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HPRT1 Disorders

Synonyms: HGprt Deficiency, HPRT Deficiency, Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency

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Summary

Clinical characteristics

HPRT1 disorders, caused by deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGprt), are typically associated with clinical evidence for overproduction of uric acid (hyperuricemia, nephrolithiasis, and/or gouty arthritis) and varying degrees of neurologic and/or behavioral problems. Historically, three phenotypes were identified in the spectrum of *HPRT1* disorders: Lesch-Nyhan disease (LND) at the most severe end with motor dysfunction resembling severe cerebral palsy, intellectual disability, and self-injurious behavior; *HPRT1*-related neurologic dysfunction (HND) in the intermediate range with similar but fewer severe neurologic findings than LND and no self-injurious behavior; and *HPRT1*-related hyperuricemia (HRH) at the mild end without overt neurologic deficits. It is now recognized that these neurobehavioral phenotypes cluster along a continuum from severe to mild.

Diagnosis/testing

The diagnosis of an *HPRT1* disorder is established in a male proband with suggestive clinical and laboratory findings and a hemizygous pathogenic variant in *HPRT1* identified by molecular genetic testing and/or low HGprt enzyme activity identified on biochemical testing.

Management

Treatment of manifestations: Hyperuricemia is most commonly treated with the xanthine oxidase inhibitor allopurinol to reduce the risk for nephropathy, gouty arthritis, and tophi. Febuxostat may be used in case of allopurinol hypersensitivity. Multidisciplinary specialists may be needed to manage the neurologic manifestations. Depending on needs, specialists in medical genetics, neurology, behavioral management, developmental pediatrics, physical medicine and rehabilitation, physical therapy, occupational therapy, speech-language pathology, dentistry, and nephrology may be required.

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Surveillance: HPRT1 disorders are not clinically progressive; however, surveillance is important for all *HPRT1* disorders. While overproduction of uric acid does not get worse with time, chronic overproduction of uric acid – especially if not well controlled – may lead to cumulative pathology in the kidneys and/or joints. Similarly, new or worsening neurologic problems are not expected over time; however, some evolution of the neurologic problems occurs in the first few years of life, which reflects development of the nervous system in response to a static insult.

Agents/circumstances to avoid: Probenecid and other drugs that increase the risk for precipitation of uric acid in the urinary system and may cause acute renal failure; certain chemotherapy agents, such as methotrexate, that block synthesis or use of purines; periods of relative dehydration because they increase the risk for renal stones or urate nephropathy.

Evaluation of relatives at risk: It is appropriate to clarify the status of males at risk for *HPRT1* disorders immediately after birth in order to identify as early as possible those who would benefit from prompt initiation of xanthine oxidase inhibitors and anticipation of future needs.

Genetic counseling

HPRT1 disorders are X linked. The risk to sibs of a male proband depends on the genetic status of the mother. If the mother of the proband has an *HPRT1* variant, the chance of transmitting it in each pregnancy is 50%: males who inherit a pathogenic *HPRT1* variant will be affected. Females who inherit the pathogenic variant will be heterozygotes and will virtually always be clinically normal. If the proband represents a simplex case (i.e., a single occurrence in a family) and if the proband has a known *HPRT1* variant that cannot be detected in his mother's leukocyte DNA, the risk to sibs is low but greater than that of the general population because of the possibility of maternal mosaicism. Once an *HPRT1* pathogenic variant has been identified in an affected family member, heterozygote testing for females and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

HPRT1 Disorders [1]
• Lesch-Nyhan disease (LND) • *HPRT1*-related neurologic dysfunction (HND) • *HPRT1*-related hyperuricemia (HRH)

1. For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

HPRT1 disorders, which are associated with deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGprt), **should be suspected** in males with the following clinical and supportive laboratory findings.

Clinical findings

Table 1. *HPRT1* Disorders: Clinical Findings by Phenotype

HPRT1 Phenotype	Clinical Findings			
	Hyperuricemia, nephrolithiasis, or gouty arthritis	NDD w/motor impairment resembling severe cerebral palsy	ID	Self-injurious behavior
Lesch-Nyhan disease	+++	+++	++	+++

Table 1. continued from previous page.

HPRT1 Phenotype	Clinical Findings			
	Hyperuricemia, nephrolithiasis, or gouty arthritis	NDD w/motor impairment resembling severe cerebral palsy	ID	Self-injurious behavior
HPRT1-related neurologic dysfunction	+++	+ to +++	+ to ++	
HPRT1-related hyperuricemia	+++	NA	NA	

ID = intellectual disability; NA = not applicable; NDD = neurodevelopmental delay

Supportive (but not diagnostic) laboratory findings

- Hyperuricemia is often evident. Serum uric acid concentration greater than 8 mg/dL defines hyperuricemia in adults; however, the upper limit of normal, which varies by age, is lower in children.
- The urate:creatinine ratio, calculated from the concentration of uric acid and creatinine in a spot urine, provides a reliable measure of uric acid overproduction. A urate:creatinine ratio greater than two is characteristic for all *HPRT1* disorders.
- Uric acid kidney stones or uric acid crystals present in the urine.

Note: Absence of a known family history does not preclude the diagnosis of an *HPRT1* disorder.

Establishing the Diagnosis

Male proband. The diagnosis of an *HPRT1* disorder is established in a male proband with suggestive clinical and laboratory findings and a hemizygous pathogenic variant in *HPRT1* identified by molecular genetic testing (see Table 2) and/or low HGprt enzyme activity identified on biochemical testing.

Note: Identification of a hemizygous *HPRT1* variant of uncertain significance does not establish or rule out a diagnosis of this disorder.

Molecular Genetic Testing

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

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 in whom the diagnosis of an *HPRT1* disorder has not been considered are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1

- **Single-gene testing.** Sequence analysis of *HPRT1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. 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 multigene panel** (such as those for developmental delay, dystonia, spasticity, intellectual disability, or seizures) that includes *HPRT1* 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 this condition. (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(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

  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 for *HPRT1* Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
HPRT1	Sequence analysis [3]	~80% [4]
	Gene-targeted deletion/duplication analysis [5]	~20% [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. Fu et al [2014], Madeo et al [2019]
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.

Biochemical Testing

HGprt enzyme activity. Several enzyme tests are clinically available. These tests can be done on any tissue. Although erythrocyte-based assays are most commonly used because they are technically easiest, assays based on cultured fibroblasts correlate better with phenotypic severity [Fu et al 2015].

- Individuals with Lesch-Nyhan disease tend to have residual enzyme levels lower than 2%.
- Individuals with *HPRT1*-related neurologic dysfunction tend to have residual enzyme activity from 2% to 8%.
- Individuals with *HPRT1*-related hyperuricemia tend to have residual enzyme greater than 10%.

Clinical Characteristics

Clinical Description

Affected Males

Pathogenic variants in *HPRT1* are almost always associated with clinical evidence for overproduction of uric acid (hyperuricemia, nephrolithiasis, and/or gouty arthritis) as well as a range of neurobehavioral phenotypes.

Historically, three phenotypes recognized in the spectrum of *HPRT1* disorders were Lesch-Nyhan disease (LND) at the most severe end, the intermediate phenotype *HPRT1*-related neurologic dysfunction (HND), and *HPRT1*-related hyperuricemia (HRH) at the mild end (see Table 1). In reality, these neurobehavioral phenotypes cluster along a continuum from severe to mild [Fu et al 2014].

Overproduction of uric acid is present from birth. The serum uric acid concentration is usually elevated. This finding is often missed because hyperuricemia can be mild; rarely, serum uric acid concentration can be normal.

If untreated, overproduction of uric acid leads to precipitation of uric acid crystals in the urinary system. Crystals appear as an orange sandy material in the diapers. Larger stones may appear as "gravel" in diapers. Larger stones may be difficult to pass. Stones may cause hematuria and increase the risk for urinary tract infections. While crystals or gravel in the diaper may be an early feature, their significance is often not appreciated for years.

Another potential consequence of untreated overproduction of uric acid is gouty arthritis caused by precipitation of uric acid in the joints. Complex precipitates mixed with proteins may form visible swellings known as tophi. Gout is uncommon in children and typically develops long after other manifestations are present.

If overproduction of uric acid is not treated, renal failure is common. Some individuals develop renal failure even with treatment.

Lesch-Nyhan Disease (LND)

LND is characterized by uric acid overproduction, motor dysfunction resembling severe cerebral palsy, intellectual disability, and self-injurious behavior.

Motor dysfunction. Boys with LND typically have normal prenatal and perinatal histories. The most common initial findings during the first year of life are hypotonia and delayed motor skills. Children with LND fail to reach normal milestones such as sitting, crawling, and walking [Jinnah et al 2006].

Within the first few years of life, abnormal movements emerge. The characteristic feature in all individuals is severe action dystonia [Jinnah et al 2006]. Children with LND may also develop opisthotonos, choreoathetosis, and sometimes ballismus. Approximately one third develop corticospinal signs such as spasticity, hyperreflexia, and clonus. The neurologic picture resembles dyskinetic or athetoid cerebral palsy.

The motor disability is sufficiently severe that children with LND do not walk and are usually confined to a wheelchair. Most need assistance with feeding and hygiene.

Cognitive disturbances. Most individuals with LND are cognitively impaired. The degree of impairment is difficult to assess because the neurobehavioral problems make interpretation of standardized tests difficult [Schretlen et al 2001].

In general, individuals with LND do not have severe intellectual disability. Formal psychological testing typically yields scores in the mild-to-moderate range of dysfunction.

Behavioral abnormalities. Almost all affected individuals develop the hallmark feature of recurrent self-injurious behaviors [Schretlen et al 2005]. This problem most often develops between ages two and four years. In some instances, it may begin as early as the first year of life, or it may be delayed until the late teenage years.

Self injury most often involves biting of the fingers, hands, lips, and cheeks [Robey et al 2003]. It may also involve banging the head or limbs against hard objects. The severity and patterns of this behavior evolve over time, but they generally occur daily.

In addition to self-injurious behavior, affected individuals often have other difficult behaviors including impulsiveness, aggressiveness, oppositional defiance, recurrent vomiting, spitting at others, and coprolalia.

Other manifestations can include the following:

- Testicular atrophy with delayed growth and puberty is very common.
- Macrocytic anemia unresponsive to vitamin supplements is very common, but does not usually require treatment [Cakmakli et al 2019].
- Neuroimaging often reveals nonspecific changes of atrophy in the central nervous system with reduced cerebral volume and reduced caudate nucleus volume [Schretlen et al 2013].
- Approximately one third have seizures [Leeman-Markowski & Jinnah 2018]. EEG shows nonspecific slowing or disorganization in most others.
- Approximately one third require gastrostomy because of dysphagia and/or recurrent aspiration [Jinnah et al 2006].
- Uncommon but particularly troublesome problems may include respiratory irregularities such as recurrent unexplained apnea [Neychev & Jinnah 2006], recurrent unexplained emesis, or dystonic crisis with severe autonomic changes.

Life expectancy. LND is not a progressive neurodegenerative disorder [Göttle et al 2014]. If management of manifestations is effective, individuals with LND may survive into the second to fourth decades of life.

The most common causes of death include pulmonary failure (from pneumonia or recurrent aspiration from dysphagia), renal failure, or sepsis from different causes. Sudden unexplained death in an otherwise well-tended individual may also occur [Neychev & Jinnah 2006].

HPRT1-Related Neurologic Dysfunction (HND)

HND is similar to LND, except the neurologic features are often less severe and self-injurious behavior does not occur. The spectrum of the severity of neurologic features in HND is broad. The most severely affected individuals are neurologically indistinguishable from those with LND; the least severely affected individuals may have only minor clumsiness with fine motor activity or relatively minor cognitive deficits [Jinnah et al 2010]. Intermediate grades of severity may also occur.

The severity and spectrum of problems related to uric acid are indistinguishable from LND.

Macrocytic anemia is common, but many of the other problems such as growth delay, dysphagia, seizures, and sudden death are less common.

Life span is longer than in LND and may be normal for the least severely affected.

HPRT1-Related Hyperuricemia (HRH)

HRH is similar to HND, except that clinically obvious neurologic deficits do not occur. While mild clumsiness may occur, clinically overt problems are not usually apparent and are only evident on detailed neurologic examination [Jinnah et al 2010].

Mild cognitive deficits, especially problems with attention, are common but are not usually identified without formal neuropsychological testing [Schretlen et al 2001].

The severity and spectrum of problems related to uric acid are indistinguishable from LND and HND.

Life span is normal.

Heterozygous Females

Heterozygous females are virtually always clinically normal without evidence for motor or cognitive deficits. Production of uric acid may be slightly elevated, and some heterozygous females may develop gout when they are older [Puig et al 1998].

Rarely the LND phenotype has been observed in heterozygous females as the result of skewed (nonrandom) X-chromosome inactivation of the chromosome bearing the normal *HPRT1* allele. (Of note, discordant phenotypes were observed in monozygotic twin girls [1 normal; 1 with LND] due to skewed X-chromosome inactivation [De Gregorio et al 2005].)

Presence of biallelic *HPRT1* pathogenic variants has also been reported in females [Fu et al 2014].

Genotype-Phenotype Correlations

Because the amount of residual HGprt enzyme activity correlates with the severity of the phenotype [Fu et al 2014, Fu et al 2015], some general genotype-phenotype correlations are seen.

LND is associated with complete or near-complete loss of enzyme activity from the following types of *HPRT1* variants:

- Loss-of-function variants such as nonsense variants or frameshift variants due to small or large insertions or deletions
- Missense variants with absent or near-absent enzyme activity. These variants may reduce enzyme activity through different mechanisms including impaired kinetic properties, impaired dimerization of HGprt subunits required for functional activity, and poor protein stability.
- Most (but not all) splice site variants that result in major changes in the protein coding region

HND is associated with *HPRT1* variants that result in small amounts of residual enzyme activity (usually 2%-8% of normal):

- Most HND-causing variants are missense variants.
- Occasionally variants affect splice sites, leaving a small proportion of correctly spliced transcripts.
- Rare variants are duplications, which may rarely revert to normal to varying degrees in different tissues, producing somatic mosaicism with varying residual HGprt enzyme activity [Fu et al 2014].

HRH is associated with missense *HPRT1* variants that retain the highest level of abnormal enzyme activity (usually >8% of normal):

- Most individuals with the same *HPRT1* variant have the same phenotype, although exceptions exist [Fu et al 2014].
- Splice site variants have been associated with variable phenotypes, sometimes in the same family, presumably due to differences in splicing fidelity.
- Some missense variants have been associated with variable phenotypes, sometimes in the same family, presumably due to differences in protein stability [Ceballos-Picot et al 2013].

Nomenclature

Although LND may also be referred to as Lesch-Nyhan syndrome, Lesch-Nyhan disease is the more accurate term because the cause of phenotypic elements that constitute the disorder is known.

HRH may also be referred to as Kelley-Seegmiller syndrome.

Prevalence

The prevalence of LND is approximately 1:380,000. The prevalence of the milder phenotypes (HND and HRH) is not well studied, but they appear to be less common than LND.

HPRT1 disorders occur in all populations that have been studied, and with relatively equal frequency.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *HPRT1*.

Differential Diagnosis

Lesch-Nyhan disease (LND). When fully developed with the three clinical elements of uric acid overproduction, neurologic dysfunction, and cognitive and behavioral disturbances, the diagnosis of LND is straightforward. There are no other genetic causes of the full phenotype. The main diagnostic difficulties arise during early stages when all the features are not yet apparent, and in individuals who have milder phenotypes.

The index of suspicion is raised when developmental delay is associated with evidence of overproduction of uric acid, such as hyperuricemia, uric acid nephrolithiasis or crystals in the urine, or gouty arthritis.

LND is first suspected when self-injurious behavior emerges. However, self-injurious behaviors occur in other conditions, including nonspecific intellectual disability, autism spectrum disorder, Tourette syndrome, McLeod neuroacanthocytosis syndrome, Rett syndrome, Cornelia de Lange syndrome, glutaric acidemia type 1, familial dysautonomia, chorea-acanthocytosis, sensory neuropathy including hereditary sensory neuropathy type 1 (see *SPTLC1* Hereditary Sensory Neuropathy), and several psychiatric conditions. Finger and lip biting is so severe and so characteristic of LND that it is referred to as a behavioral phenotype. In other self-injury syndromes, the behavior tends to be less severe, and the topography of behaviors is different, with head banging and/or nonspecific self biting but not biting of the fingers and lips that results in tissue damage.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and the needs in an individual diagnosed with an *HPRT1*-related phenotype, the evaluations summarized in Tables 3, 4, and 5 are recommended. These tables begin with *HPRT1*-related hyperuricemia (HRH) because these needs are shared by all phenotypes (Table 3). Table 4 adds the needs for neurologic assessment in *HPRT1*-related neurologic dysfunction (HND). Since neurologic involvement varies considerably, the assessment must be tailored to individual needs. Table 5 adds the needs for behavioral assessment in Lesch-Nyhan disease (LND).

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *HPRT1* Disorders: HRH

System/Concern	Evaluation	Comment
Hyperuricemia	Serum uric acid	Establish baseline uric acid & need for allopurinol.

Table 3. continued from previous page.

System/Concern		Evaluation	Comment
Nephropathy	**Renal function**	Serum chemistry incl BUN & creatinine	Establish any renal dysfunction.
	Urolithiasis	Abdominal US for renal calculi	Establish existence of: • Any renal stones. Note: Uric acid stones are radiolucent & may not appear on std x-rays. • Any additional renal pathology (e.g., nephrocalcinosis, dystrophy).
Gout		Assessment of joints	Establish existence of: • Gouty arthritis; • Any tophaceous deposits.
Macrocytic anemia		Complete blood count	Typically unresponsive to vitamins & only rarely requires treatment
Genetic counseling		Provide patients & families w/: • Info on nature, MOI, & implications of HRH to help make informed medical & personal decisions; • Risk assessment & testing options to clarify genetic status of family members.	

BUN = blood urea nitrogen; HRH = *HPRT1*-related hyperuricemia; MOI = mode of inheritance; US = ultrasound

Table 4. Additional Recommended Evaluations Following Initial Diagnosis in Individuals with *HPRT1* Disorders: HND

System/Concern	Evaluation	Comment
Motor abnormalities	• Neurologic eval • Developmental eval • PT/rehab eval • PT/OT eval	Assess: • Motor disorder; • Contractures (& if present, address); • Dysarthria; • History of seizures; • ADL.
Intellectual/ behavioral problems	Neurocognitive & behavioral assessments	Assess: • Cognitive abilities & need for intervention; • Any behavioral problems.
Communication	Speech-language pathology eval	Assess dysarthria & need for intervention.
Feeding/Nutrition	Gastroenterology / nutrition / feeding team eval	Assess nutritional status & aspiration risk.
Family support/ resources		Assess need for: • Social worker interventions; • Home nursing referral.

ADL = activities of daily living; HND = *HPRT1*-related neurologic dysfunction; OT = occupational therapist; PT = physical therapist

Table 5. Additional Recommended Evaluations Following Initial Diagnosis in Individuals with *HPRT1* Disorders: LND

System/Concern	Evaluation	Comment
Self-injurious behavior	History & exam for evidence of self injury	• Poorly controlled self injury leads to multiple scars. • Injuries may become infected or life threatening.
Behavioral assessment	History & exam for other difficult behaviors	• Assess for oppositional defiant & other difficult behaviors. • Provide counseling to therapists & teachers re mgmt of difficult behaviors.
Teeth	Dental eval	• Assess for occult biting of oral mucosa & establish plan for tooth extraction when needed. • >50% of all persons may need dental extraction because of self biting.

LND = Lesch-Nyhan disease

Treatment of Manifestations

Following initial evaluations (Tables 3, 4, and 5), treatments for specific problems may be needed. Treatment recommendations are summarized in Tables 6, 7, and 8. They begin with HRH because these needs are shared by all phenotypes (Table 6). Table 7 adds the needs for neurologic interventions in HND. Since neurologic involvement varies considerably, needs vary. Table 8 adds the needs for behavioral interventions in LND [Olson & Houlihan 2000].

A multidisciplinary team may be needed. Depending on needs, this team may require specialists in medical genetics, neurology, behavioral management, developmental pediatrics, physical medicine and rehabilitation, physical therapy, occupational therapy, speech-language pathology, dentistry, and nephrology.

Table 6. Treatment of Manifestations in Individuals with *HPRT1* Disorders: HRH

Manifestation/ Concern	Treatment	Considerations/Other
Hyperuricemia	Xanthine oxidase inhibitor	• Allopurinol most commonly used; febuxostat in case of allopurinol hypersensitivity • Treatment required to ↓ risk for nephropathy, gouty arthritis, & tophi • Titrate to maintain uric acid levels w/in normal limits. • Avoid suppressing uric acid below normal limits because this ↑ risk of xanthine stones.
Renal complications	Xanthine oxidase inhibitor	• Treatment ↓ risk of renal complications. • Avoid dehydration, which concentrates purine metabolites in urinary system. • Renal insufficiency or failure may occur despite medical therapy.
	Lithotripsy or surgery	Renal stones that form despite treatment may require lithotripsy or surgery.
Gouty arthritis	Xanthine oxidase inhibitor	• When gouty arthritis occurs even w/treatment, consider compliance or insufficient hydration. Tophaceous deposits: • May be painful when they erode overlying skin or underlying tissues; • May become infected.
Macrocytic anemia	None	• Folate & B_{12} supplements do not usually work. • Treatment often is not needed because problem does not produce disability.

HRH = *HPRT1*-related hyperuricemia

Table 7. Additional Treatments for Individuals with *HPRT1* Disorders: HND

Manifestation/ Concern	Treatment	Considerations/Other
Motor impairments	Pharmacologic	• No medication reliably controls dystonia in HND. • Antispasticity agents may be useful for spasticity.
Orthopedic problems	PT/OT	Helpful to limit contractures
	Surgical intervention	Orthopedic interventions may be required to address contractures, dislocations, & related problems.
Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	• Cognitive problems may not be apparent w/o neuropsychological testing. • Problems w/attention are common & create learning disability.

HND = *HPRT1*-related neurologic dysfunction; OT = occupational therapy; PT = physical therapy

Table 8. Additional Treatments for Individuals with *HPRT1* Disorders: LND

Manifestation/ Concern	Treatment	Considerations/Other
Self-injurious behavior	Physical protective devices (restraints)	• Required by virtually all persons at some point; often required daily • LND is exempt from laws that prevent use of restraints for extended periods.
	Behavior therapy	• Negative reinforcement methods (punishment) worsen behavior & should not be used. • Extinction methods work best, & require special expertise to implement.
	Pharmacologic interventions	• No medications reliably control self injury in LND. • Benzodiazepines often used to ↓ anxiety • Neuroleptics may worsen the dystonia.
	Dental interventions	• Tooth & mouth guards rarely reliable • Dental extraction required in the majority
Other difficult behaviors	Behavior therapy	Extinction methods sometimes required to suppress other negative behaviors incl hitting, spitting, or foul language
Family/ Community	Social worker intervention	Many families benefit from online chat services where families share experiences.

LND = Lesch-Nyhan disease

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 and special educators. 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.

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.

Surveillance

HPRT1 disorders are not clinically progressive. For example, overproduction of uric acid does not get worse with time. However, chronic overproduction of uric acid over years may lead to cumulative pathology in the kidneys and/or joints, especially if hyperuricemia is not well controlled. Therefore, some surveillance is important for all *HPRT1* disorders (Table 9). Sudden worsening of renal function should lead to suspicion for new stones or a secondary process.

Similarly, new or worsening neurologic problems are not expected over time [Jinnah et al 2006, Jinnah et al 2010]. Some evolution of the neurologic problems occurs in the first few years of life, which reflects development of the nervous system in response to a static insult and is not a neurodegenerative process. Some evolution of disability may occur with aging, analogous to cerebral palsy. Sudden worsening of neurologic status therefore should be investigated for secondary causes.

The behavioral phenotype may wax and wane in severity over the years. Sudden worsening occurs with stress, for example relating to the pain of a kidney stone or change in social environment. In very young children with HND, self-injurious behavior may emerge, leading to reclassification of the diagnosis to LND. This behavior typically emerges between age two and four years but may be delayed until the teenage years.

Table 9. Recommended Surveillance for Individuals with *HPRT1* Disorders: HRH

System/Concern	Evaluation	Frequency
Hyperuricemia	Serum uric acid	• Monitor 3-6x/yr during allopurinol titration. • Annual assessments are sufficient after stable dose is achieved.
Renal complications	Serum chemistry incl BUN & creatinine	Monitor annually to assess for renal insufficiency.
	Renal US	Check for: • Urinary system stones if clinically suspected; • Evidence of worsening renal function.
Gouty arthritis	Physical exam	Check at least annually; more often if clinically indicated due to pain or joint swelling.
	Plain x-rays	Assess for any joint damage.

BUN = blood urea nitrogen; HRH = *HPRT1*-related hyperuricemia; US = ultrasound

Table 10. Additional Recommended Surveillance for Individuals with *HPRT1* Disorders: HND

System/Concern	Evaluation	Frequency
Neurologic	Neurologic or developmental assessment for new or worsening problems (e.g., contractures, dysarthria/dysphagia, seizures)	At least annually
DD/ID	Monitor developmental progress & educational needs	
New onset of self-injurious or other deleterious behaviors	History & physical exam	At least annually through teen yrs
Family/Community	Assessment of caregiver needs (e.g., respite care, home nursing, coordination of multiple subspecialty appointments, equipment, medications, & supplies)	At least annually

DD = developmental delay; HND = *HPRT1*-related neurologic dysfunction; ID = intellectual disability

Table 11. Additional Recommended Surveillance for Individuals with *HPRT1* Disorders: LND

System/Concern	Evaluation	Frequency
Behavioral	History & physical exam for evidence of uncontrolled self injury	At least annually
Self biting	Dental exam for evidence of occult biting (e.g., of buccal mucosa, tongue)	
Family/ Community	Assessment of caregiver needs (e.g., respite care, home nursing, coordination of multiple subspecialty appointments, equipment, medications, & supplies)	

LND = Lesch-Nyhan disease

Agents/Circumstances to Avoid

Avoid the following:

- Probenecid and other drugs that reduce serum uric acid concentration by increasing renal excretion of uric acid; these drugs increase the risk of precipitation of uric acid in the urinary system and may cause acute renal failure.
- Certain chemotherapy agents, such as methotrexate, that block synthesis or use of purines. Individuals with all *HPRT1* disorders are especially sensitive to these agents, since all tissue purines derive from purine synthesis when HGprt-mediated purine salvage is deficient.
- Periods of relative dehydration because they concentrate purine metabolites in the urinary system and increase the risk for renal stones or urate nephropathy

Evaluation of Relatives at Risk

It is appropriate to clarify the status of males at risk for *HPRT1* disorders immediately after birth in order to identify as early as possible those who would benefit from prompt initiation of xanthine oxidase inhibitors and preparation for future needs.

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

Therapies Under Investigation

Numerous small-scale studies have reported benefits from a wide array of therapies including various types of mouth guards and dental appliances, deep brain stimulation, bone marrow transplantation, gabapentin, carbamazepine, S-adenosylmethionine, risperidone, and others. In all instances, follow-up experiences have not confirmed a significant long-term benefit. Because of their follow-on nature and frequent negative outcome, these attempts to confirm benefits often are not published. However, many families post their experience online using social media and, by searching these posts, the clinician can get a good feel for the likelihood that an experimental therapy will have a positive (or negative) impact on the affected individual and their family [Cotton et al 2018].

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

HPRT1 disorders – Lesch-Nyhan disease (LND), *HPRT1*-related neurologic dysfunction (HND), and *HPRT1*-related hyperuricemia (HRH) – are X linked. Males who are hemizygous for an *HPRT1* pathogenic variant are affected. Heterozygous females are virtually always clinically unaffected.

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 *HPRT1* 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 likely to be heterozygous. If a woman has more than one affected child and no other affected relatives and if the proband has a known *HPRT1* variant that 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 or the affected male may have a *de novo HPRT1* variant, in which case the mother is not a heterozygote. If a woman is the first in her family with an affected son, Haldane's rule predicts a two thirds chance that she is a carrier and a one third chance that the son has a *de novo* germline variant.

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

- If the mother of the proband has an *HPRT1* variant, the chance of transmitting it in each pregnancy is 50%:
  - Males who inherit a pathogenic *HPRT1* variant will be affected;
  - Females who inherit the pathogenic variant will be heterozygotes and will virtually always be clinically normal. In rare instances, a heterozygous female may become symptomatic because of skewed (nonrandom) X-chromosome inactivation of the normal *HPRT1* allele [Fu et al 2014] (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the proband has a known *HPRT1* variant that cannot be detected in his mother's leukocyte DNA, the risk to sibs is low but greater than that of the general population because of the possibility of maternal mosaicism [Willers 2004].

Offspring of a male proband

- Males with LND or HND do not reproduce.
- Males with HRH transmit the *HPRT1* pathogenic variant to:
  - All of their daughters, who will be heterozygotes and will virtually always be clinically normal (see Clinical Description, Heterozygous Females);
  - None of their sons.

Other family members of a male proband. The proband's maternal aunts may be at risk of being heterozygotes, and the aunt's offspring, depending on their sex, may be at risk of being heterozygotes (and virtually always clinically normal) or hemizygous and affected.

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.

Carrier Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *HPRT1* pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous will virtually always be clinically normal but may have increased uric acid excretion and some may develop hyperuricemia in later years. (2) Identification of female heterozygotes requires either (a) prior identification of the *HPRT1* pathogenic variant in the family or, (b) 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.

Biochemical testing. In females, measurement of HGprt enzyme activity for heterozygote detection is technically demanding and not widely used.

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, clarification of genetic status, 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, are heterozygous, or are at risk of being heterozygous.

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).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once an *HPRT1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for the variant are possible.

Biochemical testing. Assay of HGprt enzyme activity in cultured amniocytes or chorionic villus cells is the preferred method for prenatal testing if the *HPRT1* pathogenic variant has not been identified in the family [Nyhan et al 2003].

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 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)
Lesch-Nyhan Syndrome Information Page

- **National Library of Medicine Genetics Home Reference**
  Lesch-Nyhan syndrome
- **NCBI Genes and Disease**
  Lesch-Nyhan syndrome

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. HPRT1 Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HPRT1	Xq26.2-q26.3	Hypoxanthine-guanine phosphoribosyltransferase	HPRT1 database Lesch-Nyhan.org	HPRT1	HPRT1

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 HPRT1 Disorders (View All in OMIM)

300322	LESCH-NYHAN SYNDROME; LNS
300323	HYPERURICEMIA, HPRT-RELATED; HRH
308000	HYPOXANTHINE GUANINE PHOSPHORIBOSYLTRANSFERASE 1; HPRT1

Molecular Pathogenesis

HPRT1 encodes the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGprt), which catalyzes the conversion of hypoxanthine to inosine monophosphate (inosinic acid, IMP) and guanine to guanine monophosphate (guanylic acid, GMP) in the presence of phosphoribosylpyrophosphate. Thus, it recycles purines from DNA and RNA that are otherwise degraded.

Mechanism of disease causation. The proximate etiology is loss of function, or at least reduced function of the HGprt enzyme activity [Fu et al 2015].

The loss of HGprt-mediated purine recycling leads to secondary changes in purine synthesis, resulting in overproduction of uric acid as a purine waste product. Uric acid is not very soluble in body fluids, so its accumulation results in precipitation in the urinary system (nephrolithiasis) and joints (gouty arthritis).

The mechanisms responsible for the neurobehavioral phenotype are not entirely understood, but are thought to relate to dysfunction of basal ganglia circuits [Visser et al 2000].

Notable *HPRT1* variants. The majority of *HPRT1* variants are private, and reported for individual families. However, some variants have arisen multiple times, apparently independently, in unrelated families [Sampat et al 2011, Fu et al 2014]. There are a few recognized hot spots for specific pathogenic variants (see Table 12).

Founder variants occurring in extended families are uncommon because males with LND do not reproduce. Males with HND rarely reproduce, but those with HRH may have families. Therefore, several families with multiple affected members have been reported [Fu et al 2014].

For comprehensive information on *HPRT1* variants, see the database curated by the Lesch-Nyhan Disease International Study Group at www.lesch-nyhan.org.

Table 12. Notable *HPRT1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000194.3 NP_000185.1	c.143G>A	p.Arg48His	Most common phenotype is HRH; mild neurologic impairment may be present (HND).
	c.151C>T	p.Arg51Ter	LND phenotype expected due to enzyme activity <2%
	c.289_290delGT	Frameshift	
	c.508C>T	p.Arg170Ter	

HND = *HPRT1*-related neurologic dysfunction; HRH = *HPRT1*-related hyperuricemia; LND = Lesch-Nyhan disease
Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Jinnah is Professor of Neurology and Human Genetics with more than 20 years of experience in research on and clinical management of Lesch-Nyhan disease and its milder variants. He has an NIH-funded laboratory program devoted to developing a better understanding of the abnormalities in brain function that lead to the neurobehavioral aspects of the disease, and has conducted numerous experimental clinical trials.

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- 8 February 2005 (me) Comprehensive update posted live
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- 20 March 2000 (jn) Original submission

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