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PPP1R12A-Related Urogenital and/or Brain Malformation Syndrome

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Summary

Clinical characteristics

Individuals with *PPP1R12A*-related urogenital and/or brain malformation syndrome (UBMS) usually present with multiple congenital anomalies, most commonly involving the brain and/or urogenital systems. The brain abnormalities are variable, with the most severe belonging to the holoprosencephaly spectrum and associated with moderate-to-profound intellectual disability, seizures, and feeding difficulties. In individuals without brain involvement, variable degrees of developmental delay and/or intellectual disability may be present, although normal intelligence has been seen in a minority of affected individuals. Eye (strabismus, microphthalmia/anophthalmia) and skeletal abnormalities (kyphoscoliosis, joint contractures) can also be present in affected individuals of either sex. Regardless of the presence of a brain malformation, affected individuals with a 46,XY chromosome complement may have a difference of sex development (DSD) with gonadal dysgenesis associated with ambiguous genitalia or phenotypic female genitalia.

Diagnosis/testing

The diagnosis of *PPP1R12A*-related UBMS is established in a proband with suggestive findings and a heterozygous pathogenic variant in *PPP1R12A* identified by molecular genetic testing.

Management

Treatment of manifestations: Gonadectomy should be considered in individuals with dysgenetic gonads; referral of 46,XY undervirilized individuals to a urologist or gynecologist for consideration of surgery to address hypospadias, bifid scrotum, urogenital sinus abnormalities, and cryptorchidism; referral to an endocrinologist for treatment for induction of puberty and postpubertal hormonal issues for those with gonadal abnormalities; referral to a psychologist or multidisciplinary DSD clinic, if available. Treatment of feeding difficulties including consideration of gastrostomy tube placement for those with persistent feeding issues or failure to thrive;

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standard treatment for renal anomalies, epilepsy, developmental delay/intellectual disability, constipation, bowel atresia, hearing impairment, vision abnormalities/strabismus, kyphoscoliosis, and joint contractures, as needed.

Surveillance: Regular follow up by an interdisciplinary DSD team (if available) including endocrinology, genetics, gynecology, psychology, and urology for those who had DSD as part of their features. Measurement of growth parameters, evaluation of nutritional status and safety of oral intake, assessment for constipation, monitoring of developmental progress and educational needs, monitoring for changes in seizures, and assessment for new neurologic manifestations at each visit; monitoring for timing and progression of puberty at each visit starting in late childhood through adolescence; assessment for scoliosis or kyphosis at each visit until growth is complete; ophthalmology and audiology evaluations annually or as clinically indicated.

Genetic counseling

PPP1R12A-related UBMS is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. If the *PPP1R12A* 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 theoretic possibility of parental germline mosaicism. Once the *PPP1R12A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *PPP1R12A*-related urogenital and/or brain malformation syndrome (*PP1R12A*-related UBMS) have been published.

Suggestive Findings

PPP1R12A-related UBMS **should be suspected** in individuals with the following clinical and imaging findings.

Clinical findings

- Atypical external genitalia in individuals with a 46,XY chromosome complement, including:
  - Normal female external genitalia
  - Urogenital sinus abnormalities
  - Undervirilized male external genitalia with a high insertion of the scrotum, bifid scrotum with or without cryptorchidism, micropenis, hypospadias with or without chordee, and anterior positioning of the anus.
- Microcephaly or macrocephaly with variable degrees of developmental delay, intellectual disability, and/or autistic features
- Brain malformations (See **Imaging findings**.)
- Eye abnormalities such as strabismus, microphthalmia/anophthalmia
- Skeletal anomalies (e.g., unilateral or bilateral fifth-finger clinodactyly, syndactyly of the toes, kyphoscoliosis)

Imaging findings

- Brain MRI imaging demonstrating:
  - Alobar, semilobar, or middle interhemispheric variant holoprosencephaly
  - Abnormalities of the corpus callosum
  - Anencephaly
  - Cortical dysplasia (polymicrogyria, heterotopia)
- Abdominal/pelvic ultrasound/MRI demonstrating:

- Abnormal internal genitalia in 46,XY individuals, including müllerian duct remnants (uterine structure, cervix and/or upper part of the vagina)
- Structural renal abnormalities including duplicated renal collecting system

Establishing the Diagnosis

The diagnosis of *PPP1R12A*-related UBMS **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *PPP1R12A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *PPP1R12A* variant of uncertain significance does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with undervirilization in 46,XY individuals and/or brain malformations are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and imaging findings suggest the diagnosis of *PPP1R12A*-related UBMS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *PPP1R12A* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A differences of sex development or brain malformation multigene panel** that includes *PPP1R12A* 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*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by brain malformations and/or undervirilization in a 46,XY individual, comprehensive genomic testing may be considered. **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 *PPP1R12A*-Related Urogenital and/or Brain Malformation Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2, 3] Identified by Method
PPP1R12A	Sequence analysis [4]	12/12 [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

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. Fourteen additional individuals with contiguous gene deletions (not included in these calculations) have been reported in the literature [Niclass et al 2020] or in the Decipher database (see Genetically Related Disorders).
4. 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.
5. Hughes 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. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Individuals with *PPP1R12A*-related UBMS present with multiple congenital anomalies including brain abnormalities (holoprosencephaly spectrum and others) and urogenital malformations. To date, 12 individuals have been identified with a pathogenic variant in *PPP1R12A* [Hughes et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *PPP1R12A*-Related Urogenital and/or Brain Malformation Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
46,XY DSD & genitourinary anomalies	9/12	
Developmental delay	7/12	
Brain malformations	5/12	Typically along the holoprosencephaly spectrum
Eye or vision problems	3/12	

DSD = disorders/differences of sex development

46,XY differences of sex development (DSD) / genitourinary anomalies are the primary manifestations in *PPP1R12A*-related UBMS.

- Atypical external genitalia in individuals with a 46,XY karyotype range from mild to severe undervirilization and can include:
  - Micropenis

    - Chordee
    - Variable degrees of hypospadias
    - Bifid and high insertion of the scrotum
    - Urogenital sinus abnormalities
    - Normal appearing female external genitalia
- Gonadal abnormalities can range from cryptorchidism to complete gonadal dysgenesis.
    - Gonads may be dysgenetic.
    - In the most severe cases, streak gonads have been found.
- Müllerian structures, including fallopian tubes, uterus, and upper part of the vagina, may be present.

Neurologic. Variable degrees of developmental delay and intellectual disability were reported in seven of 12 affected individuals. Neurodevelopmental abnormalities included attention-deficit/hyperactivity disorder (ADHD) and autistic features. Other neurologic features reported in single individuals include dystonia, appendicular hypotonia with foot pronation, unsteady gait, and seizure disorder. Normal intelligence has also been reported in some cases.

Brain imaging findings. Two individuals with holoprosencephaly (semilobar and syntelencephaly/middle interhemispheric variant) and two with corpus callosum abnormalities have been reported. Other anomalies reported in single individuals include: encephalocele, colpocephaly, acrania/exencephaly, absent septum pellucidum, Chiari malformation, cortical dysplasia/polymicrogyria, leukomalacia, and gray matter heterotopia.

Feeding. In individuals with a severe brain malformation, feeding may be difficult. Neonates with feeding difficulties can develop hyperbilirubinemia. Feeding often improves during the first few months of life, but typically worsens if seizures develop.

- Poor feeding in newborns is usually managed by nasogastric tube feedings, as the feeding problems often improve during the first weeks of life (see Management, Treatment of Manifestations).
- Feeding may worsen with intercurrent illnesses and with advancing age and size. In this scenario, gastrostomy tube placement may be considered.
- Individuals with low central tone frequently develop constipation.

Eye findings. Three of 12 affected individuals were reported with various eye abnormalities including strabismus, astigmatism, hyperopia, unilateral or alternating esotropia, rod and cone dysfunction, decreased vision, and latent nystagmus.

Limb/skeletal anomalies have included fifth-finger clinodactyly, syndactyly of all toes, kyphoscoliosis, joint contractures (not otherwise specified), and ulnar deviation of the hand

Manifestations reported in single individuals

- Growth abnormalities: microcephaly, macrocephaly, intrauterine growth restriction (IUGR), postnatal growth restriction/failure to thrive (FTT) and decreased subcutaneous fat
- Dysmorphic features including long face, facial asymmetry, arched eyebrows, widely-spaced eyes, hypotelorism/closely-spaced eyes, ptosis, long or short palpebral fissures, long eyelashes, epicanthal folds, short and upturned nose, micrognathia, large low-set and protruding ears, preauricular pit, earlobe creases, long philtrum
- Gastrointestinal: omphalocele; jejunal and ileal atresia with aberrant mesenteric blood supply
- Pyelectasis
- Patent ductus arteriosus

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

PPP1R12A-related UBMS is rare: 12 individuals have been reported to date [Hughes et al 2020]. The prevalence has not been determined.

Genetically Related (Allelic) Disorders

Deletion 12q21. Fourteen individuals with a contiguous gene deletion involving *PPP1R12A* and surrounding genes in the 12q21 region have been reported in the literature [Niclass et al 2020] or in the Decipher database. Variable features were reported in individuals with partial or complete deletion of the whole gene include dysmorphic facial features, developmental delay, hydrocephalus or ventriculomegaly, growth restriction, ectodermal anomalies, spastic diplegia or axial hypotonia, congenital heart defects, and renal malformations. No individuals with 46,XY DSD were identified in this group of individuals [Niclass et al 2020].

Sporadic tumors. Somatic copy number variants in *PPP1R12A* or fusion proteins with *PPP1R12A* at the 12q21.1 to 12q21.31 locus that are not present in the germline [Zhang et al 2015, Gupta et al 2019] have been reported in colorectal cancer and alveolar and sarcomatoid rhabdomyosarcoma. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *PPP1R12A*-Related Urogenital and/or Brain Malformation Syndrome

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*PPP1R12A*-related UBMS	Distinguishing from *PPP1R12A*-related UBMS
Conditions w/genitourinary abnormalities				
AR	Androgen insensitivity syndrome	XL	GU abnormalities & sex reversal	Lack of multiple malformation & DD/ID
ATRX	Alpha-thalassemia X-linked intellectual disability syndrome	XL	GU malformation incl abnormal genitalia & sex reversal	Distinctive craniofacial features; mild anemia secondary to alpha-thalassemia
WT1	Denys-Drash syndrome (See *WT1* Disorder.)	AD	GU malformation incl ambiguous genitalia & müllerian structures on ultrasound	Diffuse mesangial sclerosis on renal biopsy; Wilms tumor; lack of DD/ID
CDKN1C	IMAGe syndrome	AD	IUGR; GU abnormalities (males)	Adrenal hypoplasia congenita; metaphyseal dysplasia
Conditions w/genitourinary abnormalities & brain malformations				
DHCR7	Smith-Lemli-Opitz syndrome	AR	Hypospadias; ambiguous genitalia; 2-3 toe syndactyly; microcephaly; holoprosencephaly; IUGR/short stature	Characteristic facial features (narrow forehead, epicanthal folds, ptosis, short mandible w/preservation of jaw width, short nose, anteverted nares, & low-set ears); postaxial polydactyly; cleft palate
ARX	X-linked lissencephaly w/ ambiguous genitalia (OMIM 300215)	XL	GU malformation incl ambiguous genitalia; brain malformations incl cortical malformation & corpus callosum abnormalities	Perinatal encephalopathy w/intractable seizures; lissencephaly a predominant finding; chronic diarrhea; high male lethality in 1st 3 mos of life

Table 3. continued from previous page.

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*PPP1R12A*-related UBMS	Distinguishing from *PPP1R12A*-related UBMS
RAB18	Warburg micro syndrome (OMIM 614222)	AR	GU malformation incl hypogonadism; microcephaly; corpus callosum abnormalities	Ophthalmologic abnormalities incl congenital cataracts, atonic pupils, optic nerve atrophy, microphthalmia, microcornea

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; GU = genitourinary; ID = intellectual disability; IUGR = intrauterine growth restriction; MOI = mode of inheritance; XL = X-linked

Other disorders to consider in the differential diagnosis of *PPP1R12A*-related UBMS include the following (shared clinical findings indicated in parentheses):

- Trisomy 13 (holoprosencephaly, GU malformation)
- Pseudotrisomy 13 syndrome (OMIM 264480) (holoprosencephaly)

Management

No clinical practice guidelines for *PPP1R12A*-related UBMS have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PPP1R12A*-related UBMS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *PPP1R12A*-Related Urogenital and/or Brain Malformations

System/Concern	Evaluation	Comment
Genitourinary	Assessment of external genitalia for anomalies, incl: • Attempt to palpate gonads in the scrotum/ labioscrotal folds • Inspection of scrotum / labioscrotal folds, phallic structure for length, breadth, chordee, foreskin, & location of urethral opening, labio/ scrotal-anal distance • Presence of vaginal dimple/introitus • Assessment of labioscrotal folds for fusion, rugation, & pigmentation	Consider referral to a multidisciplinary DSD team incl urology, endocrinology, genetics, gynecology, & psychology, if possible.
	Consider karyotype w/FISH for *SRY* or chromosomal microarray.	In those w/external genital anomalies & in phenotypic females
	Renal/abdominal/pelvic ultrasound	To assess for renal anomalies & müllerian structures
Endocrinology	Consider obtaining hormone studies [1] between age 2 wks & 3 mos & at pubertal age to assess gonadal function.	Consider referral to endocrinologist in those w/46,XY DSD.
Neurology	Neurology eval	• To incl brain MRI • Consider EEG if seizures are a concern.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Constitutional	Measurement of growth parameters	To incl weight, length/height, & head circumference
GI/Feeding	Gastroenterology/nutrition/feeding team eval in those w/feeding issues &/or FTT	• To incl eval of nutritional status & aspiration risk • Consider eval for nasogastric or gastrostomy tube placement in those w/severe feeding issues, dysphagia, &/or aspiration risk. • Consider eval for structural GI issues, if signs/symptoms are consistent w/obstruction.
Ophthalmology	Ophthalmologic eval	To assess for strabismus, cone/rod dysfunction, & refractive error
Audiology [2]	Audiology eval	To assess for hearing loss in those w/speech delay &/or a known brain malformation
Skeletal	Assess for digital & joint anomalies.	Consider referral for orthopedics assessment / hand surgery if needed.
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI & implications of *PPP1R12A*-related UBMS 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.	

DSD = differences of sex development; FISH = fluorescence in situ hybridization; FTT = failure to thrive; GI = gastrointestinal; MOI = mode of inheritance

1. Including but not limited to total testosterone, dihydrotestosterone, inhibin B, anti-müllerian hormone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) to assess for gonadal function

2. Although hearing loss is not a primary feature of *PPP1R12A*-related UBMS, assessment of hearing in an individual with significant developmental delay and/or brain malformation is recommended.

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

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *PPP1R12A*-Related Urogenital and/or Brain Malformations

Manifestation/ Concern	Treatment	Considerations/Other
46,XY DSD	• Consider gonadectomay in those w/dysgenetic gonads. • In 46,XY undervirilized persons, referral to urologist or gynecologist for standard treatment of atypical genitalia/hypospadias, cryptorchidism, &/or urogenital sinus anomalies • Standard treatment of hormonal issues at & after puberty, incl sex HRT	• Consider referral to endocrinologist for hormonal issues. • Consider referral to psychologist or a multidisciplinary DSD clinic, if available. • For further details on 46,XY DSD mgmt see Nonsyndromic Disorders of Testicular Development.
Renal anomalies	Standard treatment per nephrologist &/or urologist	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Epilepsy	Treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain/FTT/ GERD/ Aspiration	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues or FTT.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia, incl episodes of aspiration pneumonia
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Bowel atresia	Standard treatment per surgeon & gastroenterologist	
Hearing impairment	Standard therapy per audiologist	
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
Kyphoscoliosis/ Joint contractures	Standard treatment per orthopedist	
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. • Ensure psychological support for those w/gender identity concerns.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

DSD = differences of sex development; ASM = anti-seizure medication; DD = developmental delay; FTT = failure to thrive; GERD = gastroesophageal reflux disease; HRT = hormone replacement therapy; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

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.

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 ADHD, when necessary.

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

Surveillance

Table 6. Recommended Surveillance for Individuals with *PPP1R12A*-Related Urogenital and/or Brain Malformations

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation & feeding difficulties.	
Development	Monitor developmental progress & educational needs.	
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations such as seizures, changes in tone, movement disorders.	
DSD [1]	• Monitor timing & progression of puberty & need for puberty induction & hormone replacement therapy. • Assess for gender identity concerns.	At each visit starting in late childhood & through adolescence
Skeletal	Monitor skeletal complications such as scoliosis or kyphosis.	At each visit until growth is completed
Eyes	Ophthalmology eval	Annually or as clinically indicated
Hearing	Audiology eval	
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

DSD = disorder/differences of sex development
1. Routine follow up by an interdisciplinary DSD team (if available) including endocrinology, genetics, obstetrics/gynecology, psychology, and urology.

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

PPP1R12A-related urogenital and/or brain malformation syndrome (*PPP1R12A*-related UBMS) 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 *PPP1R12A*-related UBMS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable counseling regarding recurrence risk and prenatal diagnosis options.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. (To date, parental mosaicism has not been reported in *PPP1R12A*-related UBMS.) 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 a parent of the proband is known to have the pathogenic variant identified in the proband, the risk to the sibs for inheriting the pathogenic variant is 50%.
- If the *PPP1R12A* 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 theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with *PPP1R12A*-related UBMS has a 50% chance of inheriting the *PPP1R12A* pathogenic variant.

Other family members. Given that all probands with *PPP1R12A*-related UBMS reported to date have the disorder as a result of a *de novo* pathogenic variant, the risk to other family members is presumed to be 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 PPP1R12A* 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 and preimplantation 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.

- **National Human Genome Research Institute (NHGRI)**
  Learning About Holoprosencephaly
- **Accord Alliance**
  Phone: 602-492-4144
  www.AccordAlliance.org
- **Families for Hope**
  1219 North Wittfield Street
  Indianapolis IN 46229
  Phone: 888-533-4443
  Email: Info@FamiliesforHoPE.org
  www.familiesforhope.org
- **Genetic and Rare Diseases Information Center (GARD)**
  Holoprosencephaly
- **InterNational Council on Infertility Information Dissemination, Inc. (INCIID)**
  Phone: 703-379-9178
  Fax: 703-379-1593
  Email: INCIIDinfo@inciid.org
  www.inciid.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Holoprosencephaly Information Page

- **National Organization for Rare Disorders (NORD)**
  Holoprosencephaly

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. PPP1R12A-Related Urogenital and/or Brain Malformation Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PPP1R12A	12q21.2-q21.31	Protein phosphatase 1 regulatory subunit 12A	PPP1R12A	PPP1R12A

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 PPP1R12A-Related Urogenital and/or Brain Malformation Syndrome (View All in OMIM)

602021	PROTEIN PHOSPHATASE 1, REGULATORY SUBUNIT 12A; PPP1R12A
618820	GENITOURINARY AND/OR BRAIN MALFORMATION SYNDROME; GUBS

Molecular Pathogenesis

PPP1R12A encodes a component of myosin phosphatase (MP), a key enzyme instrumental in the regulation of cell morphology and motility [Grassie et al 2011, Kiss et al 2019]. MP activates when PP1c is unphosphorylated and bound. Phosphorylation of specific consensus sites on PPP1R12A by protein kinases leads to inhibition of its activity [Ito et al 2004]. Pathogenic variants in *PPP1R12A* prevent PPP1R12A from binding to PP1c and result in a nonfunctional MP [Huang et al 2008].

Mechanism of disease causation. Loss of function

Cancer and Benign Tumors

The number of copies of *PPP1R12A* was correlated with the prediction of recurrence and survival in individuals with Stage III colorectal cancer treated with oxaliplatin-based chemotherapy [Zhang et al 2015]. Moreover, both a pure alveolar and sarcomatoid rhabdomyosarcoma of the urinary bladder demonstrated a novel fusion involving *PPP1R12A* fusions at the 12q21.1 to 12q21.31 locus; the exact role of this fusion has not been defined [Gupta et al 2019].

Chapter Notes

Revision History

- 7 March 2024 (ea) Revision: removed information regarding individuals with a 46,XX chromosome complement
- 9 September 2021 (ma) Review posted live
- 8 January 2021 (ea) Original submission

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