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VPS35-Related Parkinson Disease

Synonyms: PARK17, PARK-*VPS35*

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Summary

Clinical characteristics

VPS35-related Parkinson disease (PARK-*VPS35*) is indistinguishable from Parkinson disease of unknown cause representing a simplex case (also referred to as "sporadic" Parkinson disease). PARK-*VPS35* is characterized by typical parkinsonism (resting tremor, bradykinesia, rigidity, disturbance of postural reflexes) presenting on average a decade earlier than in individuals with simplex Parkinson disease of unknown cause. Median age of onset is approximately 50 years, with a range of onset spanning the third to eighth decade of life. PARK-*VPS35* subtypes can include tremor dominant, akinetic rigid, gait difficulty, or mixed. Asymmetric presentation is typical. The disease course is usually milder than that of simplex Parkinson disease of unknown cause, with a decreased incidence of atypical signs. Dyskinesia and motor fluctuations may occur. Neuropsychiatric manifestations (depression and schizophrenia), learning difficulties, mild cognitive impairment, and dementia have been reported, albeit with lower occurrence than in simplex Parkinson disease of unknown cause. Additional findings include impaired sense of smell and autonomic manifestations including orthostasis and constipation.

Diagnosis/testing

The diagnosis of PARK-*VPS35* is established in a proband with parkinsonism (bradykinesia with rigidity and/or resting tremor) and a heterozygous *VPS35* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: To date, treatment of PARK-*VPS35* does not differ from that of simplex Parkinson disease of unknown cause. Drugs to treat motor manifestations include levodopa, in combination with a peripheral dopa decarboxylase inhibitor (carbidopa, benserazide), dopamine agonists, inhibitors of catechol-O-methyltransferase or monoamine oxidase-B, anticholinergics, and amantadine. Most individuals respond well to

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levodopa and other dopaminergic medications. Individuals benefit from physical, occupational, and speech therapies. Due to the lower risk of atypical signs, neuropsychiatric disturbances, and dementia, individuals with PARK-*VPS35* seem to be good candidates for treatment with dopamine agonists. In addition, in those with dyskinesia and motor fluctuations, subthalamic deep brain stimulation and apomorphine intermittent injections or continuous therapy with an infusion pump should be considered. Peak-dose dyskinesia may be ameliorated with amantadine and dopaminergic treatment reduction (if tolerated). Low-dose clozapine, quetiapine, or pimavanserin and reduction of dopaminergic therapy can decrease delusions and hallucinations. Standard treatments for depression; consider droxidopa for orthostasis; symptomatic treatment for constipation.

Surveillance: Neurologic evaluations to assess tremor, bradykinesia, rigidity, gait, neuropsychiatric symptoms, cognition, and treatment efficacy every six to 12 months or as needed; neuropsychiatric and cognitive assessments as needed; assess for symptoms of orthostasis, measure blood pressure, and assess for constipation at each visit; echocardiogram as needed in those treated with ergot-derived dopamine agonists; assess family and social work needs at each visit.

Agents/circumstances to avoid: Drugs that may induce or exacerbate parkinsonism include but are not limited to neuroleptics, antidepressants, calcium channel blockers, valproate, lithium, and amiodarone. Ergot-derived dopaminergic drugs should be discontinued if fibrotic heart-valve changes are identified.

Genetic counseling

PARK-*VPS35* is inherited in an autosomal dominant manner. About 90% of individuals diagnosed with PARK-*VPS35* have positive family history of Parkinson disease. Each child of an individual with PARK-*VPS35* has a 50% chance of inheriting the *VPS35* pathogenic variant. Once the *VPS35* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

VPS35-related Parkinson disease (PARK-*VPS35*) **should be considered** in individuals with the following clinical, imaging, and family history findings.

Clinical findings. The clinical manifestations of PARK-*VPS35* are similar to those of Parkinson disease of unknown cause representing a simplex case (also referred to as "sporadic" Parkinson disease; see Nomenclature). However, onset for PARK-*VPS35* is on average a decade earlier, progression is slower, and there is a lower risk of atypical signs, neuropsychiatric disturbances, and dementia. The cardinal sign of PARK-*VPS35* is parkinsonism, defined as:

- Bradykinesia (slowness of movement AND decrement in amplitude or speed) in combination with at least one of the following:
  - Resting tremor (rhythmic tremor usually of the hands and forearms when relaxed, which disappears with active limb movement)
  - Rigidity (increased muscle tone resulting in resistance to passive movement)

Additional clinical findings of PARK-*VPS35*:

- Adult onset
- Typically unilateral onset
- Slow disease progression
- Good response to levodopa therapy

Imaging findings. Normal brain MRI

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of PARK-*VPS35* **is established** in a proband with parkinsonism (bradykinesia with rigidity and/or resting tremor) and a heterozygous *VPS35* pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1).

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 any likely pathogenic variants. (2) Identification of a heterozygous *VPS35* variant of uncertain significance does not establish or rule out the diagnosis.

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

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotypes of inherited Parkinson disease are largely indistinguishable, most individuals with PARK-*VPS35* are diagnosed by the following recommended testing or testing to consider.

Recommended Testing

A multigene Parkinson disease panel including *VPS35* and other genes of interest (see Table 3a in Differential Diagnosis) is recommended. 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*; thus, clinicians need to determine which multigene panel 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. Given the rarity of PARK-*VPS35*, some panels for Parkinson disease may not include this gene.

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

Testing to Consider

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Note: Single-gene testing (sequence analysis of *VPS35*) is typically not recommended because the phenotype overlaps with that of other inherited forms of Parkinson disease.

Table 1. Molecular Genetic Testing Used in *VPS35*-Related Parkinson Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
VPS35	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

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 detected 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. Vilariño-Güell et al [2011], Zimprich et al [2011], Ando et al [2012], Kumar et al [2012], Lesage et al [2012], Sharma et al [2012], Sheerin et al [2012], 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.

Clinical Characteristics

Clinical Description

VPS35-related Parkinson disease (PARK-*VPS35*) is indistinguishable from Parkinson disease of unknown cause representing a simplex case (also referred to as "sporadic" Parkinson disease; see Nomenclature). PARK-*VPS35* is characterized by cardinal manifestations of typical parkinsonism (resting tremor, bradykinesia, rigidity, disturbance of postural reflexes). Similar to simplex Parkinson disease of unknown cause, non-motor symptoms also occur; however, neuropsychiatric disturbances and dementia are less common. Atypical features are also of lower frequency compared to simplex Parkinson disease of unknown cause. Disturbances of postural reflexes, autonomic manifestations, and sleep disorders occur at a similar rate to simplex Parkinson disease of unknown cause. PARK-*VPS35* manifestations may be variable among affected individuals within the same family. To date, approximately 150 individuals with PARK-*VPS35* have been identified [Vilariño-Güell et al 2011; Zimprich et al 2011; Ando et al 2012; Kumar et al 2012; Lesage et al 2012; Sharma et al 2012; Sheerin et al 2012; Trinh et al 2018; Dulski et al 2022; Vollstedt et al 2023; Dulski et al, unpublished data].

Table 2. Select Features of *VPS35*-Related Parkinson Disease

Feature	% of Persons w/Feature [1]	Comment
Resting tremor	98%	
Bradykinesia	96%	
Rigidity	95%	
Disturbance of postural reflexes	67%	
Neuropsychiatric manifestations	68%	
Cognitive issues	42%	Learning difficulties, mild cognitive impairment, dementia
Good response to levodopa	80%	
Motor fluctuations	85%	
Dyskinesia	80%	
Dystonia	32%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature [1]	Comment
Autonomic manifestations	75%	

1. Trinh et al [2018]

Age of onset. Median age of onset was 52 years (interquartile range [IQR]: 45-61) in a group of 67 affected individuals [Trinh et al 2018], and 48 years (IQR: 44-56) in a group of 23 affected individuals [Vollstedt et al 2023].

Parkinson subtype. The motor manifestations do not differ from simplex Parkinson disease of unknown cause. Affected individuals may manifest tremor dominant, akinetic rigid, gait difficulty, and mixed subtypes [Dulski et al 2022].

Course of disease

- Presentation is asymmetric.
- The disease course is usually milder than that of simplex Parkinson disease of unknown cause.
- Dyskinesia and motor fluctuations may occur.
- Atypical signs are very rare. To date, atypical features were observed in only one individual, who developed classic manifestations of Parkinson disease in his early 70s, followed by bulbar symptoms, gait apraxia, falls, supranuclear gaze palsy, apraxia of eyelid opening, and dysexecutive syndrome. However, this individual also had a *FBXO7* variant, and the phenotype could have been due to double heterozygosity for *VPS35* and *FBXO7* variants. A cousin of the affected individual also had the *VPS35* variant and presented with classic late-onset Parkinson disease [Bartonikova et al 2016, Menšíková et al 2019].

Neuropsychiatric manifestations

- Depression was observed in up to 70% of individuals [Trinh et al 2018].
- Psychotic symptoms occurred in up to 25% of individuals [Trinh et al 2018].
- Anxiety is rare [Trinh et al 2018].

Cognitive issues. Impairment of cognition ranges from mild to dementia and occurs in up to 45% of individuals.

Other findings

- Impaired sense of smell was reported in most individuals. However, the reported number of affected individuals is small, and further investigation is required [Zimprich et al 2011, Sheerin et al 2012, Struhal et al 2014, Trinh et al 2018, Vollstedt et al 2023].
- Autonomic manifestations including orthostasis and gastrointestinal symptoms (constipation) affect up to 75% of individuals [Trinh et al 2018].

Functional imaging studies show presynaptic dopaminergic dysfunction, which is apparently indistinguishable from findings in other individuals with Parkinson disease.

Single photon emission computed tomography (SPECT) of cerebral blood flow was normal in one individual [Ando et al 2012, Vollstedt et al 2023].

^{18}F-fluorodopa positron emission tomography (PET) showed asymmetrically reduced striatal ^{18}F-fluorodopa uptake with a posterior predominance [Wider et al 2008].

[^{123}I]-FP-CIT SPECT showed asymmetric tracer uptake [Zimprich et al 2011].

Transcranial sonography. In one individual with Parkinson disease that started with resting tremor on the left side, transcranial sonography performed after a disease course of about 15 years showed normal echogenicity of the left substantia nigra, whereas the bone window was insufficient to allow visualization on the right side [Kumar et al 2012].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified [Dulski et al 2022].

Penetrance

To date, data is too limited to allow quantification of penetrance.

Nomenclature

Based on the International Parkinson and Movement Disorder Society Task Force for the Nomenclature of Genetic Movement Disorders, the recommended name for Parkinson disease caused by *VPS35* pathogenic variants is "PARK-*VPS35*" [Lange et al 2022].

"Idiopathic Parkinson disease" and "sporadic Parkinson disease" are terms used in the Parkinson disease medical literature to describe Parkinson disease of unknown cause diagnosed in an individual with a negative family history. Because future advances in the understanding of genetic risk factors are likely to identify genetic causes / risk factors for some Parkinson disease currently considered "idiopathic" or "sporadic," these terms are generally not used in this *GeneReview*. Instead, the term "Parkinson disease of unknown cause representing a simplex case" is preferred because "simplex case" refers specifically to an individual with no family history of Parkinson disease without implying presence or absence of a genetic factor or a specific recurrence risk.

Prevalence

PARK-*VPS35* is exceedingly rare, and to date only 150 affected individuals have been reported worldwide [Vilariño-Güell et al 2011, Zimprich et al 2011, Ando et al 2012, Kumar et al 2012, Lesage et al 2012, Sharma et al 2012, Sheerin et al 2012, Trinh et al 2018, Vollstedt et al 2023].

The largest study to date included 67 individuals with PARK-*VPS35*. Of these individuals, 45% were White, 35% were Asian, and 20% were Ashkenazi Jewish; more than half of the affected individuals were from Western Europe [Trinh et al 2018]. In a smaller study that included 26 individuals, all were White, and most were of Western European ancestry [Vollstedt et al 2023].

The prevalence of PARK-*VPS35* among persons with familial Parkinson disease is less than 1% [Dulski et al 2022].

Genetically Related (Allelic) Disorders

A germline *VPS35* pathogenic variant p.Leu625Pro was reported in an individual with early-onset Alzheimer disease [Rovelet-Lecrux et al 2015].

In another study *VPS35* variant p.Arg499His was identified in two of 1,118 individuals with dementia with Lewy bodies [Orme et al 2020]. All individuals were of northern European ethnicity. Although the prevalence of p.Arg499His in the general population is less than 0.004% (see gnomAD), identification of this variant in individuals with dementia with Lewy bodies was most likely coincidental [Orme et al 2020].

Differential Diagnosis

The differential diagnosis of PARK-*VPS35* includes other types of hereditary adult-onset Parkinson disease (see Table 3a) and simplex Parkinson disease of unknown cause (referred to as sporadic or idiopathic Parkinson disease in the literature; see Nomenclature).

Apart from a younger age at onset and typically slower progression, the phenotype of PARK-*VPS35* is clinically indistinguishable from that of simplex Parkinson disease of unknown cause (average onset is age 60 years). Thus, the differential diagnosis of PARK-*VPS35* is the same as it is for Parkinson disease in general (see Parkinson Disease Overview). In addition, an extensive list of differential diagnoses of familial parkinsonism can be found in Dulski et al [2022] and Dulski et al [unpublished data].

Table 3a. Genes Associated with Early-Onset Adult Parkinson Disease (Age 20-50 Years) and Late-Onset Adult Parkinson Disease (Age >50 Years)

Gene [1]	PD Designation [2]	MOI	% of Adult PD	Comments
GBA1 (*GBA*) [3]	PARK-*GBA* (OMIM 606463)	AD	3%-7% (20% in AJ ancestry)	• Onset age may be <50 yrs. • Higher likelihood of cognitive impairment & atypical motor findings • Faster progression • Assoc w/dementia w/Lewy bodies • Variable penetrance dependent on age, variant, & ethnicity • Consider if family history of Gaucher disease.
LRRK2	PARK-*LRRK2* (See *LRRK2* PD.)	AD	1%-2% (13%-30% in AJ ancestry; 41% in African Berber ancestry)	• Classic manifestations w/less non-motor involvement • Variable penetrance dependent on age, variant, & ethnicity
PARK7 (*DJ1*)	PARK-*DJ1* (OMIM 606324)	AR	Rare	• Phenotype similar to PARK-*Parkin* • ID &/or seizures occasionally • Risk to heterozygotes unknown
PINK1	PARK-*PINK1* (See *PINK1* Type of Young-Onset PD.)	AR	Rare (3.7% of early-onset adult PD)	• Phenotype similar to PARK-*Parkin* • Non-motor manifestations (incl psychiatric features) more common • Heterozygotes may have ↑ PD risk.
PRKN	PARK-*Parkin* (See Parkin Type of Early-Onset PD.)	AR	1% (4.6%-10.5% of early-onset adult PD)	• Slow progression • Can have lower-limb dystonia, dyskinesias, hyperreflexia • Mild non-motor manifestations • Heterozygotes may have ↑ PD risk.
SNCA	PARK-*SNCA* (OMIM 168601, 605543)	AD	Rare	• Onset age may be <50 yrs. • Cognitive & psychiatric features more likely

Table 3a. continued from previous page.

Gene [1]	PD Designation [2]	MOI	% of Adult PD	Comments
VPS13C	PARK-*VPS13C* (OMIM 616840)	AR	Rare	• Early-onset PD w/very rapid progression • Truncating variants cause severe disease.

Based on Dulski et al [2022], Dulski et al [unpublished data]
AD = autosomal dominant; AJ = Ashkenazi Jewish; AR = autosomal recessive; ID = intellectual disability; MOI = mode of inheritance; PD = Parkinson disease
1. Genes are listed in alphabetic order.
2. Nomenclature based on Lange et al [2022]
3. There is some disagreement among researchers as to whether *GBA1* should be classified as a monogenic disorder or, alternatively, a risk factor – due to its low age-related penetrance (see Parkinson Disease Overview).

Suspected genetic risk factors for Parkinson disease. Table 3b lists genetic loci reported in a small number of individuals. Additional studies are needed to confirm and clarify the role of variants in these genes in Parkinson disease causation.

Table 3b. Suspected Genetic Risk Factors for Parkinson Disease

Gene	PD Designation [1]	MOI	% of Adult PD	Comments
ARSA	PARK-*ARSA*	AD	Very rare	• Juvenile-, early-, or late-onset PD • Tremor-dominant parkinsonism • Slow progression • Good response to levodopa • Mild cognitive impairment • Autonomic dysfunction
CHCHD2	PARK-*CHCHD2*	AD	Very rare	• Early or late onset • Frequent depression • Dementia uncommon • Good response to levodopa • Persons of Asian descent
LRP10	PARK-*LRP10*	AD	Very rare	• Late-onset PD • High prevalence of dementia, which may be a first sign • Good response to levodopa
PSAP	PARK-*PSAP*	AD	Very rare	• Early- or late-onset PD • Motor fluctuations • Dyskinesia • Good response to levodopa • Persons of Japanese descent
RIC3	PARK-*RIC3*	AD	Very rare	• Early- or late-onset PD • Dystonia • Restless legs syndrome • REM sleep behavior disorder • Psychosis • Persons of South Indian descent
TMEM230 [2]	PARK-*TMEM230*	AD	Very rare	• Late-onset PD • Slow progression • Good response to levodopa

Based on Dulski et al [2022], Dulski et al [unpublished data]
1. Nomenclature based on Lange et al [2022]

2. In a large family with multiple affected family members, hereditary Parkinson disease was attributed to a variant in *DNAJC13* [Vilariño-Güell et al 2014]. In a subsequent study of the same family, Parkinson disease was reattributed to a variant in *TMEM230* [Deng et al 2016] (see OMIM 616361).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PARK-*VPS35*, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *VPS35*-Related Parkinson Disease

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	In particular, assessment of movement disorder(s)
	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Psychiatric	Neuropsychiatric eval	To assess for psychiatric manifestations (e.g., mood disorders, hallucinations, delusions, anxiety, sleep disorders)
Cognition	Cognitive assessment	
Autonomic dysfunction	• Assess for symptoms of orthostasis & measure supine & standing BP & pulse. • Assess for constipation.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of PARK-*VPS35* to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources; • Social work support; • Home nursing referral.	

ADL = activities of daily living; BP = blood pressure; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; PARK-*VPS35* = *VPS35*-related Parkinson disease

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

Treatment of Manifestations

To date, the treatment of individuals with PARK-*VPS35* does not differ from that of simplex Parkinson disease of unknown cause (also referred to as "sporadic Parkinson disease"; see Nomenclature). The following is a brief summary of recommended treatment for Parkinson disease, based on extensive existing guidelines and recommendations for pharmacotherapy of motor and non-motor manifestations of Parkinson disease as well as neurosurgical interventions for motor findings [Zesiewicz et al 2010, Oertel et al 2011a, Oertel et al 2011b, Seppi et al 2011, Ferreira et al 2013, Odin et al 2015, Trenkwalder et al 2015].

Table 5. Treatment of Manifestations in Individuals with *VPS35*-Related Parkinson Disease

Manifestation/ Concern	Treatment	Considerations/Other
Neurologic	Levodopa in combination w/peripheral dopa decarboxylase inhibitor (carbidopa, benserazide): 1. Immediate-release (IR) tablets 2. Disintegrating tablets 3. Controlled-release (CR) tablets 4. Extended-release (ER) capsules 5. Inhalation powder 6. Enteral suspension (pump) Dopamine agonists 1. IR & CR tablets 2. Subcutaneous injections & infusion pump (apomorphine) 3. Transdermal patch (rotigotine) Other drugs used in combination w/levodopa & dopamine agonists: inhibitors of catechol-O-methyltransferase or monoamine oxidase-B, anticholinergics, & amantadine.	• A good levodopa response was seen in nearly all persons w/PARK-*VPS35*. • Since there is low risk of neuropsychiatric symptoms in PARK-*VPS35*, treatment w/dopamine agonist should be considered. • To ↓ or delay side effects (e.g., dyskinesias, hallucinations, impulse control disorder) of levodopa & dopaminergic medication, doses should not exceed levels required for satisfactory clinical response. • In younger persons, treatment w/ dopamine agonists should be given preference.
	• PT &/or OT to improve &/or maintain gross motor & fine motor skills. • Speech therapy	
Dyskinesias	Treatment options: • Reduction of levodopa dose • Use of dopamine receptor agonists • Deep brain stimulation • Continuous application of levodopa or apomorphine	Deep brain stimulation & apomorphine pump may be considered for persons who develop motor fluctuations & disabling dyskinesia.
Neuropsychiatric manifestations	• Atypical neuroleptic agents such as low-dose clozapine, quetiepine, or pimavanserin & reduction of dopaminergic therapy can ↓ delusions & hallucinations. • Standard treatments for depression	
Dementia	Treatment w/cholinesterase inhibitor (rivastigmine) should be considered.	
Orthostasis	Consider treatment w/droxidopa, midodrine, fludrocortisone.	
Constipation	Symptomatic treatment	

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Recommended Surveillance for Individuals with *VPS35*-Related Parkinson Disease

System/Concern	Evaluation	Frequency
Neurologic	Neurologic eval to assess motor & non-motor symptoms & treatment effects	Every 6-12 mos or as needed
Psychiatric	Neuropsychiatric eval	In those w/mood disorder or psychotic symptoms, or as needed

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Cognition	Cognitive assessment	In those w/cognitive impairments or neuropsychiatric symptoms (psychosis), or as needed
Autonomic dysfunction	• Assess for symptoms of orthostasis & measure supine & standing BP & pulse. • Assess for constipation.	At each visit
Cardiac manifestations [1]	Echocardiogram to assess for fibrotic heart-valve changes	As needed in those treated w/ergot-derived dopaminergic drugs
Family support & resources	Assess need for: • Community or online resources; • Social work support; • Home nursing referral.	At each visit

BP = blood pressure
1. Caused by ergot-derived dopamine agonists

Agents/Circumstances to Avoid

Neuroleptic drugs may increase the severity of parkinsonism in individuals with PARK-*VPS35* (as in Parkinson disease in general). In general, atypical neuroleptics are less likely to exacerbate parkinsonism than typical neuroleptics; in particular clozapine, quetiapine, or pimavanserin are considered well tolerated and effective in Parkinson disease. Other drugs that may induce or exacerbate parkinsonism include but are not limited to antidepressants, calcium channel blockers, valproate, lithium, and amiodarone [Bondon-Guitton et al 2011, Bohlega & Al-Foghom 2013].

Ergot-derived dopaminergic drugs should be discontinued if fibrotic heart-valve changes are identified [Antonini & Poewe 2007].

Evaluation of Relatives at Risk

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

Pregnancy Management

Reports addressing pregnancy management in women with PARK-*VPS35* are not available.

The effect of Parkinson disease of any cause on pregnancy has not been well characterized, since pregnancy is uncommon in women with Parkinson disease. In general, half of affected individuals experience improvement or no change in manifestations during pregnancy, whereas half experience worsening manifestations [Seier & Hiller 2017]. Monotherapy with levodopa seems to be the best treatment option for pregnant individuals, both in terms of safety and efficacy [Seier & Hiller 2017].

No long-term outcome data exist for children born to mothers with Parkinson disease.

- Levodopa has not been linked with a higher risk of spontaneous abortions, teratogenicity, or birth complications [Seier & Hiller 2017].
- There is insufficient evidence to determine the safety of dopamine agonists, selegiline, and rasagiline in affected individuals during pregnancy [Seier & Hiller 2017].
- Anticholinergics were associated with minor birth defects, but no other complications [Seier & Hiller 2017].

- Amantadine should be avoided during pregnancy due to teratogenicity [Seier & Hiller 2017].

Discussion of the risks and benefits of using a given medication during pregnancy should ideally take place prior to conception. See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

VPS35-related Parkinson disease (PARK-*VPS35*) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 90% of individuals diagnosed with PARK-*VPS35* have a positive family history of Parkinson disease. Of note, PARK-*VPS35* manifestations may be variable among affected individuals within the same family.
- About 10% of individuals with PARK-*VPS35* represent simplex cases (i.e., a single occurrence in a family). However, the parents of these individuals have not been evaluated sufficiently to determine if the pathogenic variant occurred *de novo* in the proband; therefore, the proportion of PARK-*VPS35* caused by a *de novo* pathogenic variant is unknown.
- If the proband appears to be the only affected family member, molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with PARK-*VPS35* may appear to be negative because of failure to recognize the disorder in family members, age-related or reduced penetrance of the disease in a heterozygous parent, or early death of the parent before the onset of disease manifestations. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *VPS35* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.

    - To date, data are too limited to allow quantification of penetrance; the likelihood that a sib who inherits a familial *VPS35* pathogenic variant will develop manifestations of PARK-*VPS35* is not known.
    - The manifestations of PARK-*VPS35* may be variable among affected family members with the same pathogenic variant.
- If the *VPS35* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *VPS35* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for PARK-*VPS35* because of the possibility of age-related or reduced penetrance in a parent and the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with PARK-*VPS35* has a 50% chance of inheriting the *VPS35* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *VPS35* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic, at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *VPS35* pathogenic variant has been identified in an affected family member. The utility of predictive testing for a known familial *VPS35* pathogenic variant may be of limited clinical use because current data are too limited to allow quantification of penetrance (i.e., the likelihood that an asymptomatic individual found to be heterozygous for a familial *VPS35* pathogenic variant will develop PARK-*VPS35* is not known).
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals found to be heterozygous) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.
- Predictive testing may facilitate participation in research to better understand PARK-*VPS35* and, in the long term, contribute to the discovery of biomarkers and therapy.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

Note: It is appropriate to consider testing symptomatic individuals regardless of age in a family with an established diagnosis of PARK-*VPS35*.

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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *VPS35* pathogenic variant has 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.

- **Parkinson's Disease Society (UK)**
  United Kingdom
  Phone: 0808 800 0303
  Email: hello@parkinsons.org.uk
  www.parkinsons.org.uk
- **American Parkinson Disease Association (APDA)**
  Phone: 800-223-2732
  Fax: 718-981-4399
  Email: apda@apdaparkinson.org
  www.apdaparkinson.org
- **Fox Trial Finder**
  foxtrialfinder.michaeljfox.org
- **MedlinePlus**
  Parkinson disease
- **Michael J. Fox Foundation for Parkinson's Research**
  Phone: 800-708-7644 (toll-free)
  Email: info@michaeljfox.org
  www.michaeljfox.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Parkinson's Disease Information Page
- **Parkinson's Foundation**
  Phone: 800-4PD-INFO (473-4636)
  Email: contact@parkinson.org
  www.parkinson.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. VPS35-Related Parkinson Disease: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
VPS35	16q11.2	Vacuolar protein sorting-associated protein 35	VPS35	VPS35

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 VPS35-Related Parkinson Disease (View All in OMIM)

601501	VPS35 RETROMER COMPLEX COMPONENT; VPS35
614203	PARKINSON DISEASE 17; PARK17

Molecular Pathogenesis

VPS35 encodes vacuolar protein sorting-associated protein 35 (VPS35), which is part of the retromer, an evolutionarily conserved complex that associates with the cytosolic face of endosomes. The retromer is involved in the retrograde transport of transmembrane cargo (receptors, including dopamine receptors, transporters, adhesion molecules, and other proteins) from endosomes to the trans-Golgi network and to the plasma membrane; its cargo proteins are either recycled or degraded [Williams et al 2022].

The retromer comprises two assembling subunits: one consists of a trimeric complex of VPS35, VPS26, and VPS29 proteins and is also termed a cargo-selective complex, and the other consists of a sortin nexin dimer (SNX). VPS35 forms a horseshoe-shaped alpha-helical solenoid predicted to contain 33 helices [Lucas et al 2016]. It functions as the central platform for binding to other retromer proteins. VPS35 also mediates the association with the WASH complex, which includes FAM21. FAM21 binds to VPS35 through its extended unstructured "tail" domain, thereby allowing WASH-dependent retromer-mediated sorting of proteins (reviewed in Burd & Cullen [2014]).

VPS35 pathogenic variants have been shown to:

- Increase the activation of the LRRK2 kinase, thus exerting similar effects as *LRRK2* pathogenic variants [Mir et al 2018, Williams et al 2022];
- Affect VPS35 binding to FAM21 of the WASH complex, resulting in impairment of recruitment of the WASH complex to endosomes, retromer-mediated sorting of proteins, and autophagy [Follett et al 2014, McGough et al 2014, Zavodszky et al 2014a, Zavodszky et al 2014b, Williams et al 2022];
- Redistribute endosomes to a perinuclear localization [Follett et al 2014];
- Enlarge endosomes [Follett et al 2014];
- Lead to lysosomal dysfunction through abnormal sorting of cathepsin D [Follett et al 2014, Williams et al 2022];
- Impair VPS35 interaction with dopamine receptor D1 (DRD1), causing dysregulation of DRD1 trafficking and impairment of DRD1-mediated dopamine signaling [Wang et al 2016];
- Damage dopaminergic pathways, including loss of dopaminergic neurons and axonal degeneration [Williams et al 2022];
- Lead to lysosomal dysfunction through abnormal sorting of cathepsin D [Williams et al 2022];
- Cause mitochondrial dysfunction [Williams et al 2022];
- Induce tau pathology and accumulation of total alpha-synuclein in animal models [Williams et al 2022].

Mechanism of disease causation. Gain of function or partial loss of function; the exact mechanism remains to be elucidated [Williams et al 2022].

Table 7. Notable *VPS35* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_018206.6 NP_060676.2	c.1858G>A	p.Asp620Asn	Common variant found on several haplotypes; suspected mutational hot spot

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

Chapter Notes

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Contact Dr Zbigniew Wszolek (wszolek.zbigniew@mayo.edu) to inquire about the review of *VPS35* variants of uncertain significance.

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References

Literature Cited

Ando M, Funayama M, Li Y, Kashihara K, Murakami Y, Ishizu N, Toyoda C, Noguchi K, Hashimoto T, Nakano N, Sasaki R, Kokubo Y, Kuzuhara S, Ogaki K, Yamashita C, Yoshino H, Hatano T, Tomiyama H, Hattori N. VPS35 mutation in Japanese patients with typical Parkinson's disease. Mov Disord. 2012;27:1413-7. PubMed PMID: 22991136.

Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet Neurol. 2007;6:826-9. PubMed PMID: 17706566.

Bartonikova T, Mensikova K, Mikulicova L, Vodicka R, Vrtel R, Godava M, Vastik M, Kaiserova M, Otruba P, Dolinova I, Nevrly M, Kanovsky P. Familial atypical parkinsonism with rare variant in VPS35 and FBXO7 genes: A case report. Medicine (Baltimore). 2016;95:e5398. PubMed PMID: 27861377.

Bohlega SA, Al-Foghom NB. Drug-induced Parkinson's disease: a clinical review. Neurosciences (Riyadh). 2013;18:215-21. PubMed PMID: 23887211.

Bondon-Guitton E, Perez-Lloret S, Bagheri H, Brefel C, Rascol O, Montastruc JL. Drug-induced parkinsonism: a review of 17 years' experience in a regional pharmacovigilance center in France. Mov Disord. 2011;26:2226-31. PubMed PMID: 21674626.

Burd C, Cullen PJ. Retromer: a master conductor of endosome sorting. Cold Spring Harb Perspect Biol. 2014;6. PubMed PMID: 24492709.

Deng HX, Shi Y, Yang Y, Ahmeti KB, Miller N, Huang C, Cheng L, Zhai H, Deng S, Nuytemans K, Corbett NJ, Kim MJ, Deng H, Tang B, Yang Z, Xu Y, Chan P, Huang B, Gao XP, Song Z, Liu Z, Fecto F, Siddique N, Foroud T, Jankovic J, Ghetti B, Nicholson DA, Krainc D, Melen O, Vance JM, Pericak-Vance MA, Ma YC, Rajput AH, Siddique T. Identification of TMEM230 mutations in familial Parkinson's disease. Nat Genet. 2016;48:733-9. PubMed PMID: 27270108.

Dulski J, Uitti RJ, Ross OA, Wszolek ZK. Genetic architecture of Parkinson's disease subtypes -review of the literature. Front Aging Neurosci. 2022;14:1023574. PubMed PMID: 36337703.

Ferreira JJ, Katzenschlager R, Bloem BR, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Friedman A, Kanovsky P, Kostic V, Nieuwboer A, Odin P, Poewe W, Rascol O, Sampaio C, Schüpbach M, Tolosa E, Trenkwalder C, Schapira A, Berardelli A, Oertel WH. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. Eur J Neurol. 2013;20:5-15. PubMed PMID: 23279439.

Follett J, Norwood SJ, Hamilton NA, Mohan M, Kovtun O, Tay S, Zhe Y, Wood SA, Mellick GD, Silburn PA, Collins BM, Bugarcic A, Teasdale RD. The Vps35 D620N mutation linked to Parkinson's disease disrupts the cargo sorting function of retromer. Traffic. 2014;15:230-44. PubMed PMID: 24152121.

Kumar KR, Weissbach A, Heldmann M, Kasten M, Tunc S, Sue CM, Svetel M, Kostić VS, Segura-Aguilar J, Ramirez A, Simon DK, Vieregge P, Münte TF, Hagenah J, Klein C, Lohmann K. Frequency of the D620N mutation in VPS35 in Parkinson disease. Arch Neurol. 2012;69:1360-4. PubMed PMID: 22801713.

Lange LM, Gonzalez-Latapi P, Rajalingam R, Tijssen MAJ, Ebrahimi-Fakhari D, Gabbert C, Ganos C, Ghosh R, Kumar KR, Lang AE, Rossi M, van der Veen S, van de Warrenburg B, Warner T, Lohmann K, Klein C, Marras C, et al. Nomenclature of Genetic Movement Disorders: recommendations of the International Parkinson and Movement Disorder Society Task Force - an update. Mov Disord. 2022;37:905-35. PubMed PMID: 35481685.

Lesage S, Condroyer C, Klebe S, Honoré A, Tison F, Brefel-Courbon C, Dürr A, Brice A, et al. Identification of VPS35 mutations replicated in French families with Parkinson disease. Neurology. 2012;78:1449-50. PubMed PMID: 22517097.

Lucas M, Gershlick DC, Vidaurrazaga A, Rojas AL, Bonifacino JS, Hierro A. Structural mechanism for cargo recognition by the retromer complex. Cell. 2016;167:1623-35.e14. PubMed PMID: 27889239.

McGough IJ, Steinberg F, Jia D, Barbuti PA, McMillan KJ, Heesom KJ, Whone AL, Caldwell MA, Billadeau DD, Rosen MK, Cullen PJ. Retromer binding to FAM21 and the WASH complex is perturbed by the Parkinson disease-linked VPS35(D620N) mutation. Curr Biol. 2014;24:1670-6. PubMed PMID: 24980502.

Menšíková K, Tučková L, Kolařiková K, Bartoníková T, Vodička R, Ehrmann J, Vrtěl R, Procházka M, Kaňovský P, Kovacs GG. Atypical parkinsonism of progressive supranuclear palsy-parkinsonism (PSP-P) phenotype with rare variants in FBXO7 and VPS35 genes associated with Lewy body pathology. Acta Neuropathol. 2019;137:171-3. PubMed PMID: 30374525.

Mir R, Tonelli F, Lis P, Macartney T, Polinski NK, Martinez TN, Chou MY, Howden AJM, König T, Hotzy C, Milenkovic I, Brücke T, Zimprich A, Sammler E, Alessi DR. The Parkinson's disease VPS35[D620N] mutation enhances LRRK2-mediated Rab protein phosphorylation in mouse and human. Biochem J. 2018;475:1861-83. PubMed PMID: 29743203.

Odin P, Ray Chaudhuri K, Slevin JT, Volkmann J, Dietrichs E, Martinez-Martin P, Krauss JK, Henriksen T, Katzenschlager R, Antonini A, Rascol O, Poewe W, et al. Collective physician perspectives on non-oral

medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: consensus from an international survey and discussion program. Parkinsonism Relat Disord. 2015;21:1133-44. PubMed PMID: 26233582.

Oertel WH, Berardelli A, Bloem BR, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Ferreira JJ, Friedman A, Kanovsky P, Kostic V, Nieuwboer A, Odin P, Poewe W, Rascol O, Sampaio C, Schüpbach M, Tolosa E, Trenkwalder C. Early (uncomplicated) Parkinson's disease. In: Gilhus NE, Barnes M, Brainin M, eds. *European Handbook of Neurological Management.* Vol 1. 2 ed. Oxford: Blackwell Publishing Ltd; 2011a:217-36.

Oertel WH, Berardelli A, Bloem BR, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Ferreira JJ, Friedman A, Kanovsky P, Kostic V, Nieuwboer A, Odin P, Poewe W, Rascol O, Sampaio C, Schüpbach M, Tolosa E, Trenkwalder C. Late (complicated) Parkinson's disease. In: Gilhus NE, Barnes M, Brainin M, eds. *European Handbook of Neurological Management*. Vol 1. 2 ed. Oxford: Blackwell Publishing Ltd; 2011b:237-67.

Orme T, Hernandez D, Ross OA, Kun-Rodrigues C, Darwent L, Shepherd CE, Parkkinen L, Ansorge O, Clark L, Honig LS, Marder K, Lemstra A, Rogaeva E, St George-Hyslop P, Londos E, Zetterberg H, Morgan K, Troakes C, Al-Sarraj S, Lashley T, Holton J, Compta Y, Van Deerlin V, Trojanowski JQ, Serrano GE, Beach TG, Lesage S, Galasko D, Masliah E, Santana I, Pastor P, Tienari PJ, Myllykangas L, Oinas M, Revesz T, Lees A, Boeve BF, Petersen RC, Ferman TJ, Escott-Price V, Graff-Radford N, Cairns NJ, Morris JC, Pickering-Brown S, Mann D, Halliday G, Stone DJ, Dickson DW, Hardy J, Singleton A, Guerreiro R, Bras J. Analysis of neurodegenerative disease-causing genes in dementia with Lewy bodies. Acta Neuropathol Commun. 2020;8:5. PubMed PMID: 31996268.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Al Turki S, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126-33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rovelet-Lecrux A, Charbonnier C, Wallon D, Nicolas G, Seaman MN, Pottier C, Breusegem SY, Mathur PP, Jenardhanan P, Le Guennec K, Mukadam AS, Quenez O, Coutant S, Rousseau S, Richard AC, Boland A, Deleuze JF, Frebourg T, Hannequin D, Campion D, et al. De novo deleterious genetic variations target a biological network centered on Aβ peptide in early-onset Alzheimer disease. Mol Psychiatry. 2015;20:1046-56. PubMed PMID: 26194182.

Seier M, Hiller A. Parkinson's disease and pregnancy: an updated review. Parkinsonism Relat Disord. 2017;40:11-7. PubMed PMID: 28506531.

Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, Hametner EM, Poewe W, Rascol O, Goetz CG, Sampaio C. The Movement Disorder Society Evidence-Based Medicine Review Update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord. 2011;26:S42-80. PubMed PMID: 22021174.

Sharma M, Ioannidis JP, Aasly JO, Annesi G, Brice A, Bertram L, Bozi M, Barcikowska M, Crosiers D, Clarke CE, Facheris MF, Farrer M, Garraux G, Gispert S, Auburger G, Vilariño-Güell C, Hadjigeorgiou GM, Hicks AA, Hattori N, Jeon BS, Jamrozik Z, Krygowska-Wajs A, Lesage S, Lill CM, Lin JJ, Lynch T, Lichtner P, Lang AE, Libioulle C, Murata M, Mok V, Jasinska-Myga B, Mellick GD, Morrison KE, Meitnger T, Zimprich A, Opala G, Pramstaller PP, Pichler I, Park SS, Quattrone A, Rogaeva E, Ross OA, Stefanis L, Stockton JD, Satake W, Silburn PA, Strom TM, Theuns J, Tan EK, Toda T, Tomiyama H, Uitti RJ, Van Broeckhoven C, Wirdefeldt K, Wszolek Z, Xiromerisiou G, Yomono HS, Yueh KC, Zhao Y, Gasser T, Maraganore D, Krüger R, et al. A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants. J Med Genet. 2012;49:721-6. PubMed PMID: 23125461.

Sheerin UM, Charlesworth G, Bras J, Guerreiro R, Bhatia K, Foltynie T, Limousin P, Silveira-Moriyama L, Lees A, Wood N. Screening for VPS35 mutations in Parkinson's disease. Neurobiol Aging. 2012;33:838.e1-5. PubMed PMID: 22154191.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Struhal W, Presslauer S, Spielberger S, Zimprich A, Auff E, Bruecke T, Poewe W, Ransmayr G, et al. VPS35 Parkinson's disease phenotype resembles the sporadic disease. J Neural Transm (Vienna). 2014;121:755-9. PubMed PMID: 24557499.

Trenkwalder C, Chaudhuri KR, García Ruiz PJ, LeWitt P, Katzenschlager R, Sixel-Döring F, Henriksen T, Sesar Á, Poewe W, Baker M, Ceballos-Baumann A, Deuschl G, Drapier S, Ebersbach G, Evans A, Fernandez H, Isaacson S, van Laar T, Lees A, Lewis S, Martínez Castrillo JC, Martinez-Martin P, Odin P, O'Sullivan J, Tagaris G, Wenzel K, et al. Expert Consensus Group report on the use of apomorphine in the treatment of Parkinson's disease: clinical practice recommendations. Parkinsonism Relat Disord. 2015;21:1023-30. PubMed PMID: 26189414.

Trinh J, Zeldenrust FMJ, Huang J, Kasten M, Schaake S, Petkovic S, Madoev H, Grünewald A, Almuammar S, König IR, Lill CM, Lohmann K, Klein C, Marras C. Genotype-phenotype relations for the Parkinson's disease genes SNCA, LRRK2, VPS35: MDSGene systematic review. Mov Disord. 2018;33:1857-70. PubMed PMID: 30357936.

Vilariño-Güell C, Rajput A, Milnerwood AJ, Shah B, Szu-Tu C, Trinh J, Yu I, Encarnacion M, Munsie LN, Tapia L, Gustavsson EK, Chou P, Tatarnikov I, Evans DM, Pishotta FT, Volta M, Beccano-Kelly D, Thompson C, Lin MK, Sherman HE, Han HJ, Guenther BL, Wasserman WW, Bernard V, Ross CJ, Appel-Cresswell S, Stoessl AJ, Robinson CA, Dickson DW, Ross OA, Wszolek ZK, Aasly JO, Wu RM, Hentati F, Gibson RA, McPherson PS, Girard M, Rajput M, Rajput AH, Farrer MJ. DNAJC13 mutations in Parkinson disease. Hum Mol Genet. 2014;23:1794-801. PubMed PMID: 24218364.

Vilariño-Güell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, Lincoln SJ, Soto-Ortolaza AI, Cobb SA, Wilhoite GJ, Bacon JA, Behrouz B, Melrose HL, Hentati E, Puschmann A, Evans DM, Conibear E, Wasserman WW, Aasly JO, Burkhard PR, Djaldetti R, Ghika J, Hentati F, Krygowska-Wajs A, Lynch T, Melamed E, Rajput A, Rajput AH, Solida A, Wu RM, Uitti RJ, Wszolek ZK, Vingerhoets F, Farrer MJ. VPS35 mutations in Parkinson disease. Am J Hum Genet. 2011;89:162-7. PubMed PMID: 21763482.

Vollstedt EJ, Schaake S, Lohmann K, Padmanabhan S, Brice A, Lesage S, Tesson C, Vidailhet M, Wurster I, Hentati F, Mirelman A, Giladi N, Marder K, Waters C, Fahn S, Kasten M, Brüggemann N, Borsche M, Foroud T, Tolosa E, Garrido A, Annesi G, Gagliardi M, Bozi M, Stefanis L, Ferreira JJ, Correia Guedes L, Avenali M, Petrucci S, Clark L, Fedotova EY, Abramycheva NY, Alvarez V, Menéndez-González M, Jesús Maestre S, Gómez-Garre P, Mir P, Belin AC, Ran C, Lin CH, Kuo MC, Crosiers D, Wszolek ZK, Ross OA, Jankovic J, Nishioka K, Funayama M, Clarimon J, Williams-Gray CH, Camacho M, Cornejo-Olivas M, Torres-Ramirez L, Wu YR, Lee-Chen GJ, Morgadinho A, Pulkes T, Termsarasab P, Berg D, Kuhlenbäumer G, Kühn AA, Borngräber F, de Michele G, De Rosa A, Zimprich A, Puschmann A, Mellick GD, Dorszewska J, Carr J, Ferese R, Gambardella S, Chase B, Markopoulou K, Satake W, Toda T, Rossi M, Merello M, Lynch T, Olszewska DA, Lim SY, Ahmad-Annuar A, Tan AH, Al-Mubarak B, Hanagasi H, Koziorowski D, Ertan S, Genç G, de Carvalho Aguiar P, Barkhuizen M, Pimentel MMG, Saunders-Pullman R, van de Warrenburg B, Bressman S, Toft M, Appel-Cresswell S, Lang AE, Skorvanek M, Boon AJW, Krüger R, Sammler EM, Tumas V, Zhang BR, Garraux G, Chung SJ, Kim YJ, Winkelmann J, Sue CM, Tan EK, Damásio J, Klivényi P, Kostic VS, Arkadir D, Martikainen M, Borges V, Hertz JM, Brighina L, Spitz M, Suchowersky O, Riess O, Das P, Mollenhauer B, Gatto EM, Petersen MS, Hattori N, Wu RM, Illarioshkin SN, Valente EM, Aasly JO, Aasly A, Alcalay RN, Thaler A, Farrer MJ, Brockmann K, Corvol JC, Klein C, et al. Embracing monogenic Parkinson's disease: the MJFF Global Genetic PD cohort. Mov Disord. 2023;38:286-303. PubMed PMID: 36692014.

Wang C, Niu M, Zhou Z, Zheng X, Zhang L, Tian Y, Yu X, Bu G, Xu H, Ma Q, Zhang YW. VPS35 regulates cell surface recycling and signaling of dopamine receptor D1. Neurobiol Aging. 2016;46:22-31. PubMed PMID: 27460146.

Wider C, Skipper L, Solida A, Brown L, Farrer M, Dickson D, Wszolek ZK, Vingerhoets FJ. Autosomal dominant dopa-responsive parkinsonism in a multigenerational Swiss family. Parkinsonism Relat Disord. 2008;14:465-70. PubMed PMID: 18342564.

Williams ET, Chen X, Otero PA, Moore DJ. Understanding the contributions of VPS35 and the retromer in neurodegenerative disease. Neurobiol Dis. 2022;170:105768. PubMed PMID: 35588987.

Zavodszky E, Seaman MN, Moreau K, Jimenez-Sanchez M, Breusegem SY, Harbour ME, Rubinsztein DC. Mutation in VPS35 associated with Parkinson's disease impairs WASH complex association and inhibits autophagy. Nat Commun. 2014a;5:3828. PubMed PMID: 24819384.

Zavodszky E, Seaman MN, Rubinsztein DC. VPS35 Parkinson mutation impairs autophagy via WASH. Cell Cycle. 2014b;13:2155-6. PubMed PMID: 24963965.

Zesiewicz TA, Sullivan KL, Arnulf I, Chaudhuri KR, Morgan JC, Gronseth GS, Miyasaki J, Iverson DJ, Weiner WJ, et al. Practice parameter: treatment of nonmotor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74:924-31. PubMed PMID: 20231670.

Zimprich A, Benet-Pagès A, Struhal W, Graf E, Eck SH, Offman MN, Haubenberger D, Spielberger S, Schulte EC, Lichtner P, Rossle SC, Klopp N, Wolf E, Seppi K, Pirker W, Presslauer S, Mollenhauer B, Katzenschlager R, Foki T, Hotzy C, Reinthaler E, Harutyunyan A, Kralovics R, Peters A, Zimprich F, Brücke T, Poewe W, Auff E, Trenkwalder C, Rost B, Ransmayr G, Winkelmann J, Meitinger T, Strom TM. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am J Hum Genet. 2011;89:168-75. PubMed PMID: 21763483.

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