



## VPS13A Disease

Synonyms: Chorea-Acanthocytosis (ChAc), Choreoacanthocytosis

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## Summary

### Clinical characteristics

*VPS13A* disease, caused by *VPS13A* loss-of-function pathogenic variants, is characterized by a spectrum of movement disorders (chorea, dystonia, tics, sometimes parkinsonism); predominant orofacial choreic and dystonic movements and tics (with involuntary tongue protrusion on attempted swallowing, habitual tongue and lip biting resulting in self-mutilation, involuntary vocalizations); dysarthria and dysphagia; psychiatric, cognitive, and behavioral changes ("frontal lobe type"); seizures; and progressive neuromuscular involvement. Huntingtonism (triad of progressive movement disorder and cognitive and behavioral alterations) is a typical presentation. Phenotypic variability is considerable even within the same family, including for monozygotic twins. Mean age of onset is about 30 years. *VPS13A* disease runs a chronic progressive course and may lead to major disability within a few years. Some affected individuals are bedridden or wheelchair dependent by the

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third decade. Age at death ranges from 28 to 61 years; several instances of sudden unexplained death or death during epileptic seizures have been reported.

## Diagnosis/testing

The diagnosis of *VPS13A* disease is **established** in a proband with suggestive findings and biallelic pathogenic variants in *VPS13A* identified by molecular genetic testing.

## Management

*Treatment of manifestations:* There is no cure for *VPS13A* disease. Supportive treatment to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields of neurology, psychiatry, physiatry, physical therapy (PT), occupational therapy (OT), speech-language therapy, feeding, neuropsychology, and medical genetics. Pharmacotherapy for movement disorders may include dopamine antagonists/depleters such as atypical neuroleptics or tetrabenazine (or its derivatives) for limb and trunk dystonia and orofaciolingual dystonia (which may also benefit from botulinum toxin). Issues with mobility, activities of daily living, and need for assistive devices can be addressed by physiatry, PT, and OT. In persons with dysphagia, feeding assistance can include speech therapy and gastrostomy tube placement as needed to reduce weight loss and/or risk of aspiration. For dysarthria or mutism, therapy can include the use of technical means for augmentative and alternative communication, such as speech-generating devices. Seizure management can include use of phenytoin, clobazam, valproate, and levetiracetam. For psychiatric/behavioral issues, antidepressant or antipsychotic medications are used per conventional approaches.

*Surveillance:* Regular monitoring of existing manifestations, the individual's response to pharmacotherapy and other supportive care, and the emergence of new manifestations is recommended per the multidisciplinary treating specialists.

*Agents/circumstances to avoid:* Seizure-provoking circumstances (e.g., sleep deprivation, alcohol intake) and anticonvulsants that may worsen involuntary movements (e.g., carbamazepine, lamotrigine).

## Genetic counseling

*VPS13A* disease is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *VPS13A* 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 *VPS13A* 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.

## Diagnosis

"*VPS13A* disease" refers to the disorder commonly known as chorea-acanthocytosis; the genetically precise term "*VPS13A* disease" is preferred because the presence of chorea and/or acanthocytosis is neither necessary nor sufficient to diagnose the disorder [Walker & Danek 2021].

## Suggestive Findings

*VPS13A* disease **should be suspected** in probands with the following clinical, laboratory, and imaging findings and family history. "Red flag" findings are summarized in Table 1, and more detailed information follows the table.

**Table 1.** VPS13A Disease: Red Flag Findings

| VPS13A Disease: Red Flag Findings |  |
|-----------------------------------|--|
| <b>Clinical findings</b>          | Triad of progressive movement disorder (e.g., chorea, dystonia, in later stages parkinsonism), cognitive alterations, & behavioral alterations ("huntingtonism") |
|                                   | Prominent orofacial chorea, dystonia (feeding dystonia), & tics  |
|                                   | Epileptic seizures   |
|                                   | Weak to absent tendon stretch reflexes   |
| <b>Laboratory findings</b>        | HyperCKemia  |
|                                   | Presence of acanthocytes in peripheral blood <sup>1</sup>  |
| <b>Neuroimaging</b>               | Atrophy of the caudate on neuroimaging   |

1. Acanthocytosis is neither necessary nor sufficient to diagnose the disorder.

## Clinical Findings

Suggestive clinical findings include:

- Huntingtonism triad of progressive deterioration of movement, cognition, and behavior
- Progressive movement disorder
  - Commonly chorea and dystonia in early disease stages
  - Sometimes a parkinsonian syndrome, especially in later disease stages
  - Predominant orofacial choreic and dystonic movements and tics
    - Orofacial chorea
    - Unintended tongue protrusion on attempted swallowing (i.e., feeding dystonia) [Bader et al 2010, Paucar et al 2015]
    - Habitual tongue and lip biting with self-mutilation [Walker et al 2006]
    - Involuntary vocalizations
    - Bruxism
- Dysarthria and dysphagia with resultant weight loss
- Progressive cognitive and behavioral changes (of "frontal lobe type," i.e., executive dysfunction, impaired social cognition) [Walterfang et al 2008]
- Psychosis
- Seizures, which can be the initial manifestation; sometimes suggestive of a familial temporal lobe epilepsy [Al-Asmi et al 2005, Scheid et al 2009]
- Progressive neuromuscular involvement characterized by distal muscle wasting and weakness. This can be subclinical (only creatine kinase [CK] elevation). Electromyography commonly reveals chronic denervation and, in some instances, also myopathic changes [Vaisfeld et al 2021].
- Peripheral neuropathy with impaired deep tendon reflexes and vibration sense contributing to muscle weakness and atrophy. Electrophysiologic tests demonstrate a sensory or sensorimotor axonopathy.

## Family History

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

## Supportive Laboratory Findings

### Muscle and liver enzymes, markers of hemolysis

- Increased serum concentration of muscle CK is observed in the majority of individuals.
- Less commonly, serum concentrations of aspartate transaminase and alanine transaminase are increased.

- Levels of haptoglobin can be reduced and levels of lactate dehydrogenase can be increased due to chronic (subclinical) hemolysis [Rampoldi et al 2002].

**Acanthocytosis.** Acanthocytes usually comprise 5%-50% of the red blood cell population in individuals with *VPS13A* disease; however, in some cases, acanthocytes may be absent [Bayreuther et al 2010] or may appear only late in the disease course [Sorrentino et al 1999].

Note: (1) The proportion of acanthocytes does not correlate with disease severity. (2) Presence of acanthocytes is neither "specific" nor "sensitive" for the diagnosis of *VPS13A* disease. (3) The following methods, which are appropriate for testing, are not ubiquitously available.

- A standard routine procedure is to dilute blood 1:1 with 0.9% saline containing 10 U/mL heparin, and examine it using phase-contrast microscopy after 30 minutes' incubation in a shaker and wet blood smear preparation. In control samples, fewer than 6.3% of cells are speculated [Storch et al 2005].

Note: (1) Dry blood smears seem inadequate [Alawneh et al 2012]. (2) The suggestion to perform blood smears on three (or more) occasions [Sokolov et al 2012] in order to exclude acanthocytosis is unfounded.

- Scanning electron microscopy of erythrocytes fixed with glutaraldehyde is probably the most reliable method of detecting acanthocytes but is not routinely available. Distinguishing acanthocytes from erythrocytes of other shapes can be difficult, as their definitions may appear insufficient in the individual case [Peikert et al 2022b]. Although use of artificial neural networks to discriminate acanthocytes from other abnormally shaped erythrocytes might be useful [Simionato et al 2021, Peikert et al 2022b], this is not yet clinically available.
- Decreased erythrocyte sedimentation rate may emerge as a simpler indirect indicator of acanthocytosis [Darras et al 2021].

Detection of **absent or marked reduction of VPS13A protein** (formerly chorein). See Molecular Genetics, ***VSP13A*-specific laboratory technical considerations.**

## Neuroimaging

Cranial CT and brain MRI reveal atrophy of the caudate nuclei with dilatation of the anterior horns of the lateral ventricles. The extent of basal ganglia atrophy is best appreciated on sections in the frontal plane. MRI may show T<sub>2</sub>-weighted signal increase in the caudate and putamen; occasionally iron deposition may be observed [Lee et al 2011, Kaul et al 2013].

In addition to the caudate nucleus, the putamen also shows significant and marked reduction in volume compared with controls [Walterfang et al 2011b].

Hippocampal sclerosis and atrophy are also frequently seen [Al-Asmi et al 2005, Huppertz et al 2008, Scheid et al 2009, Mente et al 2017].

There may be mild generalized cerebral cortical atrophy.

Although cerebellar atrophy has been reported in a few individuals, to date genetic diagnoses have not been established in these individuals [Tsai et al 1997, Katsube et al 2009, Jiang et al 2012, Sharma et al 2014].

## Establishing the Diagnosis

The diagnosis of *VPS13A* disease is **established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *VPS13A* identified by molecular genetic testing (see Table 2).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can

be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *VPS13A* variants of uncertain significance (or of one known *VPS13A* pathogenic variant and one *VPS13A* variant of uncertain significance) does not establish or rule out the diagnosis.

**Molecular genetic testing approaches.** Gene-targeted testing requires that the clinician determines which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *VPS13A* disease 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 generalized chorea and/or epileptic seizures may be more likely to be diagnosed using genomic testing (see Option 2).

Note: Single-gene testing (sequence analysis of *VPS13A*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

## Option 1

**A chorea/dystonia multigene panel** that includes *VPS13A* and other genes of interest (see Differential Diagnosis) may be considered 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 genes are likely involved. **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 2.** Molecular Genetic Testing Used in *VPS13A* Disease

| Gene <sup>1</sup> | Method   | Proportion of Pathogenic Variants <sup>2</sup> Detectable by Method |
|-------------------|--|---|
| <i>VPS13A</i>     | Sequence analysis <sup>3</sup>                           | 70%-90% <sup>4</sup>  |
|                   | Gene-targeted deletion/duplication analysis <sup>5</sup> | 10%-30% <sup>6</sup>  |

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. Rampoldi et al [2001], Dobson-Stone et al [2002], Tomiyasu et al [2011], Nishida et al [2019], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

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. Deletion of exons 60-61 seems common in the Japanese population [Ueno et al 2001, Tomiyasu et al 2011], and deletion of exons 70-73 has been observed in the French Canadian population [Dobson-Stone et al 2005]; therefore, the proportion of pathogenic variants detected by sequence or gene-targeted deletion/duplication analysis varies by population.

## Clinical Characteristics

### Clinical Description

*VPS13A* disease is characterized by a progressive movement disorder, orofacial choreic and dystonic movements and tics, dysarthria and dysphagia, progressive cognitive and behavioral changes, psychosis, seizures, and progressive neuropathy and myopathy. Phenotypic variability is considerable and requires consideration of the diagnosis in a wide range of clinical conditions (including epilepsy, myopathy, and Tourette syndrome), with the huntingtonism triad as one typical presentation ("Huntington disease-like"). Acanthocytes may be found in blood smears, but the relevance of their presence or absence has been overstated (see Nomenclature). Mean age of onset in *VPS13A* disease is about age 30 years. *VPS13A* disease runs a chronic progressive course and may lead to major disability within a few years. Table 3 provides an overview of the major clinical findings.

**Table 3.** Select Features of *VPS13A* Disease

| Feature   | Relative Prevalence                         | Comment   |   |
|---|---|---|---|
| <b>Limb &amp; trunk chorea</b>                          | +++   | Most prominent in early disease stages  |   |
| <b>Prominent orofacial chorea, dystonia, &amp; tics</b> | <b>Orofacial chorea</b>                     | +++   |   |
|   | <b>Tongue protrusion / feeding dystonia</b> | ++  | Suggests diagnosis when present   |
|   | <b>Tongue &amp; lip biting</b>              | ++  | Highly suggestive for diagnosis when present; may be caused by behavioral compulsion or tic |
|   | <b>Involuntary vocalizations</b>            | ++  | Typically meet criteria for tics  |
| <b>Parkinsonism</b>                                     | +   | Typically more prevalent at later disease stages, but can also occur early or be presenting feature |   |
| <b>Dysphagia</b>  | +++   |   |   |
| <b>Dysarthria</b>                                       | +++   |   |   |
| <b>Cognitive decline</b>                                | ++  | Variable  |   |

Table 3. continued from previous page.

| Feature                               | Relative Prevalence | Comment   |
|---------------------------------------|---------------------|---|
| <b>Behavioral/psychiatric changes</b> | ++                  | Variable; compulsive behaviors can be prominent             |
| <b>Epilepsy</b>                       | ++                  | Can predate other features                                  |
| <b>Axonal neuropathy</b>              | ++                  | Often mild, but diminished tendon reflexes are a "red flag" |
| <b>Myopathy</b>                       | +                   | Often mild, yet some persons have severe weakness/atrophy   |
| <b>Oculomotor abnormalities</b>       | +                   | Rarely conspicuous  |

+++ = very common; ++ = common; + = uncommon

**Limb and trunk chorea** is common and can include flinging arm and leg movements, shoulder shrugs, and pelvic thrusts. Stance and gait are typically affected by involuntary movements such as foot or leg chorea and dystonia. Violent trunk spasms may occur with sudden flexion or extension movements; head drops and head banging with a risk of head and neck injury can also occur [Schneider et al 2010].

A peculiar "rubber person gait" may appear due to a sudden lapse of muscle tone in the trunk or legs [Thomas & Jankovic 2003, Termsarasab & Frucht 2018] and may be interpreted as being functional (psychogenic). Impaired postural reflexes may result in falls, as may sudden buckling of knees [Yamamoto et al 1982] and equinovarus foot deformity, the latter related to dystonia as well as atrophy of the peroneal muscles.

The choreic syndrome gradually evolves into predominant parkinsonism with dystonia in about one third of affected individuals. Increased rigid muscle tone, rest tremor, impaired postural reflexes, bradykinesia, facial masking, and micrographia may appear. Occasionally, parkinsonism may be the presenting manifestation.

**Orofacial chorea, dystonia, and tics.** Predominance of orofacial chorea is very common. The involuntary movements that affect the face, mouth, tongue, pharynx, and larynx are the most characteristic.

Action-induced dystonic protrusion of the tongue while feeding is typical and causes the tongue to push the food out of the mouth. "Feeding dystonia" is the term commonly applied for this pattern of movement [Bader et al 2010].

Continuous tongue and lip biting caused by behavioral compulsion or tic/chorea can lead to self-mutilation, which can result in serious and challenging infections of the oral region. Affected individuals typically try to avoid this by keeping an object such as a handkerchief between the teeth, which may function either as a sensory trick to reduce dystonia or as a mechanical obstacle.

Involuntary vocalizations (vocal tics) are present in about two thirds of affected individuals [Saiki et al 2004]. The variety of described vocalizations (tics) include clicking, gasping, sighing, whistling, blowing, sucking, grunting noises, perseveration of word elements or phrases, and continuous humming.

There may be habitual teeth grinding (bruxism), spitting, or involuntary belching [Wihl et al 2001, Sibon et al 2004].

**Dysphagia.** The oral phase of swallowing is often impaired (while pharyngeal and esophageal phases seem intact), resulting in dysphagia with drooling and reduced caloric intake and potentially severe weight loss.

**Dysarthria** is common; slurred speech may be a presenting manifestation. In the course of VPS13A disease, communication may become limited to grunting or whispering. The hyperkinetic orofacial state may eventually progress to mutism [Aasly et al 1999].



**Cognitive decline** is common. Memory and executive functions, such as the ability to sustain concentration over time, planning, and modifying behavior, seem particularly affected. These findings resemble those of frontotemporal dementia [Danek et al 2004].

**Behavioral/psychiatric changes.** Changes in personality and behavior along with psychopathologic abnormalities occur in about two thirds of affected individuals [Danek et al 2004]. Apathy, depression, and bradyphrenia (slowness of thought) can be seen, but hyperactivity, irritability, distractibility, and emotional instability can also be observed. Individuals may behave in a disinhibited manner that can include sexual disinhibition. They may show obsessive-compulsive behavior including trichotillomania [Lossos et al 2005, Walterfang et al 2008] and self-inflicted chronic excoriations on the head [Walker et al 2006]. Loss of insight, self-neglect, anxiety, paranoia, aggression against others, and autoaggression are observed. Suicide and suicidal ideation are part of the disease spectrum [Sorrentino et al 1999].

**Epilepsy** is observed in almost half of affected individuals and can be the initial manifestation [Al-Asmi et al 2005]. It usually manifests as generalized tonic-clonic seizures and is probably secondarily generalized, for example, from temporal lobe foci [Scheid et al 2009, Bader et al 2011]. There may be prolonged states of memory impairment and confusion most likely corresponding to nonconvulsive seizures [Bader et al 2011, Mente et al 2017].

EEG may show temporal spikes, both interictally and with seizure onset [Scheid et al 2009].

**Neuropathy and myopathy.** Nerve and muscle involvement resulting in ankle areflexia is seen in almost all affected individuals and muscle atrophy and weakness in at least half of affected individuals. Symptoms suggestive of motor neuron disease have been reported [Neutel et al 2012]. Primary myopathic alterations can also be detected [Vaisfeld et al 2021]. Sensory loss is usually slight or may only be detected as reduced vibration sense. Pyramidal tract signs are usually absent, but bilateral extensor plantar responses were noted in one individual [Neutel et al 2012], and upper motor neuron involvement was found post mortem in another [Miki et al 2010].

**Ocular motor abnormalities** have been noted on occasion, with apraxia of lid opening, intermittent blepharospasm, frequent square wave jerks, slowing of saccades (mainly vertical), and reduced saccadic range [Gradstein et al 2005].

### Other clinical findings

- Dilated cardiomyopathy is rare [Kageyama et al 2007]; however, mild cardiac involvement may be more common than previously thought [Quick et al 2021].
- Splenomegaly is occasionally noted and may be caused by erythrocyte dysfunction and hemolysis, as shown by reduced levels of hemoglobin and haptoglobin.
- Hepatomegaly may be present, along with elevated liver enzymes; to date the clinical significance of this is unclear.
- Autonomic nervous system dysfunction was described in one affected individual [Kihara et al 2002].
- In a few individuals, sleep disturbance was demonstrated by polysomnography [Dolenc-Groselj et al 2004].
- Chance co-occurrences with other conditions may complicate the clinical diagnostic process [Anheim et al 2010].

### Other studies

- **MR spectroscopy** may reveal abnormal proton spectra from the basal ganglia [Niemelä et al 2020].
- **Tracer imaging studies** of the type presently available in most major medical centers may support a suspicion of *VPS13A* disease. Regional cerebral glucose metabolism, measured using <sup>18</sup>F-fluorodeoxy-



glucose positron emission tomography, shows striatal hypometabolism [Ehrlich & Walker 2017, Niemelä et al 2020].

- **Imaging of dopaminergic and serotonergic transmission.** Although ratios of binding to striatal dopamine transporters and serotonin transporters in the hypothalamus midbrain area as determined using (123)I-beta-CIT-SPECT fell within the normal ranges in two affected individuals, a significant difference in binding to presynaptic striatal dopamine transporters was observed [Müller-Vahl et al 2007]. Presynaptic dopaminergic deficiency was identified in some individuals [Niemelä et al 2020].
- **CT scanning of leg muscles** reveals a selective pattern of symmetric fatty change [Ishikawa et al 2000].
- **Cerebrospinal fluid studies**, when reported, have been normal.
- **Serum neurofilament light chain** is significantly increased in affected individuals compared to healthy controls [Peikert et al 2020], as it is in many other neurodegenerative disorders.
- **Peripheral nerve biopsy** has demonstrated loss of myelinated fibers, particularly those of larger diameter. Unmyelinated fibers may also be affected. Signs of regeneration have been observed [Sorrentino et al 1999].
- **Muscle biopsy** revealed findings indicative of both neurogenic and myopathic atrophy [Vaisfeld et al 2021]. "Nemaline" rods in muscle have been reported, although their exact composition is unknown [Tamura et al 2005].

**Neuropathology.** Systematic neuropathologic studies are still lacking. Click [here](#) (pdf) for more information.

**Prognosis.** Life expectancy is reduced. Age at death ranges from 28 to 61 years.

Several instances of sudden unexplained death or death during epileptic seizures have been reported [Walker et al 2019].

## Genotype-Phenotype Correlations

To date, available data are inconclusive with regard to genotype-phenotype correlations involving clinical manifestations and laboratory findings for *VPS13A* disease.

## Nomenclature

To incorporate the genetic etiology of the disorder, Walker & Danek [2021] proposed that chorea-acanthocytosis be renamed *VPS13A* disease. The term "*VPS13A* disease" is preferred because the presence of chorea and/or acanthocytosis is neither necessary nor sufficient to diagnose the disorder [Walker & Danek 2021].

"Neuroacanthocytosis" – a nonspecific umbrella term that may refer to any disorder with neurologic abnormalities and acanthocytosis (including [McLeod neuroacanthocytosis syndrome](#)) – should be used with great caution and is not a substitute for a definitive genetic diagnosis [Walker & Danek 2021].

The term "Levine-Critchley syndrome" is obsolete [Velayos-Baeza et al 2011; Danek et al, unpublished data].

Other outdated terms include "chorea-amyotrophy-acanthocytosis syndrome" and "familial amyotrophic chorea with acanthocytosis."

## Prevalence

The number of individuals with *VPS13A* disease worldwide is estimated to be approximately 1:1,000,000 [Jung et al 2011].

The following observations might speak to founder effects; however, to date the overall prevalence of the following variants and *VPS13A* disease in these populations is unknown (see Table 8).

- An intragenic deletion of exons 60-61 was observed in several Japanese families [Ueno et al 2001, Tomiyasu et al 2011].
- An intragenic deletion of exons 70-73 was observed in French Canadian families [Dobson-Stone et al 2005].
- The variant c.2343delA was reported in three Jewish families from Djerba Island, Tunisia.

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *VPS13A*.

## Differential Diagnosis

Because of the protean manifestations of *VPS13A* disease, a wide range of disorders needs to be considered in the differential diagnosis, including the general categories of parkinsonian syndromes (see [Parkinson Disease Overview](#)), [hereditary dystonia](#), choreiform and other movement disorders, epilepsy disorders, and neuromuscular disorders.

**Table 4.** Genes of Interest in the Differential Diagnosis of *VPS13A* Disease

| Gene(s)                       | Disorder  | MOI | Features of Disorder   |  |
|-------------------------------|---|-----|--|--|
|                               |   |     | Overlapping w/ <i>VPS13A</i> Disease   | Distinguishing from <i>VPS13A</i> Disease  |
| <i>ANGPTL3</i><br><i>APOB</i> | Hypobetalipoproteinemia (See <a href="#">APOB-Related Familial Hypobetalipoproteinemia</a> .) | AR  | <ul style="list-style-type: none"> <li>• Acanthocytosis</li> <li>• Dysarthria, neuropathy, &amp; areflexia</li> </ul>  | <ul style="list-style-type: none"> <li>• Absence of basal ganglia movement disorder</li> <li>• Hallmark findings of pigmentary retinopathy, vitamin E deficiency, &amp; steatorrhea</li> <li>• Spinocerebellar syndrome &amp; sensorimotor neuropathy</li> </ul> |
| <i>ATN1</i>                   | <a href="#">DRPLA</a>   | AD  | <ul style="list-style-type: none"> <li>• Choreoathetosis</li> <li>• Epilepsy</li> </ul>  | Ataxia   |
| <i>ATP7B</i>                  | <a href="#">Wilson disease</a>  | AR  | <ul style="list-style-type: none"> <li>• ↑ liver enzymes</li> <li>• Tremor, poor coordination, loss of fine motor control, chorea, &amp; choreoathetosis OR rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement)</li> <li>• Psychiatric disturbance (depression, neurotic behaviors, disorganization of personality &amp;, occasionally, intellectual deterioration)</li> </ul> | <ul style="list-style-type: none"> <li>• Low serum copper &amp; ceruloplasmin concentrations &amp; ↑ urinary copper excretion, esp after chelator challenging</li> <li>• Prominent MRI abnormalities during disease progression</li> </ul>                       |
| <i>ELAC2</i>                  | Combined oxidative phosphorylation deficiency-17 (COXPD17) (OMIM 615440)                      | AR  | Chorea, psychosis, acanthocytosis <sup>1</sup>   | Apart from a single adult case w/ <i>ELAC2</i> pathogenic variant, <sup>1</sup> clinical findings & presentation age (early childhood) in COXPD17 differ greatly from <i>VPS13A</i> disease.   |

Table 4. continued from previous page.

| Gene(s)      | Disorder  | MOI | Features of Disorder   |  |
|--------------|---|-----|--|--|
|              |   |     | Overlapping w/ <i>VPS13A</i> Disease   | Distinguishing from <i>VPS13A</i> Disease  |
| <i>HPRT1</i> | Lesch-Nyhan disease (See <a href="#">HPRT1 Disorders.</a> )   | XL  | <ul style="list-style-type: none"> <li>Cognitive &amp; behavioral disturbances</li> <li>Self-injurious behavior (biting of lips, cheeks fingers, hands; head/limb banging)</li> <li>Neurologic dysfunction (dystonia, choreoathetosis, opisthotonos)</li> </ul>  | <ul style="list-style-type: none"> <li>Age at manifestation (early childhood) very different from <i>VPS13A</i> disease</li> <li>Hyperuricemia</li> </ul>  |
| <i>HTT</i>   | <a href="#">Huntington disease (HD)</a>   | AD  | <ul style="list-style-type: none"> <li>Chorea syndrome, changes of personality &amp; behavior, &amp; imaging findings in HD &amp; <i>VPS13A</i> disease are almost identical.</li> <li>Parkinsonism is typical for juvenile HD (Westphal variant) &amp; transition to parkinsonism is not uncommon in late-stage HD.</li> </ul>            | <ul style="list-style-type: none"> <li>Seizures are much more common in <i>VPS13A</i> disease than in HD.</li> <li>↑ serum concentrations of CK or liver enzymes &amp; acanthocytosis are unusual for HD.</li> <li>↓ ankle reflexes are more prevalent in <i>VPS13A</i> disease.</li> <li>The neuropathology of HD is more widespread &amp; involves the cerebral cortex.</li> </ul> |
| <i>JPH3</i>  | <a href="#">Huntington disease-like 2 (HDL2)</a>  | AD  | Huntingtonism typically presenting in midlife w/progression to death over 10-20 yrs  | <ul style="list-style-type: none"> <li>Acanthocytes are not present in great majority of affected persons.</li> <li>Serum CK is normal.</li> <li>Myopathy &amp; seizures are absent.</li> <li>HDL2 has been described exclusively in persons w/ African ancestry.</li> </ul>   |
| <i>MTTP</i>  | <a href="#">Abetalipoproteinemia</a>  | AR  | <ul style="list-style-type: none"> <li>Acanthocytosis</li> <li>Dysarthria, neuropathy, &amp; areflexia</li> </ul>  | <ul style="list-style-type: none"> <li>Hallmark findings: presence of pigmentary retinopathy, vitamin E deficiency, steatorrhea, &amp; absence of basal ganglia movement disorder</li> <li>Spinocerebellar syndrome &amp; sensorimotor neuropathy</li> </ul>   |
| <i>PANK2</i> | <a href="#">Pantothenate kinase-associated neurodegeneration (PKAN) (See also Neurodegeneration with Brain Iron Accumulation Disorders Overview.)</a> | AR  | <ul style="list-style-type: none"> <li>Early childhood onset of progressive dystonia, dysarthria, rigidity, &amp; choreoathetosis</li> <li>"Atypical" presentation: onset at age &gt;10 yrs, prominent speech defects, psychiatric disturbances, &amp; more gradual progression of disease</li> <li>Acanthocytes often observed</li> </ul> | <ul style="list-style-type: none"> <li>"Eye of the tiger" MRI finding (identified on transverse images of globus pallidus as central region of hyperintensity surrounded by rim of hypointensity) in PKAN</li> <li>Much younger age of disease onset</li> </ul>  |

Table 4. continued from previous page.

| Gene(s)   | Disorder   | MOI | Features of Disorder   |   |
|-----------|--|-----|--|---|
|           |  |     | Overlapping w/ <i>VPS13A</i> Disease   | Distinguishing from <i>VPS13A</i> Disease   |
| <i>XK</i> | McLeod neuroacanthocytosis syndrome (also referred to as McLeod syndrome [MLS] or <i>XK</i> disease <sup>2</sup> ) | XL  | <ul style="list-style-type: none"> <li>• CNS manifestations (movement disorder, cognitive impairment, &amp; psychiatric symptoms)</li> <li>• Neuromuscular manifestations (mostly subclinical sensorimotor axonopathy, muscle weakness, or atrophy)</li> <li>• Red blood cell acanthocytosis &amp; compensated hemolysis</li> <li>• Usually later onset in MLS of some features shared w/ <i>VPS13A</i> disease (e.g., huntingtonism, feeding dystonia, &amp; head drops)</li> </ul> | <ul style="list-style-type: none"> <li>• The McLeod blood group phenotype<sup>3</sup> distinguishes MLS from <i>VPS13A</i> disease (in which Kell blood group antigen expression is normal).</li> <li>• Malignant arrhythmias &amp; cardiomyopathy are common.</li> </ul> |

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; MOI = mode of inheritance; XL = X-linked

1. Paucar et al [2018]

2. Because the term "neuroacanthocytosis" refers to several genetically and phenotypically distinct disorders, the terms McLeod syndrome or *XK* disease are preferred by the authors [Walker & Danek 2021; Authors, personal observation].

3. Hematologically, MLS is defined as a specific blood group phenotype (named after the first proband, Hugh McLeod; "McLeod blood group phenotype") that results from absent expression of the Kx erythrocyte antigen and weakened expression of Kell blood group antigens. Note: Transfusions of Kx-positive blood products should be avoided in persons w/the McLeod blood group phenotype. Kx-negative blood or, if possible, banked autologous or homologous blood should be used for transfusions.

**Tourette syndrome** is often diagnosed during initial stages of *VPS13A* disease [Saiki et al 2004, Müller-Vahl et al 2007, Walterfang et al 2008, Walterfang et al 2011a]. Its picture of motor and vocal tics, obsessive-compulsive behavior, and impaired impulse control can resemble the *VPS13A* disease spectrum.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *VPS13A* disease, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 5.** Recommended Evaluations Following Initial Diagnosis in Individuals with VPS13A Disease

| System/Concern  | Evaluation  | Comment   |
|---|---|---|
| <b>Neurologic</b>                                     | Assess for movement disorder(s).  | <ul style="list-style-type: none"> <li>Apply appropriate scales according to predominant movement disorder (e.g., for chorea UHDRS-TMS, for dystonia UDRS or FMDRS, for parkinsonism MDS-UPDRS Part III).</li> <li>Perform structural brain imaging (if not performed previously or not available for review); MRI preferred.</li> </ul>  |
|   | Assess for seizures.  | <ul style="list-style-type: none"> <li>Assess seizure semiology &amp; frequency.</li> <li>Perform structural brain imaging (if not performed previously or not available for review); MRI preferred to assess for hippocampal sclerosis or other epileptogenic lesions.</li> <li>Perform EEG.<sup>1</sup></li> </ul>  |
|   | Assess for neuromuscular involvement.   | <ul style="list-style-type: none"> <li>Assess muscle weakness or atrophy, DTRs, gross motor &amp; fine motor skills, mobility, ADL, &amp; need for adaptive devices.</li> <li>Determine serum CK, ALT, AST, &amp; LDH.</li> <li>Perform EMG &amp; NCV studies.</li> </ul>   |
| <b>Mobility, ADL, &amp; need for adaptive devices</b> | Eval by physiatrist, PT, OT   | <ul style="list-style-type: none"> <li>Assess need for protective devices (to counteract head banging &amp; repeated falls).</li> <li>Assess living situation (to ↓ risk of falls).</li> <li>Assess need for AFOs for foot drop secondary to muscle weakness/dystonia.</li> </ul>   |
| <b>Cognitive</b>                                      | To incl motor & speech-language eval & general cognitive skills eval                                  | <ul style="list-style-type: none"> <li>Assess executive deficits &amp; memory.</li> <li>Perform formal neuropsychological eval &amp;/or short tests such as MoCA.<sup>2</sup></li> <li>Consider involving OT &amp; neuropsychologist if needed.</li> </ul>  |
| <b>Behavioral/ Psychiatric</b>                        | Assess for OCD, personality change, anxiety, depression, bipolar disorder, schizo-affective disorder. | <ul style="list-style-type: none"> <li>Perform standardized psychiatric assessment; eval of symptom-oriented psychotherapeutic &amp; psychopharmacologic interventions.</li> <li>Consider involving psychiatry specialist, psychologist, &amp;/or neuropsychologist if needed.</li> </ul>   |
| <b>Feeding/ Dysphagia/ Dysarthria</b>                 | <ul style="list-style-type: none"> <li>Feeding/nutritional assessment</li> <li>Speech eval</li> </ul> | <ul style="list-style-type: none"> <li>Assess feeding/tongue protrusion dystonia.</li> <li>Consider clinical &amp;/or fiberoptic &amp;/or radiologic feeding eval.</li> <li>Nutrition is a significant issue; assess body weight regularly.</li> <li>Assess possible dysarthria &amp; communication skills, incl need for alternative means of communication (e.g., text-to-speech computer technology).</li> </ul> |
| <b>Cardiac</b>  | Assess for cardiomyopathy, arrhythmia.  | <ul style="list-style-type: none"> <li>Perform echocardiography, EKG, &amp; cardiac biomarker analysis (e.g., troponin T/I, pro-BNP).</li> <li>If available, perform cardiac MRI.</li> </ul>  |
| <b>Liver/Spleen</b>                                   | Assess for hepatosplenomegaly.  | <ul style="list-style-type: none"> <li>Perform abdominal ultrasound exam.</li> </ul>  |
| <b>Genetic counseling</b>                             | By genetics professionals <sup>3</sup> for facilitation of personal/medical decision making           | <ul style="list-style-type: none"> <li>Inform affected persons &amp; families re nature of condition, MOI, implications of disease.</li> </ul>  |

Table 5. continued from previous page.

| System/Concern                        | Evaluation  | Comment   |
|---------------------------------------|---|---|
| <b>Family support &amp; resources</b> | Assess need for: <ul style="list-style-type: none"> <li>Community &amp;/or online resources;</li> <li>Support by/for family, caregiver, or others.</li> </ul> | <ul style="list-style-type: none"> <li>Patient advocacy organization contact may be beneficial.</li> <li>Home nursing can be considered to ↓ burden to patient &amp; family.</li> </ul> |

ADL = activities of daily living; AFOs = ankle-foot orthoses; ALT = alanine transaminase; AST = aspartate transaminase; BNP = B-type natriuretic peptide; CK = creatine kinase; DTRs = deep tendon reflexes; EKG = electrocardiogram; EEG = electroencephalogram; EMG = electromyography; FMDRS = Fahn-Marsden Dystonia Rating Scale; LDH = lactate dehydrogenase; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; MOI = mode of inheritance; NCV = nerve conduction velocity; OCD = obsessive-compulsive disorder; OT = occupational therapist; PT = physical therapist; UDRS = Unified Dystonia Rating Scale; UHDRS-TMS = Unified Huntington Disease Rating Scale Total Motor Score

1. Early recognition and treatment of seizures are important, as potential complications may be severe and could cause premature death [Walker et al 2019].

2. Nasreddine et al [2005]

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

## Treatment of Manifestations

There is no cure for *VPS13A* disease.

**Supportive care** to improve quality of life, maximize function, and reduce complications is recommended, as for other disorders with similar findings. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6).

**Table 6.** Treatment of Manifestations in Individuals with *VPS13A* Disease

| Manifestation/Concern                         | Treatment  | Considerations/Other   |
|---|--|--|
| <b>Limb &amp; trunk chorea</b>                | <ul style="list-style-type: none"> <li>Dopamine depletors (i.e., VMAT2 inhibitors) or dopamine D2 receptor antagonists such as atypical neuroleptics should be offered.</li> <li>Amantadine may be beneficial.<sup>1</sup></li> </ul>  | <ul style="list-style-type: none"> <li>Monitor for side effects of parkinsonism &amp; depression.<sup>2</sup></li> <li>Neuroleptics can also help w/ behavioral issues.</li> </ul>   |
| <b>Orofacial chorea, dystonia, &amp; tics</b> | <ul style="list-style-type: none"> <li>Botulinum toxin may help ↓ the orolingual dystonia that interferes w/eating.<sup>3</sup></li> <li>Orofacial chorea &amp; tics can be ↓ by dopamine depletors &amp; dopamine D2 receptor antagonists.</li> </ul>   | <ul style="list-style-type: none"> <li>Keep object (e.g., handkerchief) in mouth to ↓ damage to lips &amp; tongue from involuntary biting.</li> <li>Use of mouth guard to prevent teeth grinding can also ↓ psychiatric manifestations.<sup>4</sup></li> </ul> |
| <b>Generalized dystonia</b>                   | <ul style="list-style-type: none"> <li>Standard medications for dystonia can be tried (e.g., benzodiazepines, anti-cholinergics).</li> <li>Amantadine may be beneficial.<sup>1</sup></li> <li>Physiotherapy (See <b>Mobility, ADL, &amp; need for adaptive devices</b> below.)</li> <li>Deep brain stimulation of globus pallidus pars interna may improve chorea &amp; dystonia.<sup>5</sup></li> </ul> | Consider local injections of botulinum toxin for dystonic equinovarus deformity.   |
| <b>Parkinsonism</b>                           | <ul style="list-style-type: none"> <li>Dopaminergic agents can be tried (w/caution due to psychotropic side effects).</li> <li>Physiotherapy</li> </ul>  | Medications are often not effective.   |

Table 6. continued from previous page.

| Manifestation/Concern                                 | Treatment  | Considerations/Other  |
|---|--|---|
| <b>Mobility, ADL, &amp; need for adaptive devices</b> | <ul style="list-style-type: none"> <li>• Physiatry to address need for adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs)</li> <li>• PT (balance exercises, gait training, muscle strengthening) to maintain mobility &amp; function</li> <li>• OT to optimize ADL</li> <li>• Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)</li> </ul> |   |
| <b>Dysphagia/Feeding</b>                              | <ul style="list-style-type: none"> <li>• Speech/swallowing therapy</li> <li>• Gastrostomy tube placement</li> </ul>  | To be considered early to prevent weight loss   |
| <b>Dysarthria</b>                                     | Speech-language therapy  | W/progression to mutism, eval for computer-assisted speech systems is appropriate.  |
| <b>Cardiac</b>  | Per treating cardiologist  |   |
| <b>Seizures</b>                                       | Phenytoin, clobazam, valproate, & levetiracetam are reported to be effective.  |   |
| <b>Cognitive decline</b>                              | Occupational &/or neuropsychological therapy   |   |
| <b>Behavioral/Psychiatric</b>                         | Use of psychiatric medications such as antidepressant or antipsychotic medications is based on conventional approaches.  | Behavioral compulsions, particularly those resulting in self-harm, should be aggressively treated w/antidepressant medications that target obsessive-compulsive symptoms. |
| <b>Tics</b>   | Levetiracetam <sup>6</sup> dopamine depleters & dopamine D2 receptor blockers  |   |
| <b>Family support &amp; resources</b>                 | See Resources.   |   |

ADL = activities of daily living; VMAT2 = vesicular monoamine transporter-2

1. Zayas & Walker [2022]
2. Borchardt et al [2000]
3. Schneider et al [2006], Paucar et al [2015], Walker [2015]
4. Fontenelle & Leite [2008]
5. Miquel et al [2013], He et al [2022]
6. Lin et al [2006]

## Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the following evaluations are recommended (see Table 7).

Table 7. Recommended Surveillance for Individuals with VPS13A Disease

| System/Concern  | Evaluation  | Frequency                        |
|---|---|----------------------------------|
| <b>Movement disorders</b>                             | Assess response to & evaluate dosage of dopamine-depleting drugs (evolution into predominant parkinsonism/dystonia) | At each visit, at least annually |
| <b>Mobility, ADL, &amp; need for adaptive devices</b> | Per treating physiatrist, PT, OT  | Per treating specialist          |



Table 7. continued from previous page.

| System/Concern                                    | Evaluation  | Frequency   |
|---|---|---|
| <b>Dysphagia/<br/>Feeding</b>                     | <ul style="list-style-type: none"> <li>Assess nutritional status &amp; adaptation of diet to assure adequate caloric intake &amp; prevent aspiration.</li> <li>Assess need for gastrostomy tube &amp; obtain informed consent as early as possible.</li> </ul>                                | At each visit, at least annually  |
| <b>Dysarthria</b>                                 | Per treating speech-language therapist  | Per treating speech-language therapist  |
| <b>Seizures</b>                                   | Assess response to ASM.   | Per treating neurologist & patient response to therapy                            |
|   | EEG   | Whenever new-onset seizures are suspected; at least every other year <sup>1</sup> |
| <b>Behavioral/<br/>Psychiatric/<br/>Cognitive</b> | Clinical impression   | At each visit, at least annually  |
|   | Short cognitive screening test such as MoCA <sup>2</sup> &/or per treating specialist   | At least every other year &/or per treating specialist                            |
| <b>Neuromuscular system</b>                       | Measure serum CK levels to assess for possible rhabdomyolysis.  | At each visit, esp when under neuroleptic treatment                               |
| <b>Cardiac</b>                                    | W/known cardiac involvement   | Per treating specialist   |
|   | W/o known cardiac involvement: cardiac exams (EKG, echocardiography, & cardiac biomarkers)  | Every 3-5 years   |
| <b>Family support<br/>&amp; resources</b>         | <ul style="list-style-type: none"> <li>Eval of social, psychological, &amp; financial situation</li> <li>Assess family need for palliative/respite care, home nursing, &amp; other local resources or follow-up genetic counseling if new questions arise (e.g., family planning).</li> </ul> | At each visit, at least annually  |

ASM = anti-seizure medication; CK = creatine kinase; MoCA = Montreal Cognitive Assessment; OT = occupational therapist; PT = physical therapist

1. Be aware of / monitor carefully seizure-provoking effects of antipsychotics/neuroleptics

2. Nasreddine et al [2005]

## Agents/Circumstances to Avoid

Avoid the following:

- Seizure-provoking circumstances (e.g., sleep deprivation, alcohol intake)
- Anticonvulsants that may worsen involuntary movements/tics (e.g., carbamazepine, lamotrigine)

## 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 early recognition and treatment of potential manifestations of the disease such as seizures, as possible complications (e.g., status epilepticus, sudden unexpected death in epilepsy) may be severe.

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

## Therapies Under Investigation

Several studies showed pathologically elevated tyrosine kinase Lyn activity in individuals with *VSP13A* disease and in disease models [De Franceschi et al 2011, De Franceschi et al 2012, Peikert et al 2021a, Peikert et al 2021b]. Lyn kinase inhibition was able to rescue the blood phenotype [Lupo et al 2016] and the neuronal

phenotype [Stanslowsky et al 2016]. This evidence encouraged off-label treatment with the tyrosine kinase inhibitor dasatinib in three affected individuals. Although the reduction of both elevated Lyn kinase activity and accumulated autophagy markers suggested target engagement in red blood cells during treatment, clinical parameters remained essentially unchanged; of note, no clinically relevant side effects occurred. Putative biomarkers such as creatine kinase, serum neurofilament levels, and acanthocyte count failed to show consistent effects [Peikert et al 2021a]. Experimental follow up suggested failure of central nervous system targeting by orally administered dasatinib [Peikert et al 2021b]. Tyrosine kinase inhibitors with improved blood-brain barrier penetration would thus be needed. Thus, based on currently available information, tyrosine kinase inhibitors cannot be recommended to treat *VPS13A* disease.

*VPS13A* loss of function was reported to impair PI3K signaling leading to reduced store-operated  $\text{Ca}^{2+}$  entry (SOCE) and increased cell death [Pelzl et al 2017a, Pelzl et al 2017b]. *VPS13A* upregulates the serum- and glucocorticoid-inducible kinase SGK1, which targets  $\text{Na}^+/\text{K}^+$ -ATPase, whose capacity was shown to be reduced in the absence of *VSP13A* [Hosseinzadeh et al 2020]. Both phenotypes were restored in cell models by lithium treatment. Although this observation suggests that lithium treatment might be preferable to other mood stabilizers should they be indicated in an individual with *VPS13A* disease, no systematic studies of lithium treatment have been reported to date.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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

*VPS13A* disease is inherited in an autosomal recessive manner.

Note: Previous speculation as to possible autosomal dominant inheritance of *VPS13A* disease has been disproven in the respective families [Danek et al 2012].

## Risk to Family Members

### Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *VPS13A* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *VPS13A* 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.
- Based on current knowledge, heterozygotes (carriers) do not have features of *VPS13A* disease and not at risk of developing the disorder [Walker et al 2012b].

### Sibs of a proband

- If both parents are known to be heterozygous for a *VPS13A* 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.
- Significant phenotypic variability may be observed between affected sibs who inherit the same biallelic pathogenic variants [Merwick et al 2014]; different phenotypes have even been observed in monozygotic twins [Müller-Vahl et al 2007].
- Based on current knowledge, heterozygotes (carriers) do not have features of *VPS13A* disease and are not at risk of developing the disorder [Walker et al 2012b].

**Offspring of a proband.** Unless an individual with *VPS13A* disease has children with an affected individual or a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *VPS13A* (see Related Genetic Counseling Issues, **Family planning**).

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a *VPS13A* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *VPS13A* 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 affected, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of individuals known to be affected with or carriers of *VPS13A* disease, particularly if consanguinity is likely and/or if both partners are of the same ethnic background.
  - Consanguinity has been reported in a number of families with *VPS13A* disease [Sorrentino et al 1999, Dobson-Stone et al 2002, Bohlega et al 2003, Al-Asmi et al 2005, Sokolov et al 2012].
  - Recurrent *VPS13A* pathogenic variants have been identified in individuals of Japanese, French Canadian, and Sephardic Jewish ancestry (see Table 8).

## Prenatal Testing and Preimplantation Genetic Testing

Once the *VPS13A* 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](#).

- **Advocacy for Neuroanthocytosis Patients**

United Kingdom

**Phone:** 44 (0) 20 7460-8874

**Email:** [ginger@naadvocacy.org](mailto:ginger@naadvocacy.org)

[www.naadvocacy.org](http://www.naadvocacy.org)

- **Neuroanthocytosis Advocacy USA, Inc.**

**Email:** [susan@naadvocacyusa.org](mailto:susan@naadvocacyusa.org); [joy@naadvocacyusa.org](mailto:joy@naadvocacyusa.org)

[www.naadvocacyusa.org](http://www.naadvocacyusa.org)

## 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.** VPS13A Disease: Genes and Databases

| Gene   | Chromosome Locus | Protein                                     | Locus-Specific Databases | HGMD   | ClinVar |
|--------|------------------|---|--------------------------|--------|---------|
| VPS13A | 9q21.2           | Intermembrane lipid transfer protein VPS13A | VPS13A database          | VPS13A | VPS13A  |

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 VPS13A Disease ([View All in OMIM](#))

|        |   |
|--------|---|
| 200150 | CHOREOACANTHOCYTOSIS; CHAC                    |
| 605978 | VACUOLAR PROTEIN SORTING 13 HOMOLOG A; VPS13A |

## Molecular Pathogenesis

VPS13A encodes the protein VPS13A (also called chorein), a member of a recently recognized superfamily of bridge-like lipid transfer proteins [Leonzino et al 2021, Neuman et al 2022]. These proteins are localized at membrane contact sites, where pairs of intracellular membranes are held in close apposition [Lang et al 2015, Park et al 2016, Kumar et al 2018, Yeshaw et al 2019].

VPS13A is one of four very similar mammalian VPS13 paralogues that have different subcellular localizations and functions in cell and organismal physiology [Kolehmainen et al 2003, Velayos-Baeza et al 2004, Lesage et al 2016, Gauthier et al 2018, Seong et al 2018]. VPS13 family proteins are characterized by a conserved structural organization: they are large, rod-shaped proteins with a hydrophobic channel that extends along the entire length of the protein [Li et al 2020, Dziurdzik & Conibear 2021, Leonzino et al 2021, Adlakha et al 2022, Cai et al 2022]. The ends of the protein interact with the two closely apposed membranes, so that the hydrophobic channel provides a conduit for the flow of lipids between them. VPS13A has been localized to contact sites between the endoplasmic reticulum (ER) and three different structures, the mitochondrion, the lipid droplet, and the plasma membrane [Kumar et al 2018, Yeshaw et al 2019, Guillén-Samander et al 2022]. It has also been

found at contacts between mitochondria and endosomes [Muñoz-Braceras et al 2019]. Disruption of lipid exchange at one or more of these contacts is thought to be the basis for functional impairment of neurons and red blood cells (neurodegeneration and acanthocytosis, respectively).

It is not yet known how lipid flow through VPS13A is regulated or at which of these contact sites the loss of lipid flow is relevant to disease causation. However, the extreme C-terminal end of VPS13A (a PH domain) has been shown to bind directly to the XK protein, loss of which is responsible for [McLeod neuroacanthocytosis syndrome](#) (also referred to as McLeod syndrome or XK disease), a disorder characterized by clinical manifestations very similar to those of VPS13A disease [Ho et al 1994, Urata et al 2019, Park & Neiman 2020, Guillén-Samander et al 2022, Park et al 2022, Peikert et al 2022a]. XK is a plasma membrane-localized lipid scramblase that mediates movement of phospholipids between the two leaflets of a lipid bilayer [Suzuki et al 2014, Ryoden et al 2022]. One effect of this scramblase activity is exposure to the cell surface of phosphatidylserine, a phospholipid normally confined to the cytosolic leaflet of the plasma membrane [Suzuki et al 2014, Ryoden et al 2022]. A VPS13A-XK complex is found at ER-to-plasma membrane contact sites, where it may pair transport of lipids between the ER and plasma membrane with movement of lipids between the two plasma membrane leaflets [Guillén-Samander et al 2022]. Given the similarity of VPS13A disease to McLeod syndrome, disruption of the functional partnership between the proteins VPS13A and XK is likely to have a key role in disease causation [Peikert & Danek 2023].

Loss of VPS13A has been associated with increased Lyn kinase activity, disturbed autophagy, and alteration of the actin cytoskeleton [De Franceschi et al 2011, Föllner et al 2012, Lupo et al 2016]. Indeed, inhibitors of Lyn kinase have been shown to be effective in restoring the peripheral blood cell phenotypes of individuals with VPS13A disease [Peikert et al 2021a]. However, cellular phenotypes in neuronal cells derived from individuals with VPS13A disease were only partially reverted by Lyn kinase inhibition [Stanslowsky et al 2016, Glaß et al 2018]. Given the biochemical function of VPS13A in lipid transfer, the question of how impairment of this function may cause alterations of Lyn kinase activity and of actin organization has yet to be resolved.

*Vps13a*<sup>-/-</sup> mice recapitulate key features of individuals with VPS13A disease, showing loss of VPS13A and presence of blood cell acanthocytosis, disturbed autophagy, neuronal loss, and neuroinflammation in the basal ganglia and motor disturbances, but the neurologic changes occurred late and appeared mild in comparison to findings in humans [Peikert et al 2021b]. Similar findings were reported in another mouse model, with exons 60-61 deletion in *Vps13a* [Tomemori et al 2005]. Further characterization of these mouse models is needed.

**Mechanism of disease causation.** Loss of function. In addition to the majority of VPS13A disease-associated variants being predicted to be loss-of-function variants, western blotting has shown that many result in loss of VPS13A expression. Occasionally individuals with VPS13A disease may express VPS13A that lacks the PH domain that binds to the XK protein [Park et al 2022].

**VPS13A-specific laboratory technical considerations.** Absence or marked reduction of VPS13A (also known as chorein) on western blot analysis has been shown in erythrocytes from individuals with VPS13A disease. In contrast, normal levels of VPS13A are observed in samples from individuals with [Huntington disease](#) and healthy controls [Dobson-Stone et al 2004]. Therefore, western blot analysis of VPS13A may be helpful in the following circumstances:

- Variants of uncertain significance (VUS) in VPS13A
- Negative molecular analysis of VPS13A in a proband whose phenotype is consistent with VPS13A disease
- Used as a first diagnostic indicator when DNA analysis is not affordable or generally unavailable

Individuals with reduced levels of VPS13A need further diagnostic workup by molecular genetic testing [Spieler et al 2020].

Notes: (1) Some pathogenic variants in *VPS13A* are known to be associated with normal levels of VPS13A (e.g., some missense substitutions that do not result in misfolding and protein degradation or small deletions leading to expression of a truncated protein whose electrophoretic motility is very similar to wild type protein [Park et al 2022]); therefore, the presence of normal levels of VPS13A does not exclude the diagnosis of *VPS13A* disease. (2) Because reduced VPS13A immunoreactivity has been observed in individuals with McLeod neuroacanthocytosis syndrome (most likely because of destabilization of VPS13A in the absence of the protein XK, with which it forms a complex [Urata et al 2019]), immunohistochemistry of VPS13A needs to be carefully interpreted in the context of the clinical findings.

**Table 8.** Notable *VPS13A* Pathogenic Variants

| Reference Sequences        | DNA Nucleotide Change                | Predicted Protein Change | Comment [Reference]  |
|----------------------------|--------------------------------------|--------------------------|--|
| NM_033305.3<br>NP_150648.2 | c.2343delA                           | p.Lys781AsnfsTer8        | Reported in 3 families from the Jewish population of Djerba Island, Tunisia [Benninger et al 2016] |
|                            | c.4411C>T                            | p.Arg1471Ter             | Pathogenic variants reported in several Japanese families [Nishida et al 2019]                     |
| NM_033305.3                | Deletion of exons 60-61 <sup>1</sup> | --                       | Deletion reported in French Canadian families [Dobson-Stone et al 2005]                            |
|                            | Deletion of exons 70-73 <sup>1</sup> | --                       |  |

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

## Chapter Notes

### Author Notes

The following web pages provide descriptions of our clinical work, research interests, and contact information:

- [Adrian Danek, MD](#)
- [Ruth H Walker, MD, PhD](#)
- Kevin Peikert, MD, and Andreas Hermann, MD, PhD, Translational Neurodegeneration Section "Albrecht Kossel," [Neuroacanthocytosis Syndromes](#)

As an international community of clinicians, scientists, and families dealing with *VPS13A* disease (chorea-acanthocytosis), *XK* disease (McLeod neuroacanthocytosis syndrome), and related disorders, we initiated the bimonthly virtual "**VPS13 forum.**" In this forum, we regularly discuss all aspects (from bench to bedside) of this emerging field [Peikert & Danek 2023]. For invitations to future VPS13 forum sessions, contact [kevin.peikert@med.uni-rostock.de](mailto:kevin.peikert@med.uni-rostock.de).

Drs Adrian Danek ([danek@lmu.de](mailto:danek@lmu.de)), Ruth Walker ([ruth.walker@mssm.edu](mailto:ruth.walker@mssm.edu)), Andreas Hermann ([andreas.hermann@med.uni-rostock.de](mailto:andreas.hermann@med.uni-rostock.de)), Kevin Peikert ([kevin.peikert@med.uni-rostock.de](mailto:kevin.peikert@med.uni-rostock.de)), and Hans Jung ([hans.jung@usz.ch](mailto:hans.jung@usz.ch)) are actively involved in **clinical research regarding individuals with *VPS13A* disease**. They would be happy to communicate with persons who have any questions regarding the diagnosis of *VPS13A* disease or other considerations.

Drs Adrian Danek ([danek@lmu.de](mailto:danek@lmu.de)), Ruth Walker ([ruth.walker@mssm.edu](mailto:ruth.walker@mssm.edu)), Andreas Hermann ([andreas.hermann@med.uni-rostock.de](mailto:andreas.hermann@med.uni-rostock.de)), Kevin Peikert ([kevin.peikert@med.uni-rostock.de](mailto:kevin.peikert@med.uni-rostock.de)), and Hans Jung ([hans.jung@usz.ch](mailto:hans.jung@usz.ch)) are also interested in hearing from clinicians treating families affected by **"neuroacanthocytosis" syndromes and Huntington disease-like syndromes in whom no causative variant**



**has been identified** through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Drs Gabriel Miltenberger-Miltenyi (gmiltenyi@medicina.ulisboa.pt) and/or Dr Antonio Velayos Baeza (avelayos@hotmail.com; antonio.velayos@dpag.ox.ac.uk) **to inquire about review of VPS13A variants of uncertain significance.**

**Western blot analysis** for VPS13A is currently available on a research basis (contact kevin.peikert@med.uni-rostock.de).

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## Revision History

- 30 March 2023 (bp) Comprehensive update posted live
- 18 April 2019 (avb) Revision: New information on VPS13C and VPS13D
- 30 January 2014 (me) Comprehensive update posted live
- 18 August 2011 (cd) Revision: prenatal testing available clinically as listed in the GeneTests Laboratory Directory
- 6 July 2010 (me) Comprehensive update posted live
- 13 October 2006 (me) Comprehensive update posted live



- 10 January 2005 (ad) Revision: Differential Diagnosis; Testing
- 16 July 2004 (me) Comprehensive update posted live
- 14 June 2002 (me) Review posted live
- 7 March 2002 (lr) Original submission

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