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PPP2R5D-Related Neurodevelopmental Disorder

Synonyms: Jordan's Syndrome, PPP2 Syndrome Type R5D

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Summary

Clinical characteristics

PPP2R5D-related neurodevelopmental disorder (*PPP2R5D*-NDD) is characterized by mild-to-profound neurodevelopmental delay, pronounced hypotonia, and macrocephaly. Onset of independent walking varies widely, and ataxia and movement disorders, including early-onset parkinsonism, are reported. Almost all individuals have speech impairment, with a wide range of abilities. Autism spectrum disorder is also reported in some individuals. Seizures and ophthalmologic abnormalities are reported in fewer than half of individuals. Gastrointestinal and skeletal manifestations are reported. Endocrine, cardiac, and genitourinary issues are each reported in a few individuals. To date, more than 100 individuals with *PPP2R5D*-NDD have been reported.

Diagnosis

The diagnosis of *PPP2R5D*-NDD is established in a proband by identification of a heterozygous pathogenic variant in *PPP2R5D* by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment for developmental delays, intellectual disability, neurobehavioral issues, sleep dysregulation, seizures, visual impairment, gastrointestinal and skeletal manifestations, parkinsonism, and endocrine issues. Develop transition plan to adult care; provide family any community resources.

Surveillance: Assess developmental progress and educational needs at each visit; behavior assessment as clinically indicated; ophthalmology evaluations per ophthalmologist or as needed; assess for gastrointestinal and skeletal manifestations at each visit; evaluation with neurology as needed for movement disorder; assess for impairment

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in fine motor, gross motor, and activities of daily living at each visit; assess for precocious puberty annually throughout early childhood; assess for cryptorchism at each visit in early childhood.

Genetic counseling

PPP2R5D-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Rarely, an individual diagnosed with *PPP2R5D*-NDD has the disorder as the result of a pathogenic variant inherited from an affected, heterozygous parent. Each child of an individual with *PPP2R5D*-NDD has a 50% chance of inheriting the pathogenic variant. Once the *PPP2R5D* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *PPP2R5D*-related neurodevelopmental disorder (*PPP2R5D*-NDD) have been published.

Suggestive Findings

PPP2R5D-NDD **should be considered** in individuals presenting with the following clinical and brain MRI findings.

Clinical findings

- Generalized hypotonia of infancy
- Mild-to-profound developmental delays and/or intellectual disability
- Autism spectrum disorder
- Macrocephaly
- Epilepsy (reported seizure types: generalized tonic-clonic, myoclonic, multifocal, complex partial, and generalized epileptic spasms)
- Early-onset parkinsonism

Brain MRI findings

- Macrocephaly or megalencephaly
- Nonspecific findings including focal cortical abnormalities (n=2), cavum septum pellucidum et vergae (n=3), mesial temporal sclerosis (n=1), plagiocephaly (n=1), white matter abnormalities (n=3) and mild ventriculomegaly (n=5), hydrocephalus (n=2), small or dysplastic corpus callosum (n=2), and cavum septum pellucidum (n=1)

Establishing the Diagnosis

The diagnosis of *PPP2R5D*-NDD **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *PPP2R5D* 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 likely pathogenic variants. (2) Identification of a heterozygous *PPP2R5D* 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** (typically exome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of

PPP2R5D-NDD is nonspecific and indistinguishable from many other inherited disorders, it is most likely to be diagnosed by either a multigene panel (see Option 1) or genomic testing (see Option 2).

Option 1

A **multigene panel** that includes *PPP2R5D* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. 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, and/or other non-sequencing-based tests (see Table 1).

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

Option 2

When the diagnosis of *PPP2R5D*-NDD has not been considered, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *PPP2R5D*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
PPP2R5D	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported

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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Houge et al [2015], Loveday et al [2015], Shang et al [2016], Yeung et al [2017], Levine & Chung [2023], Oyama et al [2023]
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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

PPP2R5D-related neurodevelopmental disorder (*PPP2R5D*-NDD) is characterized by mild-to-profound developmental delay and/or intellectual disability, pronounced hypotonia, and macrocephaly. Some individuals have autism spectrum disorder, seizures, coordination disorder, early-onset parkinsonism, ophthalmologic abnormalities, and skeletal, endocrine, and/or cardiac malformations. To date, more than 100 individuals with

PPP2R5D-NDD have been reported [Houge et al 2015, Loveday et al 2015, Shang et al 2016, Yeung et al 2017, Levine & Chung 2023, Oyama et al 2023]. Affected individuals range in age from 22 months to 61 years.

Table 2. *PPP2R5D*-Related Neurodevelopmental Disorder: Frequency of Select Features

Feature	Proportion of Persons w/Feature
Developmental delay / intellectual disability	40/40
Hypotonia	54/72
Language disorder	43/72
Autism spectrum disorder	19/72
Macrocephaly	48/72
Seizures/epilepsy	33/72
Ophthalmologic abnormalities	17/38

Oyama et al [2023], Sudnawa et al [2025]

Developmental delay and intellectual disability. All individuals reported to date have had developmental delay and/or intellectual disability. Developmental milestones are consistently delayed.

The age at which individuals walk independently varies widely, from age 18 months to nine years, with some individuals still unable to walk at age ten years. Most, but not all, individuals are able to achieve independent walking. Six individuals were reported to walk with an ataxic gait [Houge et al 2015, Shang et al 2016], and in-person assessments show individuals with gross motor difficulties, less functional mobility, and endurance limitations [Sudnawa et al 2025].

Almost all reported individuals had speech impairment, with a wide range of abilities. Seven individuals, ranging in age from two to 53 years, remained nonverbal. Eleven individuals were able to use words, although this ranged from two words with poor articulation at age ten years to 100-200 words and the ability to form short sentences at age 15 years. All individuals with *PPP2R5D*-NDD have had issues with language development [Yeung et al 2017]. Regardless of language eventually achieved, almost all individuals experience speech delay [Biswas et al 2020, Sudnawa et al 2025].

Neurobehavioral/psychiatric manifestations. In an analysis of 72 individuals, 16% were found to have a clinical diagnosis of autism and 16% were borderline autistic. Other common behaviors included sleep problems (16/26), with delay in sleep onset (92.3%), parasomnia (61.5%), and night waking (57.7%) [Oyama et al 2023]. Additionally, individuals are reported to be withdrawn, have attention-seeking behaviors, tantrums, aggressiveness, trouble adjusting to new situations, problems with impulse control, depression, social problems, sensory integration disorder, attention-deficit/hyperactive disorder, and distractibility [Shang et al 2016, Oyama et al 2023, Sudnawa et al 2025].

Macrocephaly. Macrocephaly was reported in 48 out of 72 individuals [Oyama et al 2023]. Head occipitofrontal circumference ranged from two standard deviations (SD) above the mean to 3.8 SD above the mean in affected individuals. Congenital macrocephaly was reported in 7/10 individuals [Sudnawa et al 2025].

Seizures have been reported in 33 individuals. Seizure types observed include generalized tonic-clonic (36.4%), myoclonic (30.3%), multifocal, complex partial, and generalized epileptic spasms. The age of onset ranged from birth to 17.8 years, with a mean age of onset of 2.3 years [Oyama et al 2023]. Two individuals reported with macrocephaly also had epilepsy [Yeung et al 2017]. Further, two affected individuals with epilepsy were described to have mild ventricular dilatation [Houge et al 2015], and one individual with complex partial seizures had cavum septum pellucidum (a nonspecific finding) on brain imaging [Shang et al 2016].

Ophthalmologic abnormalities such as strabismus (27.8%) and astigmatism (16.7%) are common. Other features include amblyopia, esotropia, ptosis, cortical visual blindness, and myopia [Houge et al 2015, Shang et al 2016, Oyama et al 2023]. One individual had cataracts at age 53 years [Houge et al 2015].

Dysmorphic facial features. Many individuals have dysmorphic facial features, including mild hypertelorism, downslanted palpebral fissures, frontal bossing, and a long, hypotonic face. Midface hypoplasia, low-set ears, and plagiocephaly have also been reported. However, dysmorphic features are mild, nonspecific, and vary widely among individuals reviewed.

Gastrointestinal manifestations. Feeding difficulties are common, along with constipation/diarrhea (23.6%), gastroesophageal reflux, and food sensitivities [Levine & Chung 2023, Oyama et al 2023].

Skeletal abnormalities observed include scoliosis (4/16), hip dysplasia, camptodactyly of the fourth toe, and middle 2/3 and 3/4 finger syndactyly [Houge et al 2015, Loveday et al 2015, Shang et al 2016].

Movement disorders. Uncoordinated gait seen in childhood, hand tremors reported in adolescence, and early-onset parkinsonism have been reported beginning in the mid-20s [Hetzelt et al 2021]. Neuropathologic analyses in one individual showed uneven and severe neuronal loss and gliosis in the substantia nigra pars compacta, but no Lewy bodies were observed [Kim et al 2020].

Other

- **Endocrine** abnormalities such as short stature (<3rd centile) were observed in three individuals [Houge et al 2015, Shang et al 2016]. However, two affected individuals with heights two SD above the mean were also reported. One individual had hypoglycemia, and another was diagnosed with poor weight gain [Houge et al 2015, Shang et al 2016]. Age of onset of these conditions was unknown. Precocious puberty has also been reported.
- **Cardiac.** Two of 23 individuals had significant cardiac abnormalities with atrial and ventricular septal defects and a bicuspid aortic valve in one individual and ventricular septal defect and patent foramen ovale in the other.
- **Genital anomalies.** One individual had hypospadias. Undescended testes have also been reported.

Genotype-Phenotype Correlations

Greater cognitive impairment has been seen in individuals with the *PPP2R5D* pathogenic variants p.Glu198Lys and p.Glu420Lys, whereas less cognitive impairment was observed in individuals with the pathogenic variants p.Glu197Lys and p.Glu200Lys [Biswas et al 2020].

Individuals with p.Glu200Lys have higher adaptive function compared to p.Glu198Lys and p.Glu420Lys [Sudnawa et al 2025].

Individuals with the *PPP2R5D* pathogenic variants p.Asp251Ala, p.Asp251Tyr, p.Asp251His, p.Asp251Val, and p.Glu200Lys pathogenic variants had better expressive language skills, personal care, and social skills compared with individuals with p.Glu198Lys and p.Trp207Arg [Oyama et al 2023].

Increased aggression was reported more often in individuals with p.Glu198Lys and p.Glu200Lys compared with individuals with pathogenic variants of amino acid residue 251 [Oyama et al 2023].

Individuals with p.Glu200Lys demonstrated increased oppositional behavior with age [Oyama et al 2023].

Seizures were commonly seen in those with pathogenic variant p.Glu198Lys (60.6%) [Oyama et al 2023].

All groups, except those with amino acid changes involving residue 251, had increased attention difficulties and hyperactivity [Oyama et al 2023].

Penetrance

The majority of the reported pathogenic variants are confirmed *de novo*. Parental results were not available for all reported cases.

There is one report of reduced penetrance. A proband with developmental delay (speech and social) and normal head circumference had a maternally transmitted *PPP2R5D* pathogenic variant c.1321C>T (p.Arg441Ter). His mother had similar cognitive issues and facial features shared with her son, including thick eyebrows, drooping eyelids, shallow orbits, blunt nasal tip, and thick, prominent vermilion of the upper and lower lips. The variant was also found in a healthy sib of the proband [Liu et al 2022].

Prevalence

The prevalence of *PPP2R5D*-NDD is unknown. To date, more than 100 individuals with *PPP2R5D*-NDD have been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PPP2R5D*.

Contiguous gene deletions and duplications of 6p21.1 that include *PPP2R5D* are reported in public databases as being associated with disease (decipher.sanger.ac.uk):

- Duplications including *PPP2R5D* have been reported in nine children with developmental delays.
- Deletions including *PPP2R5D* have been reported in nine children with overlapping phenotypes. Clinical features reported in children with these deletions included developmental delay and hypotonia.

Differential Diagnosis

Genes of interest in the differential diagnosis of *PPP2R5D*-related neurodevelopmental disorder are listed in Table 3.

Table 3. Disorders to Consider in the Differential Diagnosis of *PPP2R5D*-Related Neurodevelopmental Disorder

Gene / Genetic Mechanism	Differential Diagnosis Disorder	MOI	Features of Disorder	
			Overlapping w/*PPP2R5D*-NDD	Distinguishing from *PPP2R5D*-NDD
~593-kb 16p11.2 deletion	16p11.2 recurrent deletion	AD	• ID; speech & language disorders • Autism spectrum disorder • Seizures	• Obesity in adolescence & later in life • Congenital anomalies such as low-set ears & syndactyly of toes
AKT3 *CCND2* *PIK3R2*	MPPH (megalencephaly-polymicrogyria-polydactyly-hydrocephalus) syndrome	AD	• DD/ID; expressive language or speech delay • Epilepsy • Hypotonia • Megalencephaly	• Cortical brain malformations (particularly polymicrogyria) • Polydactyly
DNMT3A	Tatton-Brown-Rahman syndrome	AD	• ID • Macrocephaly • Hypotonia • Seizures	• Kyphoscoliosis • Dysmorphic features such as thick, low-set eyebrows, narrow palpebral fissures, & prominent upper central incisors • ↑ risk of AML

Table 3. continued from previous page.

Gene / Genetic Mechanism	Differential Diagnosis Disorder	MOI	Features of Disorder	
			Overlapping w/*PPP2R5D*-NDD	Distinguishing from *PPP2R5D*-NDD
EHMT1; 9q34.3 deletion [1]	Kleefstra syndrome	AD	• Autistic-like features • Hypotonia • ID; severe expressive speech delay w/little speech development • Seizures	• Distinctive facial features such as synophrys, arched eyebrows, protruding tongue, exaggerated Cupid's bow of vermilion of upper lip • Microcephaly & brachycephaly • Obesity
MTOR	*MTOR*-related disorders (e.g., Smith-Kingsmore syndrome) (OMIM 616638)	AD	• Autism spectrum disorder • Hypotonia • ID • Megalencephaly	• Cortical brain malformations (polymicrogyria, focal cortical dysplasia) • Pigmentary abnormalities of skin
NSD1; Deletion encompassing *NSD1* [2]	Sotos syndrome	AD	• DD/ID • Overgrowth (head circumference ≥2 SD above mean)	• Additional congenital anomalies (e.g., cardiac, skeletal) • Distinctive facial features incl high forehead, long, narrow face, & long chin
PIK3CA	*PIK3CA*-related overgrowth spectrum	AD	• ID • Autistic features • Seizures • Hypotonia • Megalencephaly	• Vascular malformations • Somatic overgrowth (that can be focal) • Lymphatic abnormalities • Digital abnormalities (syndactyly, polydactyly) • Cortical brain malformations (incl polymicrogyria)
PTEN	*PTEN* hamartoma tumor syndrome	AD	• Macrocephaly • Autism spectrum disorder • DD	• Hamartomatous overgrowths of multiple tissues • ↑ cancer predisposition

AD = autosomal dominant; AML = acute myelogenous leukemia; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; *PPP2R5D*-NDD = *PPP2R5D*-related neurodevelopmental disorder; SD = standard deviation

1. Kleefstra syndrome is associated with either a heterozygous deletion at chromosome 9q34.3 that includes at least part of *EHMT1* (~50% of individuals) or a heterozygous intragenic *EHMT1* pathogenic variant (~50% of individuals).

2. Sotos syndrome is caused by a heterozygous NSD1 pathogenic variant or a deletion encompassing NSD1.

Management

Clinical practice guidelines for *PPP2R5D*-related neurodevelopmental disorder (*PPP2R5D*-NDD) have been published [Levine & Chung 2023].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PPP2R5D*-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *PPP2R5D*-Related Neurodevelopmental Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Assessment of growth (head circumference, stature, & weight)	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	Screen persons age >12 mos for behavior concerns, sleep issues, &/or findings suggestive of ASD.
Neurologic	Neurologic eval	Incl EEG if seizures are suspected.
Eyes	Ophthalmologic eval & vision assessment	Assess for astigmatism & strabismus.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	Incl feeding assessment related to hypotonia & eval for GERD, constipation, & diarrhea.
Skeletal	Orthopedic eval	Assess for scoliosis.
Movement disorders	Orthopedics / 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)
Cardiac	Full cardiac eval if audible murmur is present	The prevalence of cardiac malformations in *PPP2R5D*-NDD is not yet known.
Genitourinary	Genitourinary eval to assess for hypospadias & undescended testes	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *PPP2R5D*-NDD to facilitate medical & personal decision making

ADL = activities of daily living; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; *PPP2R5D*-NDD = *PPP2R5D*-related neurodevelopmental disorder; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *PPP2R5D*-Related Neurodevelopmental Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Sleep dysregulation	Standard treatment(s) by sleep specialist	Consider treatment w/melatonin.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many different ASMs may be effective; none has been demonstrated effective specifically for this disorder. • In some children, seizures are well controlled using a single ASM or ketogenic diet. • Education of parents/caregivers [1]
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	
Gastrointestinal manifestations	Standard treatment for dysmotility, GERD, & food sensitivities	
Skeletal manifestations	Standard treatment for scoliosis & hip dysplasia	
Parkinsonism	Standard treatment(s) as recommended by neurologist	Consider levodopa.
Endocrine issues / Precocious puberty	Standard treatment(s) as recommended by endocrinologist	
Transition to adult care	Develop realistic plans for adult life (see American Epilepsy Society Transitions from Pediatric Epilepsy to Adult Epilepsy Care).	Starting by age ~10 yrs
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; GERD = gastroesophageal reflux disease
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC

devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

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. *PPP2R5D*-Related Neurodevelopmental Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurobehavioral/ Psychiatric	Assessment for concerns &/or findings suggestive of ASD.	As clinically indicated
Neurologic	Monitor those w/seizures.	
Eyes	Ophthalmologic eval	Subsequent ophthalmology eval per ophthalmologist or as needed depending on findings
Gastrointestinal	Assess for constipation/diarrhea, symptoms of GERD, & food sensitivities.	At each visit
Skeletal	Assess for scoliosis w/radiographs as needed.	
Movement disorder / Parkinsonism	Eval by neurologist	As needed
	Assess for impairment in fine motor & gross motor skills & ADL.	At each visit
Endocrine	Assess for precocious puberty.	Annually throughout early childhood
Genitourinary	Assess for cryptorchidism.	At each visit in early childhood
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ADL = activities of daily living; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

PPP2R5D-related neurodevelopmental disorder (*PPP2R5D*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- To date, most individuals diagnosed with *PPP2R5D*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo PPP2R5D* pathogenic variant.
- Rarely, an individual diagnosed with *PPP2R5D*-NDD has the disorder as the result of a pathogenic variant inherited from an affected, heterozygous parent.
  - In one family, the proband had the disorder as the result of a *PPP2R5D* pathogenic variant (c.1321C>T [p.Arg441Ter]) inherited from his similarly affected mother (of note, the pathogenic variant was also identified in an unaffected sib of the proband) [Liu et al 2022].
  - In another family, transmission of a *PPP2R5D* pathogenic variant from a mildly affected heterozygous parent to four affected sibs was reported [Oyama et al 2023].
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment. Note: A proband may appear to be the only affected family member because of failure to recognize the disorder in family members or reduced penetrance (reduced penetrance is rare and to date has only been described in a family segregating the c.1321C>T [p.Arg441Ter] pathogenic variant). Therefore, *de novo* occurrence of a *PPP2R5D* pathogenic variant cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the *PPP2R5D* pathogenic variant.
- 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 gonadal (or somatic and gonadal) 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 (gonadal) cells only.

* Theoretically, if the parent is the individual in whom the *PPP2R5D* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

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 is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Parent-to-child transmission of a *PPP2R5D* pathogenic variant has been reported in two families to date [Liu et al 2022, Oyama et al 2023].
- If the *PPP2R5D* pathogenic variant identified 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 possibility of parental gonadal mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *PPP2R5D* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *PPP2R5D*-NDD because of the possibility of reduced penetrance in a heterozygous parent and the possibility of parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with *PPP2R5D*-NDD has a 50% chance of inheriting the *PPP2R5D* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *PPP2R5D* pathogenic variant, the parent's family members may be at risk.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PPP2R5D* 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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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.

- **Jordan's Guardian Angels**
  Email: info@jordansguardianangels.org
  jordansguardianangels.org
- **Simons Searchlight**
  PPP2R5D

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. PPP2R5D-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PPP2R5D	6p21.1	Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunit delta isoform	PPP2R5D	PPP2R5D

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 PPP2R5D-Related Neurodevelopmental Disorder (View All in OMIM)

601646	PROTEIN PHOSPHATASE 2, REGULATORY SUBUNIT B (B56), DELTA; PPP2R5D
616355	HOUGE-JANSSENS SYNDROME 1; HJS1

Molecular Pathogenesis

PPP2R5D encodes 56 kDa regulatory subunit delta isoform (B56δ), a subunit of the serine/threonine-protein phosphatase 2A (PP2A). The PP2A complex is composed of three subunits: a scaffolding subunit A, a regulatory subunit B, and a catalytic domain C. B56δ is one of the isoforms of subunit B and is highly expressed in the brain. This protein is thought to be involved in cell growth, chromatin remodeling, and transcriptional regulation. There is evidence that the PP2A-B56δ holoenzyme interacts with the PI3K/AKT growth regulatory cascade [Loveday et al 2015].

All known pathogenic variants to date are missense variants. Four variants (p.Glu197Lys, p.Glu198Lys, p.Glu200Lys, and p.Glu420Lys) alter a highly conserved negatively charged glutamic acid to a positively charged lysine and are predicted to affect protein structure. Of these, p.Glu198Lys has been frequently encountered, identified in 48% (11/23) of individuals with *PPP2R5D*-related neurodevelopmental disorder. With the exception of variant p.Pro53Ser, pathogenic variants showed deficient holoenzyme formation in HEK293 cells [Houge et al 2015]; p.Pro53Ser has been associated with a different phenotype, including microcephaly and short stature.

Mechanism of disease causation. The p.Glu198Lys and p.Glu200Lys disease-associated variants disrupt PP2A subunit binding and impair dephosphorylation of specific substrates [Houge et al 2015]. The p.Glu420Lys variant is positioned near an active site of the catalytic subunit and is likely to disrupt holoenzyme formation or substrate recognition [Shang et al 2016]. A dominant-negative effect is proposed, supported by biochemical evidence of B56δ-dependent PP2A dysregulation [Houge et al 2015]; however, large 6p21.1-deletion phenotypes are suggestive of a loss-of-function mechanism.

Table 7. *PPP2R5D* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_006245.4 NP_006236.1	c.157C>T	p.Pro53Ser	See Molecular Pathogenesis.
	c.589G>A	p.Glu197Lys	See Genotype-Phenotype Correlations.
	c.592G>A	p.Glu198Lys	
	c.598G>A	p.Glu200Lys	
	c.1258G>A	p.Glu420Lys	
	c.619T>C	p.Trp207Arg	
	c.752A>C	p.Asp251Ala	
	c.751G>C	p.Asp251His	
	c.751G>T	p.Asp251Tyr	
	c.752A>T	p.Asp251Val	

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

Chapter Notes

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