Waisman Syndrome

X-linked intellectual disability with early-onset parkinsonism (RAB39B-related disorder)

Overview

- **Synonyms:** Waisman–Laxova syndrome; X-linked intellectual disability with early-onset parkinsonism (XLID-EOP); PARK-RAB39B (MDS nomenclature).
- **OMIM:** Waisman syndrome (WSMN) #311510; allelic non-parkinsonian XLID72 #300271; gene *RAB39B* *300774.
- **Locus / gene:** Xq28, *RAB39B* — a neuron-enriched small Rab GTPase regulating vesicular trafficking.
- **Inheritance:** X-linked recessive (hemizygous males affected); rare X-linked dominant-acting variant (p.G192R) with affected females.
- **Core triad:** intellectual disability + early-onset parkinsonism in a male + X-linked family history; ± epilepsy, autism, macrocephaly.
- **Pathology:** nigral dopaminergic loss with widespread Lewy body pathology, plus tau, iron and axonal spheroids.
- **Treatment:** symptomatic — levodopa trial, antiseizure drugs, behavioural and rehabilitative care, genetic counselling.

1. Nomenclature and history

The disorder takes its name from the Waisman Center (University of Wisconsin–Madison), where Laxova and colleagues described in 1985 a Wisconsin kindred in which males had intellectual disability together with a progressive basal ganglia disorder showing X-linked recessive transmission [1]. The genetic basis remained unknown for almost three decades.

In 2010, Giannandrea and colleagues identified loss-of-function variants in *RAB39B* in families with X-linked intellectual disability, some members of which had autism, epilepsy and macrocephaly, but parkinsonism was not the focus of that report [2]. In 2014, Wilson and colleagues linked *RAB39B* to the combined phenotype: an Australian family with three affected males carried a ~45 kb deletion removing the entire gene, and the original Wisconsin (Waisman/Laxova) kindred carried a destabilising missense variant, c.503C>A (p.Thr168Lys) [3]. This established Waisman syndrome as the parkinsonian end of the *RAB39B* spectrum.

Under the International Parkinson and Movement Disorder Society nomenclature for genetic movement disorders, the condition is designated **PARK-RAB39B**, reflecting parkinsonism as the predominant movement phenotype [4].

2. Epidemiology

- Ultra-rare: fewer than a few dozen families reported worldwide; true prevalence unknown.
- *RAB39B* variants are a rare cause of early-onset Parkinson disease even in screened cohorts, although loss-of-function variants have been found in clinically typical early-onset PD in males [5].
- Likely under-diagnosed: parkinsonism in an adult with intellectual disability is frequently attributed to antipsychotic exposure, and older patients rarely undergo exome or copy-number testing.
- No ethnic predilection established; reported families span Europe, North America, Australia and Asia.

3. Genetics

3.1 The gene

RAB39B lies in distal Xq28 and encodes a 213-amino-acid member of the Rab family of small GTPases. Rab proteins cycle between an active GTP-bound (membrane-associated) and an inactive GDP-bound (cytosolic) state and specify vesicle identity, transport and fusion. RAB39B is neuron-specific in expression and localises predominantly to the Golgi compartment and associated vesicles [2]. Its hypervariable C-terminal region mediates membrane targeting — a point relevant to the p.G192R variant, which causes mislocalisation of the protein [6].

3.2 Variant spectrum

Variant class	Examples (reported)	Functional effect / phenotype
Whole-gene deletion	~45 kb deletion (Australian family) [3]	Complete loss of protein → ID + early-onset parkinsonism with Lewy pathology
Missense (destabilising)	c.503C>A, p.Thr168Lys (Wisconsin/Waisman kindred) [3]	Unstable protein, loss of function → classic Waisman phenotype
Nonsense / splice	c.21C>A, p.Tyr7*; c.215+1G>A (MRX72 family) [2]	No protein → XLID ± autism, epilepsy, macrocephaly
Missense (mislocalising)	c.574G>A, p.Gly192Arg [6]	Mislocalised protein; clinically typical PD (mean onset ~46 y), mild or no ID; affects males and some females (X-linked dominant pattern)
Frameshift / other LoF, incl. mosaic	Various, including somatic mosaicism [5,7]	Early-onset PD ± ID; mosaicism may soften the phenotype
Copy-number gain	Distal Xq28 duplications including *RAB39B* [8]	Increased dosage → cognitive impairment in males (gene-dosage sensitivity)

Table 1. Allelic spectrum of RAB39B. Both loss and gain of dosage are pathogenic, underscoring tight dosage sensitivity.

3.3 Genotype–phenotype principles

- Complete or near-complete loss of function in males → neurodevelopmental disease from childhood with parkinsonism emerging later; the parkinsonian component is age-dependent, so a young patient may present only with ID.
- Variants that alter targeting rather than abolish the protein (p.G192R) → later-onset, more typical PD with little cognitive involvement and penetrance in some heterozygous females.
- Intrafamilial variability is substantial: the same variant may produce ID without overt parkinsonism in one male and full Waisman phenotype in another.

4. Molecular pathogenesis

Two converging mechanisms explain the dual neurodevelopmental and neurodegenerative phenotype (Figure 1).

Synaptic arm. RAB39B, in complex with the adaptor PICK1, drives trafficking of the AMPA-receptor subunit GluA2 from the endoplasmic reticulum/Golgi to the synapse. Loss of RAB39B shifts synaptic AMPA receptors toward GluA2-lacking, calcium-permeable assemblies, alters dendritic spine maturation and impairs synaptic plasticity — a plausible substrate for intellectual disability and autism [9]. Knockout mice additionally show fewer NMDA receptors in the postsynaptic density and impaired learning and memory [10].

Proteostasis arm. RAB39B deficiency reduces autophagic flux, and rapamycin-induced autophagy partly rescues memory and synaptic deficits in knockout mice [10]. In cellular models, knockdown alters α-synuclein homeostasis, reducing α-synuclein puncta in dendrites and its steady-state levels [3]. Clinico-pathological follow-up confirms a Lewy-body disease with additional proteinopathies [11,12].

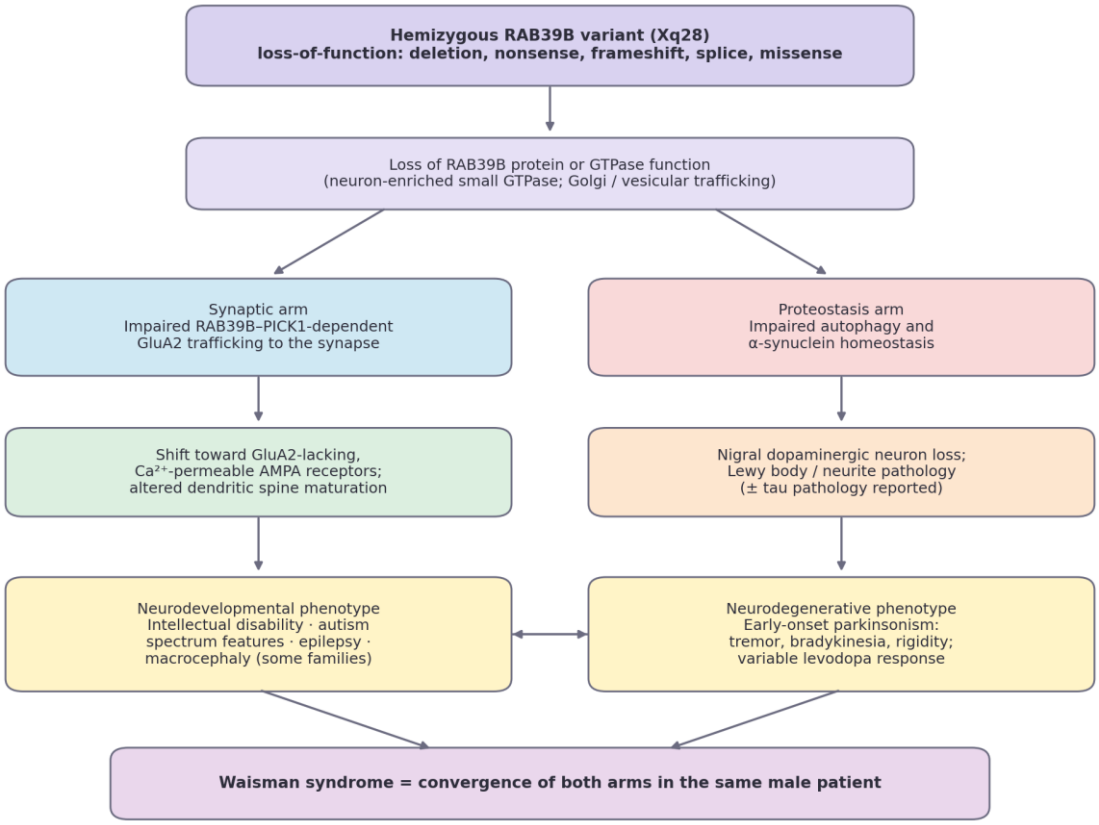

Figure 1. Pathogenic cascade in Waisman syndrome: loss of RAB39B disrupts both glutamate-receptor trafficking and α-synuclein/autophagy homeostasis.

5. Neuropathology

- Extensive loss of dopaminergic neurons in the substantia nigra with widespread classic brainstem Lewy bodies [3].
- Cortical Lewy bodies, tau immunoreactivity, brain iron accumulation and axonal spheroids — a mixed proteinopathy beyond idiopathic PD [3].
- Later case series confirm heterogeneity; a 2026 pedigree study documented variable α-synuclein and tau co-pathology among relatives carrying the same variant [11,12].
- Teaching point: Waisman syndrome is one of the few monogenic ID syndromes with *pathologically proven* Lewy-body Parkinson disease, placing RAB39B alongside SNCA, LRRK2 and GBA-related biology.

6. Clinical features

Domain	Features	Comments
Neurodevelopment	Global developmental delay; intellectual disability, usually mild to moderate (occasionally severe); speech delay	Present from early childhood; usually the first reason for referral

Domain	Features	Comments
Motor — parkinsonism	Rest and postural tremor, bradykinesia, rigidity, hypomimia, hypophonia, shuffling gait, postural instability	Onset from childhood to the fifth decade; typically progressive; may be asymmetric
Motor — other	Dystonia, pyramidal signs, clumsiness, strabismus reported in some	Mixed motor pictures should not exclude the diagnosis
Levodopa response	Ranges from good to partial or poor; dyskinesias may appear	A structured levodopa trial is always justified
Epilepsy	Seizures in a subset (various types)	More frequent in the XLID-predominant families [2]
Behaviour / psychiatry	Autism spectrum features, hyperactivity, anxiety, psychosis in some	Beware antipsychotic-induced worsening of parkinsonism
Craniofacial / somatic	Macrocephaly in some families; otherwise no consistent dysmorphism	Absence of dysmorphism helps separate from syndromic XLID
Cognitive trajectory	Baseline ID; superimposed decline possible in adulthood	Consistent with cortical Lewy and tau pathology

Table 2. Clinical spectrum of Waisman syndrome in hemizygous males [1–3,5–7,11].

6.1 Natural history

The typical trajectory is childhood developmental delay → stable intellectual disability through adolescence → emergence of tremor-dominant or akinetic-rigid parkinsonism (late childhood to middle adulthood) → gradual motor progression, falls, dysphagia and possible cognitive decline. Survival data are limited; complications are those of advanced parkinsonism (aspiration, falls, immobility).

6.2 Female heterozygotes

- With loss-of-function alleles, carrier females are usually unaffected or show mild learning difficulties; skewed X-inactivation may unmask symptoms.
- With p.G192R, females developed clinically typical PD (2 of 7 affected individuals in the index kindred), behaving as X-linked dominant with reduced penetrance [6].

7. Diagnostic approach (tiered)

There are no formal diagnostic criteria. Diagnosis rests on a compatible phenotype plus a pathogenic *RAB39B* variant. The parkinsonian component should be characterised against the MDS clinical diagnostic criteria for PD [13], and variants interpreted according to ACMG/AMP guidance [14]. Figure 2 summarises a tiered algorithm.

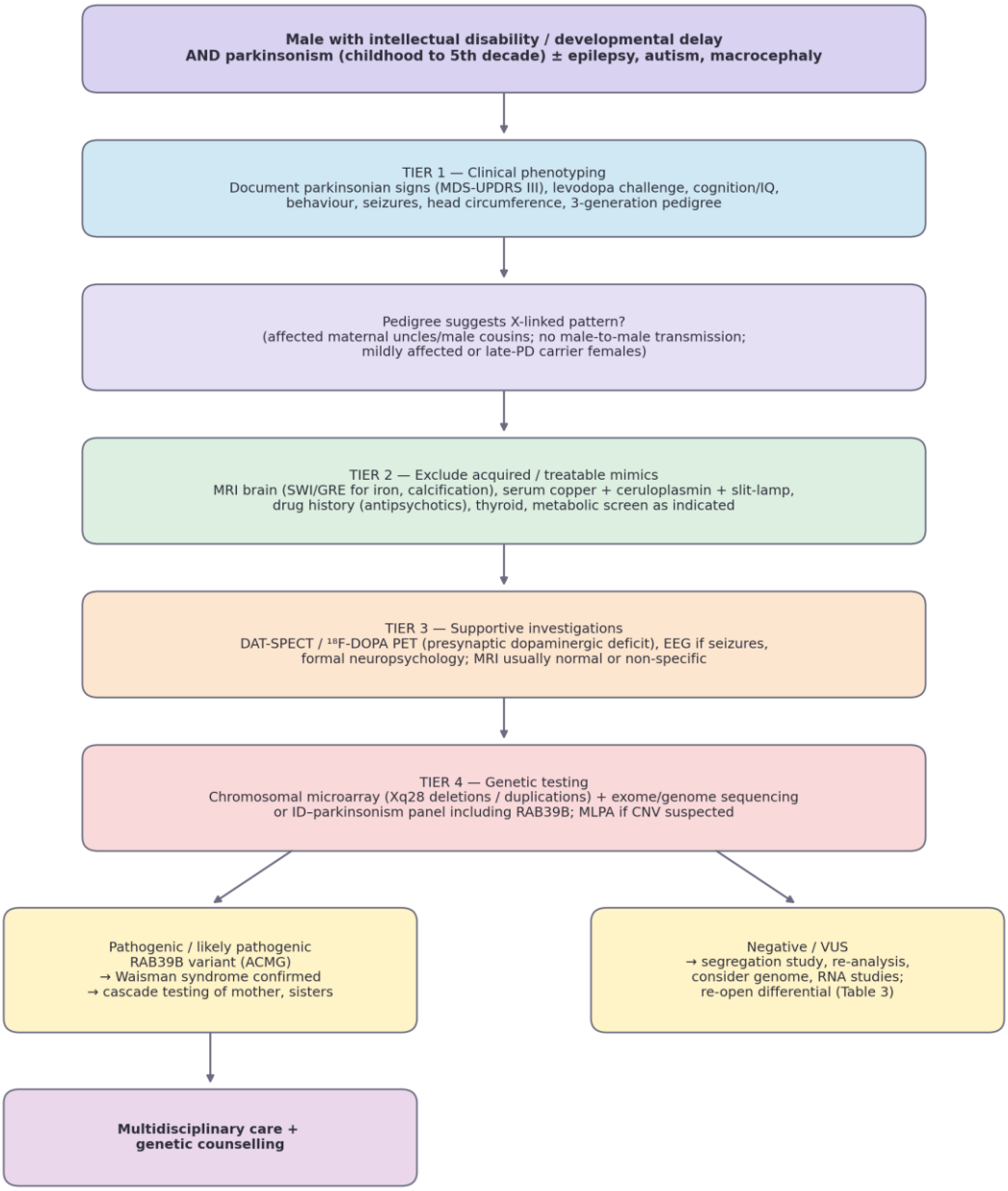

Figure 2. Tiered diagnostic algorithm for suspected Waisman syndrome.

7.1 Tier-wise investigations

Tier	Investigation	Expected finding / purpose
Tier 1 — Bedside	Detailed motor examination (MDS-UPDRS III), levodopa challenge, IQ/adaptive assessment, head circumference, three-generation pedigree	Documents parkinsonism, dopaminergic responsiveness, degree of ID; X-linked pattern
Tier 2 — Exclusion	MRI brain with SWI/GRE; serum copper, ceruloplasmin, slit-lamp; thyroid; drug review (antipsychotics, antiemetics, valproate); CT for calcification if indicated	MRI usually normal or non-specific; excludes Wilson disease, NBIA patterns, calcification, drug-induced parkinsonism
Tier 3 — Supportive	DAT-SPECT or ^{18}F-DOPA PET; EEG; neuropsychology	Presynaptic dopaminergic deficit (distinguishes from drug-induced parkinsonism); seizure characterisation

Tier	Investigation	Expected finding / purpose
Tier 4 — Genetic	Chromosomal microarray (Xq28 CNV) → exome/genome or panel incl. *RAB39B*; MLPA for small deletions; segregation and X-inactivation studies in females	Confirms diagnosis; whole-gene deletions are missed by panel sequencing without CNV calling

Table 3a. Tiered investigations.

Practical pitfalls

- Whole-gene *RAB39B* deletions are invisible on Sanger or panel sequencing without CNV analysis — request microarray or CNV-aware exome.
- A normal MRI does not argue against the diagnosis; iron deposition is a neuropathological, not a consistent radiological, feature.
- In an adult with ID on neuroleptics, parkinsonism with an abnormal DAT scan is *not* drug-induced — reconsider a genetic cause.
- A young male may show only ID; parkinsonism is age-dependent, so re-examine over time and counsel accordingly.

8. Differential diagnosis

Condition (gene)	Inheritance	Distinguishing features
BPAN (*WDR45*)	X-linked dominant, mostly de novo females	Childhood ID/epilepsy then adult dystonia-parkinsonism; SWI hypointensity of SN/GP with T1 hyperintense 'halo' in SN
X-linked dystonia-parkinsonism (*TAF1*)	X-linked recessive	Filipino (Panay) males; adult-onset focal→generalised dystonia then parkinsonism; no ID
X-linked parkinsonism with spasticity (*ATP6AP2*)	X-linked recessive	Parkinsonism with prominent spasticity; variable cognition
***MECP2* duplication / Rett syndrome**	X-linked	Duplication: males with severe ID, hypotonia, recurrent infections, epilepsy; Rett: females with regression and hand stereotypies; parkinsonism in adulthood
Kufor–Rakeb (*ATP13A2*)	Autosomal recessive	Juvenile parkinsonism, supranuclear gaze palsy, pyramidal signs, mini-myoclonus, dementia
PLAN (*PLA2G6*)	Autosomal recessive	Adult dystonia-parkinsonism, early levodopa dyskinesias, cognitive/psychiatric decline; cerebellar atrophy, ± iron
DNAJC6* / *SYNJ1	Autosomal recessive	Juvenile parkinsonism with seizures and cognitive impairment (synaptic vesicle recycling defects)
PRKN* / *PINK1* / *DJ-1	Autosomal recessive	Early-onset levodopa-responsive PD with normal cognition and development
22q11.2 deletion syndrome	Autosomal dominant / de novo	Early-onset PD, psychosis, cardiac and palatal defects, dysmorphism, hypocalcaemia
Wilson disease (*ATP7B*)	Autosomal recessive	Hepatic disease, Kayser–Fleischer rings, low ceruloplasmin; treatable — always exclude

Condition (gene)	Inheritance	Distinguishing features
Drug-induced parkinsonism	Acquired	Antipsychotic exposure, symmetric signs, normal DAT-SPECT

Table 3b. Differential diagnosis of intellectual disability with parkinsonism.

9. Management

No disease-modifying therapy exists; care is symptomatic and multidisciplinary.

Target	Approach
Parkinsonism	Levodopa/carbidopa titrated to response; dopamine agonists and MAO-B inhibitors cautiously (risk of impulse-control and psychiatric effects in ID). Monitor for dyskinesias. Deep brain stimulation is not established.
Epilepsy	Standard antiseizure medication by seizure type; avoid valproate where it may aggravate tremor/parkinsonism.
Behaviour / psychiatric	Behavioural therapy, structured environment; if an antipsychotic is unavoidable, prefer quetiapine or clozapine; avoid typical neuroleptics, risperidone and metoclopramide.
Cognition / education	Special education, adaptive-skills training, vocational support; periodic cognitive reassessment in adulthood.
Rehabilitation	Physiotherapy (gait, falls), occupational therapy, speech and swallow therapy; dietetic review for dysphagia and constipation.
Genetic counselling	Carrier testing of mother and female relatives; prenatal or preimplantation diagnosis once the familial variant is known (Section 10).
Research directions	Autophagy enhancement (rapamycin rescued deficits in *Rab39b* knockout mice [10]); patient-derived iPSC neuronal models; natural-history registries.

Table 4. Management summary.

10. Genetic counselling

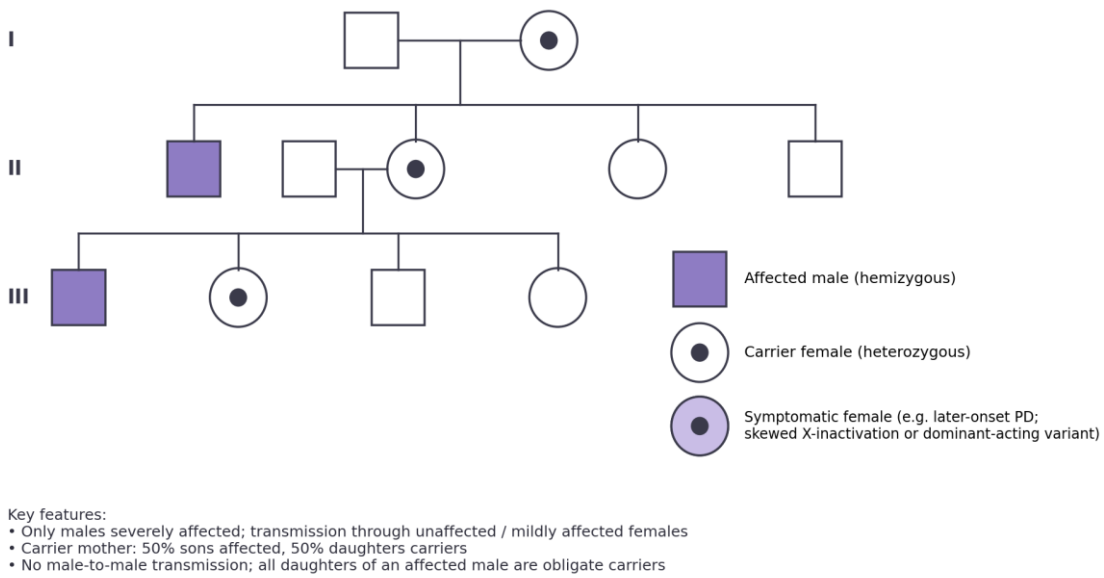

Figure 3. Illustrative X-linked recessive pedigree of Waisman syndrome.

- Mother of an affected male: carrier in most cases; de novo occurrence and germline mosaicism are possible — test her even if asymptomatic.
- Carrier female: each son has a 50% risk of being affected; each daughter a 50% risk of being a carrier.
- Affected male: all daughters are obligate carriers; no sons are affected.
- For p.G192R-type families, counsel heterozygous females about a real but reduced risk of adult-onset PD.
- Prenatal testing (CVS/amniocentesis) and preimplantation genetic testing are feasible once the familial variant is established.

References

1. Laxova R, Brown ES, Hogan K, Hecox K, Opitz JM. An X-linked recessive basal ganglia disorder with mental retardation. Am J Med Genet. 1985;21(4):681–689.
2. Giannandrea M, Bianchi V, Mignogna ML, et al. Mutations in the small GTPase gene RAB39B are responsible for X-linked mental retardation associated with autism, epilepsy, and macrocephaly. Am J Hum Genet. 2010;86(2):185–195. doi:10.1016/j.ajhg.2010.01.011
3. Wilson GR, Sim JCH, McLean C, et al. Mutations in RAB39B cause X-linked intellectual disability and early-onset Parkinson disease with α-synuclein pathology. Am J Hum Genet. 2014;95(6). doi:10.1016/j.ajhg.2014.10.015
4. Marras C, Lang A, van de Warrenburg BP, et al. Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society task force. Mov Disord. 2016;31(4):436–457.
5. Lesage S, Bras J, Cormier-Dequaire F, et al. Loss-of-function mutations in RAB39B are associated with typical early-onset Parkinson disease. Neurol Genet. 2015;1(1):e9.
6. Mata IF, Jang Y, Kim CH, et al. The RAB39B p.G192R mutation causes X-linked dominant Parkinson's disease. Mol Neurodegener. 2015;10:50. doi:10.1186/s13024-015-0045-4
7. Ciammola A, Carrera P, Di Fonzo A, et al. X-linked parkinsonism with intellectual disability caused by novel mutations and somatic mosaicism in RAB39B gene. Parkinsonism Relat Disord. 2017;44:142–146.
8. Vanmarsenille L, Giannandrea M, Fieremans N, et al. Increased dosage of RAB39B affects neuronal development and could explain the cognitive impairment in male patients with distal Xq28 copy number gains. Hum Mutat. 2014;35(3):377–383.

9. Mignogna ML, Giannandrea M, Gurgone A, et al. The intellectual disability protein RAB39B selectively regulates GluA2 trafficking to determine synaptic AMPAR composition. Nat Commun. 2015;6:6504.
10. Niu M, Zheng N, Wang Z, et al. RAB39B deficiency impairs learning and memory partially through compromising autophagy. Front Cell Dev Biol. 2020;8:598622. doi:10.3389/fcell.2020.598622
11. Gao Y, Martínez-Cerdeño V, Hogan KJ, McLean CA, Lockhart PJ. Clinical and neuropathological features associated with loss of RAB39B. Mov Disord. 2020;35(4):687–693.
12. Latimer C, et al. Heterogenous neuropathology in a pedigree with RAB39B-related Parkinson's disease. Mov Disord. 2026. doi:10.1002/mds.70341
13. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30(12):1591–1601.
14. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the ACMG and AMP. Genet Med. 2015;17(5):405–424.
15. Gao Y, Wilson GR, Stephenson SEM, Bozaoglu K, Farrer MJ, Lockhart PJ. The emerging role of Rab GTPases in the pathogenesis of Parkinson's disease. Mov Disord. 2018;33(2):196–207.