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. Assuming that the individual is safe to eat by mouth, feeding therapy, typically from an occupational or speech therapist, is recommended for affected individuals who have difficulty feeding as a result of poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

Surveillance

No specific surveillance guidelines exist. The authors recommend following standard ataxia and spasticity guidelines. Care should include regular visits to a neurologist and physiatrist. A speech therapist and a urologist should be consulted when indicated.

Table 4. Recommended Surveillance for Individuals with *VPS13D* Movement Disorder

System/Concern	Evaluation
Genitourinary	Ask about urinary urgency.
Musculoskeletal	Monitor contractures.
Neurologic	Monitor those w/seizures as clinically indicated; evaluate fall risk & gait stability.
Miscellaneous/Other	Monitor developmental progress & educational needs.

Agents/Circumstances to Avoid

No specific agents or circumstances are to be avoided aside from excessive alcohol use, which could worsen ataxia.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from developmental services and/or seizure management when appropriate.

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

Therapies Under Investigation

Studies are currently under way to understand the role of *VPS13D* in mitochondrial integrity and ultimately develop targeted treatments that can enhance mitochondrial function.

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

VPS13D movement disorder 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., carriers of one *VPS13D* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has 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. Unless an affected individual's reproductive partner also has *VPS13D* movement disorder or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *VPS13D*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *VPS13D* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *VPS13D* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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 *VPS13D* 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.

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020

Fax: 763-553-0167
Email: naf@ataxia.org
www.ataxia.org

- **NCBI Genes and Disease**
  Spinocerebellar ataxia

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. VPS13D Movement Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
VPS13D	1p36.22-p36.21	Intermembrane lipid transfer protein VPS13D	VPS13D gene homepage - vacuolar protein sorting 13 homolog D	VPS13D	VPS13D

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 VPS13D Movement Disorder (View All in OMIM)

607317	SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESSIVE 4; SCAR4
608877	VACUOLAR PROTEIN SORTING 13 HOMOLOG D; VPS13D

Gene structure. *VPS13D* (NM_015378.3) comprises 69 exons spanning approximately 281,000 nucleotides, and it encodes a 4,388-amino acid protein (NP_056193.2). See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. Pathogenic variants consist of missense, frameshift, protein-truncating, and splice site variants that are located throughout the gene. Although genotype-phenotype correlations have not been established, the more severe, early-onset hypotonia/dystonia with developmental delay phenotype is associated with a splice site variant or partial-gene duplication combined with a missense variant. However, a severely affected child with early-onset developmental delay and hypotonia was found to have biallelic missense variants (p.Thr865Ala; p.Gly1200Asp), one of which lies in a repeating coiled region. The only individual with a homozygous missense variant (c.12683G>A; p.Arg4228Gln) had onset of gait instability before age two years and mild intellectual disability [Gauthier et al 2018].

In all but one of the 12 reported families, affected individuals have compound heterozygous pathogenic variants with a loss-of-function variant and a presumptive milder missense or splice site variant [Gauthier et al 2018, Seong et al 2018]. No whole-gene duplication or deletion has been reported to date.

Table 5. *VPS13D* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.2593A>G	p.Thr865Ala	NM_015378.3 NP_056193.2
c.3599G>A	p.Gly1200Asp	
c.12683G>A	p.Arg4228Gln	

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.

Normal gene product. The 4,388-amino acid VPS13D protein is predicted to have several domains:

- N1 or chorein domain (aa 2-115)
- VPS13 2nd N-terminal domain (aa 137-356)
- Repeat coiled region domain (aa 613-901)
- UBA (ubiquitin-associated) domain (aa 2627-2679)
- SHR domain (aa 3276-3558)
- VPS13 C-terminal domain (aa 3983-4129)

The UBA domain is the only domain unique to VPS13D compared to the other VPS13 family members and is thought to be important for ubiquitin binding. Studies suggest that VPS13D is involved in mitochondrial fission and fusion [Anding et al 2018].

Abnormal gene product. Pathogenic variants are thought to cause disease by altering mitochondrial function. In most reported individuals, a loss-of-function variant is combined with a seemingly milder variant.

Abnormal mitochondrial morphology has been demonstrated in cell lines of affected individuals. Interestingly, *VPS13D* knockout models in *Drosophila* and mouse models are not compatible with life (embryonic lethal) [Anding et al 2018, Gauthier et al 2018, Seong et al 2018]. Furthermore, cell lines from affected individuals showed reduced mitochondrial function [Seong et al 2018].

Chapter Notes

Author Notes

The author recently joined the pediatric neurology team and the research center at CHU Sainte Justine, Montreal. As a clinician researcher specializing in pediatric movement disorders, she focuses on expanding our understanding of the genetic basis of pediatric movement disorders including Tourette syndrome and dystonia. Ongoing research includes investigating the role of mitochondria in the *VPS13D* movement disorder. This work will ultimately lead to improved diagnosis and care for children with complex movement disorders.

Acknowledgments

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