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# Phosphoribosylpyrophosphate Synthetase Superactivity

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## Summary

### Clinical characteristics

Phosphoribosylpyrophosphate synthetase (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 (DD) / intellectual disability (ID), 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.

### Diagnosis/testing

In male probands with the mild phenotype, detection of high activity or lack of allosteric regulation of the PRS-I enzyme (PRS-I enzyme assay) establishes the diagnosis. Molecular genetic testing of *PRPS1* fails to detect a hemizygous pathogenic variant.

In male probands with the severe phenotype, molecular genetic testing establishes the diagnosis by identification of a hemizygous PRPS1 pathogenic variant in males and a heterozygous *PRPS1* pathogenic variant in females.

In symptomatic female probands, PRS-I enzyme assay and/or *PRPS1* molecular genetic testing establishes the diagnosis.

### Management

*Treatment of manifestations:* In all individuals, hyperuricemia and hyperuricosuria can be reduced by treatment with allopurinol or febuxostat to reduce uric acid formation and thus serum urate and urinary uric acid; high daily fluid intake; and, as needed, potassium citrate to alkalinize the urine.

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In individuals with the severe phenotype, DD/ID, sensorineural hearing loss, hypotonia, and ataxia are managed per standard care.

*Surveillance:* All individuals: monthly measurement of 24-hour urinary uric acid excretion or a spot urinary urate-to-creatinine ratio helps in assessing the response to treatment; once a normal serum urate concentration is achieved, serum urate concentration should be monitored at a minimum annually to assure that target urate concentration is maintained; a 24-hour urine should be monitored at least annually for urate and xanthine particularly to ensure that urinary xanthine does not exceed solubility (<1 mmol/L).

In the severe phenotype: monitor development / educational needs, neurologic manifestations, and hearing.

*Agents/circumstances to minimize or avoid:* In all individuals: high-purine meats (i.e., red and organ meats), shellfish, oily fish (e.g., anchovies, sardines), beer, high-fructose corn syrup-containing beverages and foods, dehydration, and if possible, urate-retaining medications (e.g., low-dose aspirin, thiazide diuretics).

*Evaluation of relatives at risk:* It is appropriate to screen apparently asymptomatic older and younger at-risk relatives of an individual with PRS superactivity in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures for hyperuricemia and hyperuricosuria. Evaluations include:

- In male and female relatives: molecular genetic testing if a *PRPS1* pathogenic variant has been identified in an affected family member;
- In male relatives at risk: measurement of serum urate concentration and 24-hour urinary uric acid excretion or spot urinary urate-to-creatinine ratio. Note: Biochemical testing is unlikely to be informative in asymptomatic females.

## Genetic counseling

PRS superactivity caused by a pathogenic variant in *PRPS1* is inherited in an X-linked manner. Females who are heterozygous for a *PRPS1* pathogenic variant have a 50% chance of transmitting the pathogenic variant in each pregnancy: males who inherit the pathogenic variant will be severely affected; females who inherit the pathogenic variant will be heterozygous and may be asymptomatic or have a range of features. Males with a *PRPS1* pathogenic variant transmit the pathogenic variant to all of their daughters and none of their sons. If a *PRPS1* pathogenic variant has been identified in the proband, heterozygote testing for at-risk female relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

PRS superactivity caused by elevated *PRPS1* mRNA levels is also inherited in an X-linked manner; however, because the underlying genetic alteration has not been characterized, the mode of inheritance cannot be confirmed with certainty.

# GeneReview Scope

**Phosphoribosylpyrophosphate Synthetase (PRS) Superactivity: Phenotypes in Males and Females**

| Sex | PRS Superactivity Phenotype | Onset | Diagnosis |
|---|---|---|---|
| **Male** | Mild (75% of affected males) | 2nd or 3rd decade of life | PRS-I enzyme assay [1] |
| | Severe (25% of affected males) | 1st decade of life | PRS-I enzyme assay &/or *PRPS1* molecular genetic testing |

*Phosphoribosylpyrophosphate Synthetase (PRS) continued from previous page.*

| Sex | PRS Superactivity Phenotype | Onset | Diagnosis |
|---|---|---|---|
| **Female** | Ranges from mild (typically) to severe (rarely) depending on X-chromosome inactivation | Depending on X-inactivation status | PRS-I enzyme assay (in symptomatic females [2]) &/or *PRPS1* molecular genetic testing |

*1.* In all males with mild PRS superactivity evaluated to date, the sequence of the *PRPS1* coding region and adjacent DNA is normal and the basis of increased rates of PRPS1 transcription is unknown.
*2.* Biochemical testing is unlikely to be informative in asymptomatic females.

# Diagnosis

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

## Suggestive Findings

Phosphoribosylpyrophosphate synthetase (PRS) superactivity **should be suspected** in male and female probands with the following clinical and laboratory findings and family history.

The **mild** (onset in 2nd or 3rd decade of life) PRS superactivity phenotype **should be suspected in a male or female proband** with the following findings:

- Gouty arthritis

  Note: Absence of gout does not exclude consideration of PRS superactivity.
- Significant hyperuricemia and significantly elevated daily urinary uric acid excretion
  - The ratio of urinary urate to creatinine concentration may be more helpful for screening purposes. PRS superactivity values are typically greater than twofold the upper limit of normal.
  - Male and female adult serum urate ranges differ.
  - "Normal" serum urate concentrations and 24-hour urinary urate excretion vary by age and weight. If tested for serum urate concentrations, the individual should be on a standard diet with no medications influencing serum urate levels.
- Uric acid urolithiasis

The **severe** (onset in 1st decade of life) PRS superactivity phenotype **should be suspected in a male or female proband** with the above findings and the following additional clinical features:

- Intellectual disability
- Sensorineural hearing impairment
- Hypotonia
- Ataxia

**Family history** is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

### Enzyme Analysis

The diagnosis of the **mild** PRS superactivity phenotype **is established** in a **male or female proband** with suggestive findings by detection of high activity or lack of allosteric regulation of the PRS-I enzyme (PRS-I enzyme assay).

PRS-I enzyme activity can be analyzed in fibroblasts, lymphoblasts, and erythrocytes [Losman et al 1984, Becker et al 1987, Becker et al 1992, Torres et al 1996]. Increased PRS-I enzyme activity at all inorganic phosphate (Pi) concentrations, normal dinucleotide (ADP/GDP) inhibition of enzyme activity, normal Km for Pi activation, and increased *PRPS1* transcript (e.g., by northern blot analysis or quantitative real-time PCR) and PRS-I isoform (isoelectric focusing / western blotting) establish the diagnosis. See Table 1.

**Table 1.** Phosphoribosylpyrophosphate Synthetase (PRS) Enzyme Activity and Nucleotide Levels in PRS Superactivity

| Phenotype | PRS-I Enzyme Activity | | | Fibroblast Nucleotide Levels [1] |
|---|---|---|---|---|
| | Fibroblasts | Lymphoblasts | Erythrocytes | |
| **Mild** | High | Normal | High | High |
| **Severe** | High | High | Usually low [2] | High |

Becker et al [1986]

*1.* Adenylates (AMP, ADP, ATP) and guanylates (GMP, GDP, GTP)

*2. PRPS1* pathogenic variants (usually in the severe type) that lead to defective allosteric regulation of the activity of the PRS-I isoform contribution to total PRS activity, enhanced enzyme affinity for Pi (especially at concentrations <2-4 mmol/L), and reduced inhibition of activity by ADP and GDP are observed in cultured fibroblasts and lymphoblasts. However, PRS-I enzyme activity in erythrocytes is usually reduced or deficient because of instability of the mutated enzyme in red blood cells.

Note: Molecular genetic testing by *PRPS1* sequence analysis does not appear to be helpful in establishing the diagnosis in males with the mild PRS superactivity phenotype: in all males with mild PRS superactivity tested to date, the sequence of the *PRPS1* coding region and adjacent DNA is normal, and the basis of increased rates of *PRPS1* transcription is unknown.

## Molecular Genetic Testing

The diagnosis of the **severe** PRS superactivity phenotype **is established** in a **male proband** with suggestive findings and a hemizygous *PRPS1* pathogenic variant identified by molecular genetic testing, and in a **female proband** with suggestive findings and a heterozygous *PRPS1* pathogenic variant identified by molecular genetic testing (Table 2).

Note: *PRPS1* variants of uncertain significance can be evaluated by PRS-I enzyme activity (see Molecular Genetics, ***PRPS1*-specific laboratory technical considerations**).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) (see **Option 1**) and **comprehensive genomic testing** (exome sequencing, genome sequencing) (see **Option 2**).

### Option 1

**Single-gene testing.** Sequence analysis of *PRPS1* is performed first to detect missense variants. Although sequence analysis also identifies small intragenic deletions/insertions and nonsense and splice site variants, no such variants have been reported. Typically, 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; however, to date such variants have not been identified as a cause of this disorder.

**An intellectual disability multigene panel** that includes *PRPS1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a male or female with the severe PRS superactivity phenotype 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 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 2.** Molecular Genetic Testing Used in Phosphoribosylpyrophosphate Synthetase (PRS) Superactivity

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *PRPS1* | Sequence analysis [3] | 10 of 33 [4] |
| | Gene-targeted [5] | None reported |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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.* Six males with metabolic and neurodevelopmental abnormalities in infancy or early childhood; one male with onset of metabolic (but not neurodevelopmental) features in the teen years; three women with late childhood-onset gout who were heterozygous for a *PRPS1* pathogenic variant. All of the respective *PRPS1* pathogenic variants resulted in defects in the allosteric regulation of PRS-I enzyme activity by nucleotides and Pi (see Table 1). To date, no *PRPS1* pathogenic variant has been identified in affected individuals who have the mild PRS superactivity phenotype.
*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 two phosphoribosylpyrophosphate synthetase (PRS) superactivity phenotypes are mild (onset in 2nd or 3rd decade of life) and severe (onset in 1st decade of life).

### Males

**The mild PRS superactivity phenotype** in males is characterized by juvenile- or adult-onset gouty arthritis or uric acid urolithiasis with hyperuricemia and hyperuricosuria. Obvious neurologic findings are usually not present.

Renal impairment can potentially result from uric acid crystal deposition in the renal collecting system or from urate crystal deposition in the renal interstitium.

Kidney stones and acute kidney failure as a result of obstructive uropathy from uric acid crystal deposition (stones or gravel) were described in the first family identified [Sperling et al 1972]; the kidney failure resolved with treatment of the obstruction.

**The severe PRS superactivity phenotype** in males is characterized by infantile- or childhood-onset hyperuricemia and hyperuricosuria. Uric acid crystalluria or a urinary stone is commonly the first metabolic

clinical event, and gouty arthritis is usually a later event if serum urate concentration is not controlled. Commonly, the clinical picture is dominated by findings not directly ascribable to hyperuricemia or hyperuricosuria – usually variable combinations of sensorineural hearing loss, intellectual disability, hypotonia, and ataxia [Becker et al 1988].

### Heterozygous Females

Heterozygous females in families with the mild PRS superactivity phenotype can show the metabolic features of the disease.

Heterozygous females in families with the severe PRS superactivity phenotype can also show the metabolic and/or neurodevelopmental features of the disease [García-Pavía et al 2003]. Of the 16 women with a pathogenic *PRPS1* variant fully investigated to date, five have had hyperuricemia, nephrolithiasis, and gout; one was also deaf [Zikánová et al 2018].

## Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

## Nomenclature

"PRPP synthetase (PRS) superactivity" is the name originally applied to the overall disorder. With the increasing recognition of two varieties of defects – that is, single-nucleotide variants (SNVs) in *PRPS1* and accelerated transcription of the normal *PRPS1* (with an enzyme of normal kinetic characteristics) – it has been suggested that the term PRS "overactivity" become the overall name and that "superactivity" refer only to the phenotype associated with *PRPS1* SNVs. However, the distinction has not gained wide recognition.

## Prevalence

No prevalence has been estimated. To date, 33 individuals with PRS superactivity have been described worldwide.

# Genetically Related (Allelic) Disorders

Germline pathogenic variants in *PRPS1* are also known to be associated with phosphoribosylpyrophosphate synthetase (PRS) deficiency. Depending on the level of residual enzyme activity, PRS deficiency can be associated with features ranging from sensorineural hearing loss (mild enzyme deficiency) to peripheral neuropathy (moderate enzyme deficiency) and intellectual disability, hypotonia, ataxia, delayed motor development, profound congenital sensorineural hearing impairment, and progressive optic atrophy (severe enzyme deficiency). These phenotypes, previously thought to be distinct entities (DFNX1 nonsyndromic hearing loss and deafness, Charcot-Marie-Tooth neuropathy X type 5, and Arts syndrome), are now thought to represent a continuum.

# Differential Diagnosis

Disorders of purine and pyrimidine metabolism to consider in the differential diagnosis of phosphoribosylpyrophosphate synthetase (PRS) superactivity are:

- Hypoxanthine-guanine phosphoribosyltransferase deficiency, an X-linked disorder caused by pathogenic variants in *HPRT1* (see *HPRT1* Disorders);
- Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase, an autosomal recessive disorder caused by pathogenic variants in *AHCY* (OMIM 613752).

**Table 3.** Disorders of Purine and Pyrimidine Metabolism that Overlap with Phosphoribosylpyrophosphate Synthetase (PRS) Superactivity

| Clinical Finding | | PRS Superactivity | HPRT Deficiency | AHCY Deficiency |
|---|---|---|---|---|
| **Neurologic** | Intellectual disability | + | ± | – |
| | Ataxia | ± | – | – |
| | Hypotonia | ± | ± | + |
| | Delayed motor development | ± | + | + |
| | Loss of deep tendon reflexes | – | – | + |
| | Hearing impairment | + | – | – |
| **Uric acid overproduction** | Gout | + | + | – |
| | Kidney stones | + | + | – |

AHCY deficiency = hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase; HPRT = hypoxanthine-guanine phosphoribosyltransferase

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in a male or female diagnosed with phosphoribosylpyrophosphate synthetase (PRS) superactivity, the following evaluations are recommended.

**Mild (onset in 2nd or 3rd decade of life) PRS superactivity phenotype**

- Serum urate concentration
- Joint examination for evidence of gout – generally, evaluation of joint integrity only, except during an acute flare of arthritis or in an individual with chronic deformity or tophus formation following multiple attacks
- Assessment of kidney function and structural integrity (e.g., kidney ultrasound examination)

**Severe (onset in 1st decade of life) PRS superactivity phenotype.** In addition to evaluations listed previously for the mild phenotype:

- Neurologic evaluation for hypotonia, ataxia, presence/absence of tendon reflexes
- Audiometry for evidence of hearing loss
- Developmental assessment, including motor, adaptive, cognitive, & speech-language evaluation
- Evaluation for early intervention / special education

**All individuals.** Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of PRS superactivity in order to facilitate medical and personal decision making

## Treatment of Manifestations – All PRS Superactivity

**Hyperuricemia and hyperuricosuria** can be reduced by treatment with the following:

- Dietary changes:
  - Reduced intake of red and organ meats, poultry, and shellfish [Choi et al 2004], oily fish (e.g., anchovies, sardines), and beer
  - Avoidance of high-fructose corn syrup-containing foods and drinks
  - Increased low-fat dairy intake

- Allopurinol, a xanthine oxidase inhibitor, prescribed in doses with the ultimate aim of achieving serum urate concentrations lower than 6.0 mg/dL (360 µmol/L). The starting dose should be 100 mg once a day (in adults) with titration every three to four weeks according to the serum urate concentration. However, because of the uric acid overproduction and excessive uric acid excretion, allopurinol should be prescribed conservatively, as there is a high risk for xanthinuria and xanthine renal lithiasis; see **Gout and renal lithiasis** below.
- Febuxostat, a newer urate-lowering xanthine oxidase inhibitor. Febuxostat has not been tested in individuals with PRS superactivity, but there is no reason a priori to doubt that it will be effective in the treatment of this disorder. Febuxostat should also be prescribed conservatively, because of a high risk for xanthinuria causing renal lithiasis. Note: Excretion of >1.1 g uric acid per day in an adult is associated with a greater than 50% risk for kidney stones.
- High daily fluid intake (i.e., ≥2 L/day in an adult)
- Potassium citrate (usually administered 4x/day to alkalinize the urine) when urate urinary tract stones are present or uric acid gravel is in the urine [Becker 2008]. Xanthinuria does not respond to urinary alkalinization.

**Gout and renal lithiasis** caused by chronically elevated serum and urinary uric acid, the result of purine overproduction, can be reduced by a xanthine oxidase inhibitor. Note: By analogy to individuals with Lesch-Nyhan syndrome, who also have marked purine overproduction, xanthine oxidase inhibition with allopurinol or febuxostat may result in the formation of xanthine urinary tract stones. These radiolucent stones can be confused clinically with uric acid stones. If residual symptoms of urolithiasis occur in PRS superactivity despite the achievement of goal serum urate concentrations, a stone should be isolated for analysis and/or urinary xanthine concentration should be measured. Management of this pharmacologically induced complication includes reduction in daily allopurinol or febuxostat dosing, with the possible need to accept serum urate concentrations higher than the usual goal range (<6.0 mg/dL; 360 µmol/L).

Note: The interventions described only prevent/treat gout and the other metabolic complications of hyperuricemia; they have no known beneficial effect on hearing loss or neurodevelopmental impairment.

## Treatment of Manifestations – Severe PRS Superactivity Phenotype

**Sensorineural hearing loss** is managed in the usual manner (see Deafness and Hereditary Hearing Loss Overview, Management).

**Ataxia** is managed in the usual manner (see Hereditary Ataxia Overview, Management).

### 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.
  - 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.

### 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.

## Surveillance

### All Individuals

Monthly measurement of 24-hour uric acid excretion in the urine is particularly helpful in the assessment of the response to treatment. Alternatively, a spot urinary urate-to-creatinine ratio can be informative if accessibility to 24-hour urine samples is restricted.

Once a normal serum urate concentration is achieved and maintained, serum urate concentration should be monitored at a minimum annually to assure that the targeted concentration is maintained.

A 24-hour urine should also be monitored at a minimum annually for urate and xanthine concentrations particularly to ensure that urinary xanthine does not exceed solubility (<1 mmol/L); plasma xanthine is cleared efficiently and does not accumulate.

Note: Under usual circumstances, renal functional consequences are avoided if serum urate concentration and urinary excretion of urate are normalized and urinary xanthine does not routinely exceed its solubility (~1 mmol/L).

### Individuals with the Severe PRS Superactivity Phenotype

Audiometry should be repeated as deemed appropriate by the treating audiologist/otolaryngologist.

Neurologic evaluation should be performed annually or more frequently as recommended by the treating neurologist.

Monitor developmental progress and educational needs at each visit.

## Agents/Circumstances to Avoid

The following should be avoided in all individuals:

- Red and organ meats, shellfish, or oily fish (e.g., anchovies, sardines) in excess; beer; high-fructose corn syrup-enriched foods and drinks [Choi et al 2004]
- Dehydration
- If possible, urate-retaining medications: low-dose aspirin, thiazide diuretics

## Evaluation of Relatives at Risk

It is appropriate to screen apparently asymptomatic older and younger at-risk relatives of an individual with PRS superactivity in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures for hyperuricemia and hyperuricosuria.

Evaluations include:

- In male and female relatives at risk for the severe phenotype: molecular genetic testing if a *PRPS1* pathogenic variant has been identified in an affected family member;
- In male relatives at risk for the mild phenotype: measurement of serum urate concentration, and 24-hour urinary uric acid excretion or spot urinary urate-to-creatinine ratio. Biochemical testing is unlikely to be informative in asymptomatic females.

  Note: (1) Because collection of 24-hour urine in an infant or young child is very difficult, measurement of urinary urate-to-creatinine ratio in a spot urine sample may be helpful. (2) Sometimes the serum urate concentrations are not extremely elevated in children with PRS superactivity, probably as a result of higher renal clearance of urate; however, the urine urate excretion is abnormally high for age in all individuals.

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

## Therapies Under Investigation

Dietary *S*-adenosylmethionine (SAM) supplementation may theoretically alleviate some of the neurologic symptoms in individuals with the severe PRS superactivity phenotype by providing an oral source of purine nucleotide precursor that is not PRPP dependent. Furthermore, SAM is known to cross the blood-brain barrier. Although PRS superactivity exhibits high purine nucleotides (adenylates/guanylates) in some cells, these are low in red blood cells, which rely on purine salvage metabolism, and are believed to be low in the brain, which also relies on purine salvage metabolism. This is an experimental drug that is as yet unproven.

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.

# 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) superactivity caused by a pathogenic variant in *PRPS1* is inherited in an X-linked manner.

PRS superactivity caused by elevated *PRPS1* mRNA levels is also inherited in an X-linked manner; however, because the underlying genetic alteration has not been characterized, the mode of inheritance cannot be confirmed with certainty.

## Risk to Family Members of a Proband with a *PRPS1* Pathogenic Variant

**Parents of a male proband**

- The father of an affected male will not have PRS superactivity nor will he be hemizygous for the *PRPS1* pathogenic variant; therefore, he does not require further evaluation/testing. (Note: Because the prevalence of gout in men is high, the father may have gout unrelated to PRS superactivity.)
- 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 familial *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 PRPS1* pathogenic variants is not known.
- Molecular genetic testing of the mother is recommended to allow reliable recurrence risk assessment and to determine her need for clinical management (see Surveillance).

**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 severely affected.
  - Females who inherit the pathogenic variant will be heterozygotes and may be asymptomatic or have variable manifestations including hyperuricemia, nephrolithiasis, gout, and (rarely) neurodevelopmental features [García-Pavía et al 2003, Zikánová et al 2018] (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case and the *PRPS1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism.

**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 help to determine if the pathogenic variant was inherited.

**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% (see **Sibs of a male proband**).
- 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 either parent, the risk to sibs is low but greater than that of the general population because of the possibility of maternal or paternal germline mosaicism.

**Offspring of a proband**

- Affected males transmit the *PRPS1* pathogenic variant to:
  - All of their daughters, who will be heterozygotes and may be asymptomatic or have a range of features (see Clinical Description, Heterozygous Females);
  - None of their sons.
- Women with a *PRPS1* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child:
  - Females who inherit the pathogenic variant will be heterozygotes and may be asymptomatic or have a range of features (see Clinical Description, Heterozygous Females).
  - Males who inherit the pathogenic variant will be affected.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *PRPS1* pathogenic variant, the parent's family members may be at risk.

## Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status requires prior identification of the *PRPS1* pathogenic variant in the proband.

Of note, biochemical testing is unlikely to be informative in asymptomatic females.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**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 and/or are at risk of having PRS superactivity.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

If a *PRPS1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for PRS superactivity are possible. This approach to prenatal diagnosis is most applicable to the severe (onset in first decade of life) PRS superactivity phenotype, in which *PRPS1* pathogenic variants are identifiable.

Note: The identification of a *PRPS1* pathogenic variant in a male fetus predicts a phenotype consistent with severe PRS superactivity; the identification of a *PRPS1* pathogenic variant in a female fetus cannot be used to reliably predict the phenotype because the manifestations in heterozygous females are variable.

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
  **Fax:** 202-387-2193
  www.aaidd.org
- **American Society for Deaf Children**
  **Phone:** 800-942-2732 (ASDC)
  **Email:** info@deafchildren.org
  deafchildren.org
- **CDC - Developmental Disabilities**
  **Phone:** 800-CDC-INFO
  **Email:** cdcinfo@cdc.gov
  Intellectual Disability
- **Medline Plus**
  Gout
- **National Ataxia Foundation**
  **Phone:** 763-553-0020
  **Fax:** 763-553-0167
  **Email:** naf@ataxia.org
  www.ataxia.org
- **Purine Metabolic Patients' Association (PUMPA)**
  United Kingdom
  **Phone:** 44 (0)20 8725 5898
  **Email:** info@pumpa.org.uk
  www.pumpa.org.uk

# 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 Superactivity: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *PRPS1* | Xq22.3 | Ribose-phosphate pyrophosphokinase 1 | PRPS1 @ LOVD<br>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 Superactivity (View All in OMIM)

| | |
|---|---|
| 300661 | PHOSPHORIBOSYLPYROPHOSPHATE SYNTHETASE SUPERACTIVITY |
| 311850 | PHOSPHORIBOSYLPYROPHOSPHATE SYNTHETASE I; PRPS1 |

## Molecular Pathogenesis

PRS superactivity is an inborn error of purine metabolism. Phosphoribosylpyrophosphate synthetase 1 (also known as ribose-phosphate pyrophosphokinase 1) 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. *PRPS1* pathogenic variants that result in PRS superactivity disturb either one or both allosteric sites that are involved in the inhibition of PRS-I enzyme activity.

**Mechanism of disease causation.** Gain of function. Because all of the *PRPS1* pathogenic variants identified to date in individuals with the PRS superactivity phenotype have resulted in defective allosteric regulation of PRS-I enzyme activity, this finding is biased by the fact that pathogenic variants were sought on the basis of metabolic and neurodevelopmental phenotypes.

***PRPS1*-specific laboratory technical considerations.** Analysis of PRS-1 enzyme activity can be used to:

- Establish the diagnosis in individuals with the mild PRS superactivity phenotype;
- Evaluate novel *PRPS1* variants of uncertain significance in individuals with the severe PRS superactivity phenotype by identifying abnormal Pi activation of PRS-I enzyme activity in fibroblasts or lymphoblasts, but not erythrocytes (see Table 1). The variant PRS-I enzyme has an increased affinity for inorganic phosphate (Pi) and decreased dinucleotide (ADP/GDP) inhibition of activity.

Analysis of PRS-1 enzyme activity is available at:

**Department of Clinical Chemistry**
Amsterdam University Medical Center
Amsterdam, the Netherlands
Phone: +31(0)20-5665393
Email: gmz_dna@amc.uva.nl

# Chapter Notes

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- 23 September 2008 (me) Review posted live
- 17 July 2008 (mb) Initial submission

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