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PPP2R1A-Related Neurodevelopmental Disorder

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Summary

Clinical characteristics

PPP2R1A-related neurodevelopmental disorder (NDD) is characterized by: severe, persistent hypotonia; developmental delay with variable intellectual outcomes, typically in the moderate-to-severe intellectual disability range; seizures (more commonly seen in individuals with microcephaly and/or severe intellectual disability); attention-deficit/hyperactivity disorder and other behavioral problems (anxiousness, repetitive movements, self-injurious or destructive behavior, and autism spectrum disorder); feeding and swallowing issues; and dysmorphic features of the head and face. A minority of affected individuals have ear anomalies, hearing loss, ptosis, generalized joint hypermobility, and patent ductus arteriosus. Brain MRI findings are nonspecific but typically include complete or partial agenesis of the corpus callosum. Nonprogressive ventriculomegaly may be seen in a subset of affected individuals and is often associated with specific pathogenic variants in *PPP2R1A*: c.544C>T (p.Arg182Trp) and c.547C>T (p.Arg183Trp).

Diagnosis/testing

The diagnosis of *PPP2R1A*-NDD is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *PPP2R1A* identified by molecular genetic testing.

Management

Treatment of manifestations: Feeding therapy with consideration of gastrostomy tube placement for persistent feeding issues; standard treatment for epilepsy, developmental delay / intellectual disability, scoliosis, ear anomalies, hearing loss, dental crowding, congenital heart defects, and ptosis.

Surveillance: At each visit: measure growth parameters; evaluate nutritional status and oral intake; assess for new neurologic manifestations such as seizures and changes in muscle tone; monitor developmental progress and educational needs; assess mobility, self-help skills, and need for developmental therapies. At each visit until

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skeletal maturity: physical exam to assess for scoliosis. Annually or as clinically indicated: dental evaluation, audiology evaluation (through childhood), and behavioral assessment for anxiety, attention, and aggressive or self-injurious behavior.

Genetic counseling

PPP2R1A-related NDD is expressed in an autosomal dominant manner and typically caused by a *de novo* *PPP2R1A* pathogenic variant. The risk to other family members is presumed to be low. Once a *PPP2R1A* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *PPP2R1A*-related neurodevelopmental disorder (*PPP2R1A*-NDD) have been published to date.

Suggestive Findings

PPP2R1A-related neurodevelopmental disorder (*PPP2R1A*-NDD) **should be considered** in individuals with the following clinical and brain imaging findings.

Clinical findings include:

- Mild-to-profound developmental delay and/or intellectual disability
  - Delayed walking
  - Language delay
- Generalized hypotonia, postnatal/infantile onset

AND any of the following features presenting in infancy or childhood:

- Feeding problems
- Abnormal head circumference (macrocephaly/microcephaly)
- Epilepsy
- Behavioral problems: attention-deficit/hyperactivity disorder, autism spectrum disorder, self-injurious behavior, anxiety, destructive behaviors
- Joint hypermobility

Brain MRI findings

- Partial or complete agenesis of the corpus callosum (common)
- Ventriculomegaly (frequent)
- Periventricular leukomalacia
- Delayed myelination
- Hypoplasia of the cerebellum and/or brain stem

Family history. All cases to date have been caused by a *de novo* pathogenic missense variant in *PPP2R1A*. All probands so far represent simplex cases (i.e., a single occurrence in a family). Since the severity of the condition is so variable and correlated to the degree of biochemical disturbance, a milder end of the phenotypic spectrum compatible with autosomal dominant inheritance from a mildly affected parent may in theory exist.

Establishing the Diagnosis

The diagnosis of *PPP2R1A*-NDD **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *PPP2R1A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *PPP2R1A* variant of uncertain significance (VUS) does not establish or rule out the diagnosis of this disorder. Biochemical testing to investigate the pathogenicity of a VUS is cumbersome and is currently only done in a research setting.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with chromosomal microarray analysis (CMA). Other options include use of a multigene panel or exome sequencing. Note: Because of the nonspecific nature of the presenting clinical features, single-gene testing (sequence analysis of *PPP2R1A*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability multigene panel** that includes *PPP2R1A* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an intellectual disability multigene panel with the additional advantage that exome sequencing includes genes that may have been recently identified as causal of neurodevelopmental disorders, whereas some multigene panels may not.

  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 *PPP2R1A*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PPP2R1A	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Fewer than 50 affected individuals with pathogenic *PPP2R1A* variants have been reported in the literature to date.
5. Houge et al [2015], Wallace et al [2019], Zhang et al [2020], Lenaerts et al [2021], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. 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.
7. Only pathogenic missense variants with likely dominant-negative effects have so far been reported to cause *PPP2R1A*-NDD (see Molecular Genetics).

Clinical Characteristics

Clinical Description

To date, fewer than 50 individuals have been identified with a pathogenic variant in *PPP2R1A* [Houge et al 2015, Wallace et al 2019, Stenson et al 2020, Zhang et al 2020, Lenaerts et al 2021]. The following description of the phenotypic features associated with this condition is based on comprehensive clinical observations of individuals with confirmed pathogenic variants.

Table 2. Select Features of *PPP2R1A*-Related Neurodevelopmental Disorder

Feature	# of Persons w/Feature / # Assessed	Comment
Developmental delay	37/37 (100%)	Ranging from mild to profound
Language delay	37/37 (100%)	Some persons remain nonverbal.
Intellectual disability	36/37 (97%)	Ranging from mild to profound, usually moderate to severe
Delayed walking	28/30 (93%)	Some persons remain nonambulatory.
Hypotonia	32/35 (91%)	Persistent into childhood & adulthood in 2 known persons
Corpus callosum hypo-/aplasia	22/33 (67%)	
Head growth abnormalities	22/36 (61%)	
• Macrocephaly	12/36 (33%)	See Genotype-Phenotype Correlations.
• Microcephaly	10/36 (28%)	
Feeding difficulties	15/30 (50%)	Incl gastroesophageal reflux
Epilepsy	17/35 (49%)	See Genotype-Phenotype Correlations.
Ventriculomegaly	14/33 (42%)	Incl hydrocephalus
Joint hypermobility	14/37 (38%)	
External ear abnormalities	11/37 (30%)	Incl microtia

Table 2. continued from previous page.

Feature	# of Persons w/Feature / # Assessed	Comment
Scoliosis	9/37 (24%)	
Delayed myelination	6/33 (18%)	
Hypoplasia of cerebellum / brain stem	5/33 (15%)	
Periventricular leukomalacia	4/33 (12%)	
Hearing loss	4/37 (11%)	Incl sensorineural & hearing loss assoc w/microtia
Short stature	3/37 (8%)	
Persistent ductus arteriosus	3/37 (8%)	

Developmental delay (DD) and intellectual disability (ID). The degree of DD is variable, but often in the moderate-to-severe range. DD in most affected individuals is global, affecting both cognitive and motor skills, but speech and language development and walking appear to be especially delayed.

- The most severely affected individuals are typically nonambulatory, and those who learned to walk did so between ages one and five years (average age ~2 years).
- Delayed/absent ambulation could be related to chronic hypotonia seen in most affected individuals.
- One individual did not have ID but had a full-scale IQ of 86 and a clinical diagnosis of autism spectrum disorder [Lenaerts et al 2021]; otherwise, all reported individuals have cognitive performance that falls within the range of ID (defined as a full-scale IQ score of <70).

Language delays are similarly variable, ranging from individuals with no speech and language development to those with relatively normal verbal language skills, but on average language development is moderately to severely delayed.

Hypotonia is a common feature, and unlike the transient neonatal hypotonia that is a feature of numerous syndromes, *PPP2R1A*-related hypotonia is long-lasting and possibly permanent.

Epilepsy is present in about half of affected individuals and is often associated with moderate-to-severe ID.

- Individuals with microcephaly appear to be at an increased risk for developing epilepsy.
- Most individuals with epilepsy develop seizures within the first year of life.
- Seizure types and frequency are variable.
  - In a few individuals, seizures are multifocal and refractory to treatment.
  - The authors are aware of four children who died at young ages as a result of severe epilepsy-associated brain dysfunction; all had pathogenic variants involving p.Arg183 (c.547C) (see also Genotype-Phenotype Correlations).

Behavior problems. Problems related to behavior and sleep were variably present but not in all individuals. The most common is attention-deficit/hyperactivity disorder, but anxiousness, repetitive movements, self-injurious or destructive behavior, and autism spectrum disorders have also been reported. Behavior problems are more commonly observed in those with epilepsy [Lenaerts et al 2021].

Feeding and growth

- **Feeding difficulties** have been reported in about half of affected individuals and tend to be more common in those who are more severely affected.
  - Swallowing difficulties have been reported, causing gagging and/or choking with solid foods and necessitating soft or pureed foods.
  - Some affected individuals have gastroesophageal reflux disease that requires treatment (see Management).

- High palate (which can be associated with dental crowding) has been observed and contributes to feeding difficulties.
- The severity is variable, but some individuals need gastrostomy tube placement.

- **Head circumference.** Approximately two thirds of affected individuals present with abnormal head circumference, either macrocephaly (33%) or microcephaly (28%), which is usually congenital. While macrocephaly is usually nonprogressive, microcephaly can be progressive.
  - Most of the individuals with increased head size (macrocephaly) present with true megalencephaly, with a head circumference >3 SD and as high as 5.23 SD above the mean for age and sex in the absence of ventriculomegaly or hydrocephalus.
  - In individuals with microcephaly, head circumference is 3-6 SD below the mean for age and sex.
  - Some pathogenic variants are specifically associated with megalencephaly and moderate ID or with microcephaly (see Genotype-Phenotype Correlations).
- **Length/height** was within normal range in nearly 90% of affected individuals, and quite variable in individuals with the same pathogenic variant. Fewer than 10% have short stature (defined as length/height 2 SD below the mean for age and sex), and one had tall stature (defined as length/height 2 SD above the mean for age and sex) [Lenaerts et al 2021].

Ears

- **Hearing loss** has been reported in a minority (~10%) of individuals with *PPP2R1A*-NDD [Zhang et al 2020, Lenaerts et al 2021]. In two individuals, the hearing loss was described as sensorineural; in another two individuals it was associated with microtia.
- A range of **external ear abnormalities** not associated with hearing loss including low-set, small, cupped, simple, and asymmetric ears have also been reported.

Eyes. Although cortical blindness has been suspected in a few infants with severe features of *PPP2R1A*-NDD, no verified reports of eye or visual problems exist. However, ptosis can occur (probably as part of general muscular hypotonia).

Neuroimaging. Approximately two thirds of affected individuals have corpus callosum hypoplasia or aplasia, although almost one third have normal brain MRI findings.

- In a number of individuals, ventriculomegaly was identified and may be associated with a specific pathogenic variant (see Genotype-Phenotype Correlations).
  - In two of these individuals the detection of severe ventriculomegaly led to a suspicion of hydrocephalus and ventriculoperitoneal shunting.
  - However, there is to date no confirmation of progressive ventriculomegaly or hydrocephalus.
- Less frequent findings include:
  - Delayed myelination
  - Hypoplasia of the cerebellum and/or brain stem
  - Periventricular leukomalacia

Other associated features

- **Musculoskeletal features.** In addition to hypotonia, generalized joint hypermobility and scoliosis have been reported in about one third of individuals. In two severely affected individuals, hip dislocations were also reported; one of the two also had a knee dislocation.
- **Cardiovascular.** Persistent ductus arteriosus has been reported in three affected individuals (8%).
- **Facial features.** Facial dysmorphism is frequently seen and can be partly associated with generalized hypotonia. Recurrent features include a long face with a tall forehead or frontal bossing (especially in those with macrocephaly), widely spaced eyes (hypertelorism), short palpebral fissures, a small nose with

bulbous/prominent nasal tip, tented and/or thin vermilion of the upper lip, and, occasionally, ptosis [Lenaerts et al 2021].

Prognosis. The life span of severely affected individuals with *PPP2R1A*-NDD can be shortened, especially in the presence of severe epilepsy that is refractory to treatment [Authors, personal communication]. In individuals with milder features, there are no life-limiting clinical comorbidities. Among the few reported individuals with *PPP2R1A*-NDD, several are in their third decade and not affected by life-limiting health problems [Lenaerts et al 2021]. Even though many *PPP2R1A* missense variants are also found somatically in tumors (see Cancer and Benign Tumors), no evidence so far would indicate that *PPP2R1A*-NDD is a cancer predisposition syndrome.

Genotype-Phenotype Correlations

Individuals with a heterozygous pathogenic variant that does not affect PPP2R1A binding to PPP2R2A (B55α) – for example, c.421T>A (p.Phe141Ile), c.532A>T (p.Thr178Ser), c.533C>A (p.Thr178Asn), c.539T>C (p.Met180Thr), and c.538A>G (p.Met180Val) – are more likely to have the following [Lenaerts et al 2021]:

- Macrocephaly, defined as head circumference >2 SD for age and sex
- Less severe intellectual disability
- No seizures
- Frontal bossing / long face

Individuals with pathogenic missense variants that are more likely to cause severe epilepsy – for example, c.536C>T (p.Pro179Leu), c.544C>T (p.Arg182Trp), and c.547C>T (p.Arg183Trp) – are also more likely to have more severe intellectual disability [Lenaerts et al 2021].

Microcephaly is most often associated with the following pathogenic missense variants: c.536C>T (p.Pro179Leu), c.773G>A (p.Arg258His), and c.772C>A (p.Arg258Ser).

Most individuals with the pathogenic variants c.544C>T (p.Arg182Trp) and c.547C>T (p.Arg183Trp) have ventriculomegaly.

Prevalence

The prevalence of *PPP2RA1*-NDD is unknown. To date, about 40 individuals have been reported in the literature and about ten more are known (DECIPHER; Authors, personal communications), with a total of around 50 known affected individuals.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PPP2R1A*.

Sporadic tumors (including colorectal and endometrial cancer) occurring as single tumors in the absence of any other findings of *PPP2R1A*-related neurodevelopmental disorder frequently harbor a somatic pathogenic variant in *PPP2R1A* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Head circumference abnormalities. The wide variability of head circumference abnormalities observed in *PPP2R1A*-related neurodevelopmental disorder (*PPP2R1A*-NDD) is reminiscent of *RAC1*-related intellectual disability [Reijnders et al 2017] and *TRIO*-related intellectual disability (Trio acts as a Rac1 modulator) [Barbosa et al 2020].

Overgrowth. Individuals with macrocephaly and a heterozygous *PPP2R1A* pathogenic variant that does not affect PPP2R1A binding have features reminiscent of overgrowth syndromes, both within the overgrowth and intellectual disability spectrum (e.g., Weaver syndrome; see *EZH2*-Related Overgrowth) [Tatton-Brown et al 2017] and in the spectrum of disorders associated with disruption of the PI3K/AKT/mTOR tyrosine receptor kinase pathway (e.g., MCAP syndrome; see *PIK3CA*-Related Overgrowth Spectrum) [Burkardt et al 2019].

See Table 3 for additional disorders to consider in the differential diagnosis of *PPP2R1A*-NDD.

Table 3. Selected Disorders of Interest in the Differential Diagnosis of *PPP2R1A*-Related Neurodevelopmental Disorder

Gene	DiffDx Disorder	MOI	Features Observed in DiffDx Disorder & *PPP2R1A*-NDD	Distinguishing Features
AKT3	MPPH syndrome 2	AD	Megalencephaly, epilepsy, hypotonia	Polydactyly, hydrocephalus, polymicrogyria in MPPH2
CCND2	MPPH syndrome 3	AD	Megalencephaly, epilepsy	Polydactyly, hydrocephalus, polymicrogyria in MPPH3
EZH2	Weaver syndrome (See *EZH2*-Related Overgrowth.)	AD	Macrocephaly, seizures, frontal bossing, long face, ventriculomegaly, behavioral difficulties	↑ prenatal/postnatal length, advanced bone age, & umbilical hernias are common in persons w/ Weaver syndrome.
NSD1	Sotos syndrome	AD	Macrocephaly, neonatal hypotonia, large head, corpus callosum hypoplasia, large ventricles	↑ prenatal/postnatal length & advanced bone age are common in persons w/Sotos syndrome.
PIK3CA	MCAP syndrome (See *PIK3CA*-Related Overgrowth Spectrum.)	See footnote 1.	Megalencephaly, ventriculomegaly, hypotonia	Polymicrogyria, polydactyly in MCAP syndrome
PIK3R2	MPPH syndrome 1	AD	Megalencephaly, epilepsy	Polydactyly, polymicrogyria in MPPH1
PPP2CA	*PPP2CA*-related NDD (OMIM 618354)	AD	Hypotonia, delayed walking & speech, Macro-/microcephaly, corpus callosum hypoplasia, enlarged ventricles	None
PPP2R5D	*PPP2R5D*-related NDD	AD	Hypotonia, macrocephaly, frontal bossing, elongated face, large ventricles	Corpus callosum aplasia is more common in *PPP2R1A*-NDD.
RAC1	*RAC1*-related ID (OMIM 617751)	AD	Macro-/microcephaly, dysplastic ears, moderate-to-severe DD, seizures, enlarged ventricles	Possibly different facial dysmorphology, but otherwise none
TRIO	*TRIO*-related ID	AD	Macro-/microcephaly, ID, behavioral manifestations, scoliosis	Hand & foot skeletal abnormalities in *TRIO*-ID

AD = autosomal dominant; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MCAP = megalencephaly-capillary malformation; MOI = mode of inheritance; MPPH = megalencephaly-polymicrogyria-polydactyly-hydrocephalus; NDD = neurodevelopmental disorder

1. MCAP syndrome is not known to be inherited, as most identified pathogenic variants are somatic (mosaic). No confirmed vertical transmission or sib recurrence has been reported to date.

Management

No clinical practice guidelines for *PPP2R1A*-related neurodevelopmental disorder (*PPP2R1A*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PPP2R1A*-NDD, 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 *PPP2R1A*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To incl weight, length/height, & head circumference to assess for failure to thrive, short stature, and macro- or microcephaly, respectively
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language evals • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavioral concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Gastrointestinal/ Feeding	Gstroenterology / nutrition / feeding team eval	• To incl eval of nutritional status & gastroesophageal reflux • Consider eval for gastric tube placement in persons w/ dysphagia &/or severe feeding issues.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Scoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hearing	Audiology eval	To assess for hearing loss
ENT/Mouth	Assessment for ear anomalies, incl microtia	Consider referral to ENT specialist when present.
	Eval by dentist if teeth have erupted	High palate can be assoc w/dental crowding.
Cardiovascular	Clinical assessment for congenital cardiac issues, such as PDA	Consider referral to cardiologist as clinically indicated.
Eyes	Assessment for ptosis	Consider referral to ophthalmologist if present.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *PPP2R1A*-NDD to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; EEG = electroencephalogram; ENT = ears, nose, throat; MOI = mode of inheritance; MRI = magnetic resonance imaging; OT = occupational therapy; PDA = patent ductus arteriosus; PT = physical therapy

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

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *PPP2R1A*-Related Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Some affected persons have epilepsy that is refractory to ASM therapy or may require multiple ASMs. • Education of parents/caregivers [1]
Developmental delay / Intellectual disability / Behavioral	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Scoliosis	Standard treatment per orthopedist	
Hearing	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Ear anomalies	Standard treatment per otolaryngologist	Most ear anomalies are minor & do not require surgical intervention.
Dental crowding	Standard treatment per dentist	
Congenital heart defects	Standard treatment per cardiologist	Most described heart defects to date have not required surgical intervention.
Ptosis	Standard treatment per ophthalmologist	
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.

ASM = anti-seizure medication

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., scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

Oral motor dysfunction 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 pureed 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.

Social/Behavioral 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

Table 6. Recommended Surveillance for Individuals with *PPP2R1A*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Neurologic	• Monitor seizures as clinically indicated. • Assess for new manifestations such as seizures & changes in muscle tone.	At each visit
Development	Monitor developmental progress & educational needs.	
Growth/Feeding/ Gastrointestinal	• Measure growth parameters. • Evaluate nutritional status & safety of oral intake. • Consider whether GERD may be a contributing issue.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
	Physical exam to assess for development of scoliosis	At each visit until skeletal maturity
ENT	Dental eval	At least annually after eruption of teeth or as clinically indicated
Hearing	Audiology eval	Annually in childhood or as clinically indicated
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	As clinically indicated
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

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

PPP2R1A-related neurodevelopmental disorder (*PPP2R1A*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *PPP2R1A*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo PPP2R1A* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- 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.

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

- If the *PPP2R1A* 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 a parent of the proband is known to have the *PPP2R1A* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.

Offspring of a proband

- Each child of an individual with *PPP2R1A*-NDD has, in theory, a 50% chance of inheriting the *PPP2R1A* pathogenic variant.
- Individuals with *PPP2R1A*-related NDD are not yet known to reproduce, and it is unknown if pathogenic *PPP2R1A* variants affect fertility.

Other family members. Given that all probands with *PPP2R1A*-NDD reported to date have the disorder as a result of a *de novo PPP2R1A* pathogenic variant, the risk to other family members is presumed to be very low.

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

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo PPP2R1A* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal genetic testing may be considered.

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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  vor.net

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. PPP2R1A-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PPP2R1A	19q13.41	Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform	PPP2R1A	PPP2R1A

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 PPP2R1A-Related Neurodevelopmental Disorder (View All in OMIM)

605983	PROTEIN PHOSPHATASE 2, STRUCTURAL/REGULATORY SUBUNIT A, ALPHA; PPP2R1A
616362	HOUGE-JANSSENS SYNDROME 2; HJS2

Molecular Pathogenesis

All known pathogenic variants causing *PPP2R1A*-related neurodevelopmental disorder (*PPP2R1A*-NDD) identified to date have been missense variants, predicting an amino acid change to the PPP2R1A protein. *PPP2R1A* encodes the scaffolding subunit (A-subunit) of protein phosphatase 2A (PP2A), the most important protein phosphatase in the human body. This scaffolding subunit connects the PP2A catalytic subunit (C-subunit) to one of the many regulatory B-subunits. B-subunit type determines substrate specificity, that is, which serine/threonine phosphate residues are targeted. Protein phosphorylation and dephosphorylation is the most important general mechanism for dynamic protein regulation in a cell, and phosphorylation of a given position is an equilibrium where various serine/threonine protein kinases (like cAMP-dependent protein kinase) and protein phosphatases (like PP2A) are important.

The most important B-subunit for brain function appears to be the PP2A B56-delta subunit PPP2R5D, and pathogenic missense variants in this gene are the cause of a phenotypically overlapping condition, *PPP2R5D*-related neurodevelopmental disorder. Remarkably, all pathogenic *PPP2R1A* variants retain binding to PPP2R5D [Lenaerts et al 2021]. This strongly suggests a dominant-negative type of gain-of-function effect. In theory, pathogenic *PPP2R1A* missense variants can block B56-delta-related substrates from being dephosphorylated, and also affect binding to other substrate-binding subunits (like B55-alpha) and inhibitory subunits (like CIP2A and SET) [Verbinnen et al 2021]. All the possible biochemical consequences of these scaffolding subunit changes have not been investigated, but a dominant-negative effect on protein dephosphorylation has been shown in prior studies [Houge et al 2015, Lenaerts et al 2021].

It should be noted that *PPP2R1A* loss-of-function changes (e.g., nonsense variants or deletions) are not known to cause *PPP2R1A*-NDD, even though the gene is quite intolerant to loss-of-function changes (gnomAD pLI is 0.98).

Mechanism of disease causation. Gain of function

Table 7. Notable *PPP2R1A* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Associated Feature(s)
NM_014225.6 NP_055040.2	c.421T>A	p.Phe141Ile	Macrocephaly, moderate ID
	c.455C>T	p.Ser152Phe	Milder features w/learning problems, ASD
	c.532A>T	p.Thr178Ser	Macrocephaly, moderate ID
	c.533C>A	p.Thr178Asn	Macrocephaly, moderate ID
	c.536C>T	p.Pro179Leu	Microcephaly
	c.538A>G	p.Met180Val	Macrocephaly, moderate ID
	c.539T>C	p.Met180Thr	Macrocephaly, moderate ID
	c.544C>T	p.Arg182Trp	Severe ID w/epilepsy risk, ventriculomegaly
	c.547C>T	p.Arg183Trp	Severe ID w/epilepsy risk, ventriculomegaly
	c.548G>A	p.Arg183Gln	Severe w/more serious epilepsy
	c.656C>T	p.Ser219Leu	Usually moderate ID w/epilepsy risk
	c.658G>A	p.Val220Met	Usually moderate ID w/epilepsy risk
	c.772C>A	p.Arg258Ser	Microcephaly

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Associated Feature(s)
	c.773G>A	p.Arg258His	Microcephaly

ASD = autism spectrum diagnosis; ID = intellectual disability
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.

Cancer and Benign Tumors

Even though many of the *PPP2R1A* missense variants described here are also found in tumor tissue (see COSMIC database), *PPP2R1A*-NDD is not known to be associated with an increased risk of cancer development.

Chapter Notes

Author Notes

The first author is an international expert in clinical dysmorphology with a specific interest in overgrowth syndromes. The second author is a biochemist and the foremost authority on PP2A dysfunction in both intellectual disability and cancer. The last author is a professor of medical genetics with extensive knowledge of clinical dysmorphology, genetic variant interpretation, and basic biochemistry. The latter two authors first described *PPP2R1A*-related neurodevelopmental disorder.

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