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Phosphoribosylpyrophosphate Synthetase Deficiency

Synonym: PRS Deficiency

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Summary

Clinical characteristics

Phosphoribosylpyrophosphate synthetase (PRS) deficiency, an X-linked disorder, is a phenotypic continuum comprising three disorders previously thought to be clinically distinct: Arts syndrome, Charcot-Marie-Tooth neuropathy X type 5 (CMTX5), and X-linked nonsyndromic sensorineural hearing loss (DFNX1). In affected males, the PRS deficiency phenotypic spectrum ranges from severe congenital profound sensorineural hearing loss, intellectual disability, delayed motor development, and progressive ophthalmologic involvement (retinal dystrophy and optic atrophy) to normal cognitive abilities and relatively later-onset, somewhat milder manifestations, such as mild sensorineural hearing loss, peripheral neuropathy, and gait ataxia.

Heterozygous females can show isolated and/or milder manifestations in the PRS deficiency spectrum. To date, 40 families with PRS deficiency have been reported.

Diagnosis/testing

The diagnosis of PRS deficiency is established in a male proband with suggestive findings and a hemizygous pathogenic variant in *PRPS1* identified by molecular genetic testing. The diagnosis of PRS deficiency is usually established in a female proband with suggestive findings and a heterozygous pathogenic variant in *PRPS1* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for PRS deficiency. Supportive care to improve quality of life, maximize function, and reduce complications can include multidisciplinary care by specialists in neurology, physiatry, physical therapy, occupational therapy, audiology, otolaryngology, ophthalmology and low vision services, education, and medical genetics.

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Surveillance: Monitoring existing manifestations, the individual's response to supportive care, and the emergence of new manifestations involves scheduled follow up with the treating specialists.

Genetic counseling

PRS deficiency is inherited in an X-linked manner. If the mother of the proband has a *PRPS1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%; if the father of the proband has a *PRPS1* pathogenic variant, he will transmit it to all his daughters and none of his sons. Males who inherit the pathogenic variant will be affected. Females who inherit the pathogenic variant will be heterozygotes and will be asymptomatic or show manifestations of PRS deficiency that are typically isolated and/or milder than manifestations in hemizygous males with the same pathogenic variant. The ratio of X-chromosome inactivation adds an additional variable in predicting clinical outcome in females who inherit a *PRPS1* pathogenic variant. Once the *PRPS1* pathogenic variant has been identified in an affected family member, heterozygote testing for at-risk female relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

With the current widespread use of multigene panels and comprehensive genomic testing based on an unbiased (i.e., not phenotype-driven) approach, it has become apparent that the phenotypic continuum associated with phosphoribosylpyrophosphate synthetase (PRS) deficiency is comprised of clusters encompassing three previously clinically distinct disorders – Arts syndrome, Charcot-Marie-Tooth neuropathy X type 5 (CMTX5), and X-linked nonsyndromic sensorineural hearing loss (DFNX1). PRS deficiency refers to this entire phenotypic spectrum and emphasizes the need to evaluate an individual with a *PRPS1* pathogenic missense variant that results in loss of function for medically actionable manifestations within the spectrum regardless of the clinical findings that prompted molecular genetic testing.

PRS Deficiency: Disorders Previously Clinically Defined in the Phenotypical Continuum

Clinically Defined Disorder	Major Clinical Findings [1]				
	Sensorineural hearing loss	Peripheral neuropathy	Intellectual disability	Respiratory infection	Ophthalmologic involvement
Arts syndrome	+ (profound, congenital)	+	+	↑ liability	+
CMTX5	+ (early onset, prelingual)	+	–	–	+
DFNX1 [2]	+ (typically late onset) [3]	–	–	–	–

CMTX5 = Charcot-Marie-Tooth neuropathy X type 5; DFNX1 = X-linked nonsyndromic sensorineural hearing loss

1. Females typically have a less severe presentation than males; the ratio of X-chromosome inactivation adds an additional variable in predicting clinical outcome in females.

2. Also referred to as DFN2.

3. Although postlingual progressive nonsyndromic hearing loss is typical, one family had congenital profound nonsyndromic hearing loss [Liu et al 2010].

Diagnosis

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

No consensus clinical diagnostic criteria for phosphoribosylpyrophosphate synthetase (PRS) deficiency have been published.

Suggestive Findings

PRS deficiency **should be suspected in a male proband** with the following clinical and supportive laboratory findings and family history.

Clinical findings in males

- **Bilateral sensorineural hearing loss (SNHL)** that is moderate to profound; prelingual or postlingual in onset; and progressive or non-progressive. Note: Hearing loss that is moderate to profound in a neonate will be detected by newborn hearing screening; however, hearing loss that is mild will not.

  Audiogram shapes are usually residual or flat [Liu et al 2013].

  Temporal bone imaging is normal [Liu et al 2013].

  Vestibular function is normal.

- **Early-onset hypotonia and delayed motor development**

- **Peripheral motor neuropathy** (axonal with later sensory involvement)
  - Motor nerve conduction velocities (NCVs) reveal delayed distal latencies and decreased amplitudes with relatively normal velocities (median motor NCV ≥38 m/s), consistent with an axonal neuropathy [Nishikura et al 2019, Shirakawa et al 2022].
  - Needle electromyography (EMG) revealed fibrillation potentials and neurogenic motor unit action potentials [Park et al 2013], positive sharp waves [Synofzik et al 2014], and chronic denervation [Robusto et al 2015].

- **Intellectual disability (ID)** ranging from nonexistent (DFNX1) to moderate ID (Arts syndrome)

- **Liability to infections** especially in the upper respiratory tract

- **Ophthalmologic findings**
  - Optic neuronopathy/atrophy
    - Fundoscopic examination shows bilateral optic disc pallor.
    - Visual evoked potentials demonstrate delayed latency and decreased amplitudes of P100.
  - Retinal dystrophy [Mercati et al 2020]
    - Fundoscopic examination can show patches of retinal atrophy.
    - Electroretinogram can show abnormal cone and rod responses.

Supportive laboratory findings in males

- **Serum uric acid** concentration is lower than average (0.13-0.16 mmol/L), although still within the normal range (i.e., 0.12-0.35 mmol/L) [de Brouwer et al 2007].

  Note: (1) Serum uric acid concentration is not zero because the enzyme PRS-II, which has the same enzyme activity as the enzyme PRS-I, is active in tissues such as liver, resulting in purine nucleotide synthesis and uric acid production. (2) However, a low/normal serum uric acid concentration may be helpful in ruling out a diagnosis of PRS superactivity, in which serum uric acid concentration is usually high.

- **Purine analysis in urine**
  - Absent/low hypoxanthine concentration
  - Normal range of concentration of other purines
  - When individuals with PRS deficiency are on a low-purine diet, the uric acid-to-creatinine ratio in urine may tend to be at the lower end of normal but not zero.

Clinical findings in females. In the most severe phenotype, findings include ophthalmologic manifestations, ataxia, peripheral neuropathy, and hearing loss [Almoguera et al 2014].

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Note: (1) In families segregating a loss-of-function *PRPS1* pathogenic variant, hemizygous males are affected and heterozygous females may be asymptomatic or have variable manifestations. (2) Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of PRS deficiency **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *PRPS1* identified by molecular genetic testing (see Table 1).

Female proband. The diagnosis of PRS deficiency **is usually established** in a female proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *PRPS1* 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 hemizygous or heterozygous *PRPS1* 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, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Note: Single-gene testing (sequence analysis of *PRPS1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

An intellectual disability, ataxia, hearing loss, deafness, retinal dystrophy, optic atrophy, or peripheral neuropathy multigene panel that includes *PRPS1* 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

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is the 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 PRS deficiency

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PRPS1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants 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. Data collectively provided for *PRPS1* pathogenic variants identified in Arts syndrome, CMTX5, and DFNX1. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

The phenotype of phosphoribosylpyrophosphate synthetase (PRS) deficiency is now known to be a continuum encompassing three previously clinically defined disorders – Arts syndrome, Charcot-Marie-Tooth neuropathy X type 5 (CMTX5), and X-linked nonsyndromic sensorineural hearing loss (DFNX1). Arts syndrome (characterized by intellectual disability, hypotonia, ataxia, sensorineural hearing impairment, and progressive optic atrophy and/or retinopathy), CMTX5 (characterized by peripheral neuropathy, sensorineural hearing loss, and optic neuropathy), and DFNX1 were initially thought to represent distinct phenotypes. However, following the observation in a single family of a male with features of CMTX5 and Arts syndrome and a female with prelingual DFNX1, Synofzik et al [2014] concluded that these disorders are not distinct entities, but rather clusters on a phenotypic continuum associated with PRS deficiency.

Subsequent reports confirmed this observation and further expanded the PRS deficiency phenotype:

- Detailed clinical and neurophysiologic examination of males diagnosed with *PRPS1*-related hearing loss revealed peripheral neuropathy ranging from subclinical axonal motor neuropathy to axonal sensorimotor neuropathy [Robusto et al 2015].
- Females heterozygous for a *PRPS1* pathogenic missense variant were found to have optic atrophy and retinal dystrophy [Almoguera et al 2014].
- Mercati et al [2020] reported a male with profound developmental delay and multiorgan involvement.

Thus, the phenotypic spectrum of PRS deficiency can range from profound congenital sensorineural hearing impairment, intellectual disability, delayed motor development, and progressive optic atrophy [Arts et al 1993, de Brouwer et al 2007] to relatively later-onset, somewhat milder manifestations, such as mild sensorineural hearing loss, peripheral neuropathy, gait ataxia, and normal cognitive abilities.

To date, 40 families have been identified with PRS deficiency [Mercati et al 2020, Puusepp et al 2020, Rezende Filho et al 2021, Shirakawa et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Affected Males

Sensorineural hearing loss can be prelingual to postlingual with onset ranging from congenital to age 20 years. It can be progressive or non-progressive, and severe to profound [Liu et al 2010, Liu et al 2013, Kim et al 2016].

Early-onset hypotonia and delayed motor development. Hypotonia, which is usually mild, may be noted in infancy. Attainment of motor milestones may be mildly to moderately delayed.

Peripheral motor and sensory neuropathy. Onset of peripheral neuropathy is between ages two and 12 years [de Brouwer et al 2007]. The lower extremities are affected earlier and more severely than the upper extremities. The initial manifestation is often foot drop or gait disturbance. Deep tendon reflexes are usually absent. Motor signs predominate, but impaired sensory function may accompany motor dysfunction or develop during disease progression. With advancing disease, affected individuals may become dependent on crutches or a wheelchair.

Sural nerve biopsy showed the following:

- Loss of myelinated fibers without signs of demyelination or axonal degeneration in a boy age five years with Arts syndrome from the original Dutch family reported by Arts et al [1993].
- Mild paranodal demyelination indicative of peripheral neuropathy in a boy age two years, who had absent lower limb deep tendon reflexes and nerve conduction studies indicative of peripheral neuropathy [de Brouwer et al 2007].

Intellectual disability (ID) is mild to moderate. Brain MRI shows nonspecific abnormalities (e.g., reduction of white matter in the brain, which would indicate demyelination) [de Brouwer et al 2007].

Liability to infections, especially upper respiratory tract infections, resulted in death before age six years in 12 of the 15 boys from the two Dutch families reported with Arts syndrome [Arts et al 1993]. During infection, the acute deterioration in muscle strength in the otherwise slowly progressive muscle weakness could result in respiratory failure requiring mechanical ventilation.

Ophthalmologic involvement. Onset of visual impairment is between ages seven and 20 years. Optic neuropathy and retinopathy can progress with time.

Heterozygous Females

Heterozygous females can show isolated and/or milder manifestations, most notably late-onset (age >20 years) hearing impairment that can be either symmetric or asymmetric and ranges from mild to moderate [Liu et al 2013]. In the family described by Almoguera et al [2014], both the female proband and her mother had peripheral neuropathy and ophthalmologic manifestations (retinal dystrophy and optic atrophy). One affected sister had a milder phenotype limited to ophthalmologic findings. Ataxia, hypotonia, and hyperreflexia have been reported as well [Arts et al 1993].

Genotype-Phenotype Correlations

In the wide and continuous spectrum of clinical manifestations associated with *PRPS1* missense variants that result in a loss of function, a relationship between the type (location) of disruption of the PRS-I enzyme and phenotype has been suggested. The most severe phenotypes are caused by variants that are predicted to affect allosteric and active sites, and the milder phenotypes are caused by variants that are predicted to disrupt the structure locally [de Brouwer et al 2010].

In females, who predictably have less severe manifestations, the ratio of X-chromosome inactivation adds an additional variable in predicting clinical outcome [Synofzik et al 2014].

Prevalence

To date, 40 families with PRS deficiency have been identified worldwide deficiency [Rosenberg & Chutorian 1967, Arts et al 1993, Glick 2006, de Brouwer et al 2007, Kim et al 2007, Liu et al 2010, Liu et al 2013, Almoguera et al 2014, Synofzik et al 2014, Kim et al 2016, Maruyama et al 2016, Mercati et al 2020, Puusepp et al 2020, Lenherr et al 2021, Rezende Filho et al 2021, Shirakawa et al 2022].

Nomenclature

Charcot-Marie-Tooth neuropathy X type 5 (CMTX5) was previously referred to as Rosenberg-Chutorian syndrome [Kim et al 2007].

DFNX1 nonsyndromic hearing loss and deafness was previously referred to as DFN2 (OMIM 304500).

Genetically Related (Allelic) Disorders

Phosphoribosylpyrophosphate synthetase (PRS) superactivity. *PRPS1* gain-of-function variants that result in PRS superactivity disturb either one or both allosteric sites that are involved in the inhibition of PRS-I enzyme activity. PRS superactivity comprises two phenotypes, both characterized by hyperuricemia and hyperuricosuria. The mild phenotype (~75% of affected males) with onset in the second or third decade of life is typically limited to these biochemical findings, whereas the severe phenotype (~25% of affected males) with onset in the first decade of life has in addition to these biochemical findings variable combinations of developmental delay / intellectual disability, sensorineural hearing loss, hypotonia, and ataxia. In the mild phenotype, uric acid crystalluria or a urinary stone is commonly the first clinical finding, followed later by gouty arthritis if serum urate concentration is not controlled.

Differential Diagnosis

Intellectual disability. The phenotypic features associated with *PRPS1*-related intellectual disability are not sufficient to diagnose this condition clinically; all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series for genes associated with:

- Autosomal dominant intellectual developmental disorders
- Autosomal recessive intellectual developmental disorders
- Nonsyndromic X-linked intellectual developmental disorders
- Syndromic X-linked intellectual developmental disorders

Hearing loss. See Genetic Hearing Loss Overview.

Peripheral neuropathy. See Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Management

No clinical practice guidelines for phosphoribosylpyrophosphate synthetase (PRS) deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PRS deficiency, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 2. PRS Deficiency: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Hearing	• Otolaryngology eval • Audiology eval	Assess for sensorineural hearing loss.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	Assess: • Strength, motor skills, & presence/absence of tendon reflexes for signs of peripheral neuropathy; • Balance & coordination for evidence of ataxia.
Musculoskeletal/ Activities of daily living	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)
Eyes	Ophthalmology eval	To assess for visual acuity, ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings such as optic atrophy &/or retinal dystrophy that may require subspecialty referral or referral for low vision services
Respiratory complications	Pulmonology eval	Particularly young males w/recurrent upper respiratory disease who may be at ↑ risk of progressing to ventilator dependence
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of PRS deficiency 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.	

ADL = activities of daily living; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for PRS deficiency.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in neurology, physiatry, physical therapy, occupational therapy, audiology, otolaryngology, ophthalmology and low vision services, education, and medical genetics (see Table 3).

Table 3. PRS Deficiency: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	

Table 3. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Musculoskeletal/ Activities of daily living	Orthopedics / physical medicine & rehab / PT & OT incl stretching	
Hearing	• See Genetic Hearing Loss Overview, Management. • Cochlear implantation in 2 affected males was assoc w/improved communication skills.	Community hearing services through early intervention or school district
Ophthalmologic involvement	By ophthalmologist	Treatment of refractive errors &/or strabismus
	Low vision services	• Children: through early intervention programs &/or school district • Adults: referral to low vision clinic &/or community vision services
Respiratory	By pulmonologist &/or infectious disease specialist	Consider prophylactic antibiotics where appropriate.
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.

OT = occupational therapy; PT = physical therapy

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.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations listed in Table 4 are recommended.

Table 4. PRS Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Eval for peripheral neuropathy & ataxia	• For those not known to be affected: annually or per symptoms for clinical manifestations • For those known to be affected: annually or per treating neurologist
Musculoskeletal/ Activities of daily living	Physical medicine, OT/PT assessment of mobility, self-help skills, need for durable medical equipment for mobility, home safety	At each visit
Development	Monitor developmental progress & educational needs.	
Sensorineural hearing loss	Audiogram to assess progression &/or response to intervention per treating audiologist/otolaryngologist	Per treating clinicians
	Speech-language pathology re need for alternative forms of communication	Per treating speech-language pathologist
Vision	Ophthalmologic exam to assess visual acuity, visual fields	Per treating ophthalmologist
	Low vision clinic to assess needs re special services	Per treating low vision clinic
Respiratory	By treating pulmonologist &/or infectious disease specialist	Per treating clinicians
Family/Community	Assess family need for social work support (e.g., 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

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger male and female sibs of a proband in order to identify sibs at risk for hearing loss who may benefit from appropriate early support and management.

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

Therapies Under Investigation

Dietary supplementation with *S*-adenosylmethionine (SAM) has been investigated in individuals with *PRPS1*-related disorders [Authors, personal observation].

An anecdotal study suggested that co-therapy of SAM and nicotinamide riboside may be of additional clinical benefit [Lenherr et al 2021].

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

Phosphoribosylpyrophosphate synthetase (PRS) deficiency is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *PRPS1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *PRPS1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo PRPS1* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism.
    - The frequency of *de novo* pathogenic variants is not known.
    - Maternal germline mosaicism has not been reported to date but remains a possibility.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Parents of a female proband

- A female proband may have inherited the *PRPS1* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.

- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) can determine if the pathogenic variant was inherited.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *PRPS1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected.
  - Females who inherit the pathogenic variant will be heterozygotes and will be asymptomatic or show manifestations of PRS deficiency that are typically isolated and/or milder than manifestations in hemizygous males with the same pathogenic variant. The ratio of X-chromosome inactivation adds an additional variable in predicting clinical outcome in females who inherit a *PRPS1* pathogenic variant. See Clinical Description, Heterozygous Females.
- If the proband represents a simplex case and if the *PRPS1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism.

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

- If the mother of the proband has a *PRPS1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
- If the father of the proband has a *PRPS1* pathogenic variant, he will transmit it to all his daughters and none of his sons.
- If the proband represents a simplex case and if the *PRPS1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a male proband. Males with PRS deficiency transmit the *PRPS1* pathogenic variant to:

- All of their daughters, who will be heterozygotes and will be asymptomatic or show manifestations of PRS deficiency that are typically isolated and/or milder than manifestations in hemizygous males with the same pathogenic variant (see Clinical Description, Heterozygous Females);
- None of their sons.

Offspring of a female proband. Women with a *PRPS1* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

Other family members. If a parent of the proband also has a pathogenic variant, relatives of the heterozygous/hemizygous parent may be at risk of having a *PRPS1* pathogenic variant and manifestations of PRS deficiency.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Identification of female heterozygotes requires either prior identification of the *PRPS1* pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Note: Females who are heterozygous for this X-linked disorder may develop clinical findings related to the disorder (see Clinical Description, Heterozygous Females).

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 young adults who are affected or at risk of having a *PRPS1* pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PRPS1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**

  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)

  Fax: 202-337-8314

  Email: info@agbell.org

  Listening and Spoken Language Knowledge Center

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**

  Phone: 202-387-1968

  Fax: 202-387-2193

  www.aaidd.org

- **American Society for Deaf Children**

  Phone: 800-942-2732 (ASDC)

  Email: info@deafchildren.org

  deafchildren.org

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  babyhearing.org

- **CDC - Developmental Disabilities**

  Phone: 800-CDC-INFO

  Email: cdcinfo@cdc.gov

  Intellectual Disability

- **Charcot-Marie-Tooth Association (CMTA)**
  Phone: 800-606-2682 (toll-free); 610-427-2971
  Email: info@cmtausa.org
  www.cmtausa.org
- **CMT Research Foundation**
  Phone: 404-806-7180
  Email: info@cmtrf.org
  www.cmtrf.org
- **European Charcot-Marie-Tooth Consortium**
  Department of Molecular Genetics
  University of Antwerp
  Antwerp Antwerpen B-2610
  Belgium
  Fax: 03 2651002
  Email: gisele.smeyers@ua.ac.be
- **Hereditary Neuropathy Foundation**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **RDCRN Patient Contact Registry: Inherited Neuropathies Consortium**
  Patient Contact Registry

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. Phosphoribosylpyrophosphate Synthetase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PRPS1	Xq22.3	Ribose-phosphate pyrophosphokinase 1	PRPS1 @ LOVD PRPS1 homepage - Leiden Muscular Dystrophy pages	PRPS1	PRPS1

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 Phosphoribosylpyrophosphate Synthetase Deficiency (View All in OMIM)

301835	ARTS SYNDROME; ARTS
304500	DEAFNESS, X-LINKED 1; DFNX1
311070	CHARCOT-MARIE-TOOTH DISEASE, X-LINKED RECESSIVE, 5; CMTX5
311850	PHOSPHORIBOSYLPYROPHOSPHATE SYNTHETASE I; PRPS1

Molecular Pathogenesis

PRPS1 encodes the enzyme phosphoribosyl pyrophosphate synthetase I (PRS-I), which catalyzes the phosphoribosylation of ribose 5-phosphate to 5-phosphoribosyl-1-pyrophosphate, which is necessary for the *de novo* and salvage pathways of purine and pyrimidine biosynthesis.

Mechanism of disease causation. Missense variants that cause a loss of function of *PRPS1*

***PRPS1*-specific laboratory technical considerations.** For *PRPS1* missense variants of uncertain significance, PRS-I enzyme analysis can be performed. PRS deficiency is confirmed if:

- PRS-I enzyme activity is absent in erythrocytes (because PRS-I is the only isoform present);
- PRS-I enzyme activity is significantly lower in fibroblasts than in controls [de Brouwer et al 2007].

Chapter Notes

Author Notes

Contact Dr Arjan de Brouwer or Prof John Christodoulou to inquire about review of *PRPS1* variants of uncertain significance.

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