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# Mucopolysaccharidosis Type I

Synonyms: Alpha-L-Iduronidase Deficiency, IDUA Deficiency, MPS I

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## Summary

### Clinical characteristics

Mucopolysaccharidosis type I (MPS I) is a progressive multisystem disorder with features ranging over a continuum of severity. While affected individuals have traditionally been classified as having one of three MPS I syndromes (Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome), no easily measurable biochemical differences have been identified and the clinical findings overlap. Affected individuals are best described as having either a phenotype consistent with either severe (Hurler syndrome) or attenuated MPS I, a distinction that influences therapeutic options.

*Severe MPS I:* Infants appear normal at birth. Typical early manifestations are nonspecific (e.g., umbilical or inguinal hernia, frequent upper respiratory tract infections before age 1 year). Coarsening of the facial features may not become apparent until after age one year. Gibbus deformity of the lower spine is common and often noted within the first year. Progressive skeletal dysplasia (dysostosis multiplex) involving all bones is universal, as is progressive arthropathy involving most joints. By age three years, linear growth decreases. Intellectual disability is progressive and profound but may not be readily apparent in the first year of life. Progressive cardiorespiratory involvement, hearing loss, and corneal clouding are common. Without treatment, death (typically from cardiorespiratory failure) usually occurs within the first ten years of life.

*Attenuated MPS I:* Clinical onset is usually between ages three and ten years. The severity and rate of disease progression range from serious life-threatening complications leading to death in the second to third decade, to a normal life span complicated by significant disability from progressive joint manifestations and cardiorespiratory disease. While some individuals have no neurologic involvement and psychomotor development may be normal in early childhood, learning disabilities and psychiatric manifestations can be present later in life. Hearing loss, cardiac valvular disease, respiratory involvement, and corneal clouding are common.

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## Diagnosis/testing

The diagnosis of MPS I is established in a proband with suggestive clinical and laboratory findings by: detection of deficient activity of the lysosomal enzyme α-L-iduronidase (IDUA) in combination with elevation of glycosaminoglycan levels; and/or identification of biallelic pathogenic variants in *IDUA* on molecular genetic testing. Identification of the causative *IDUA* variants plays an important role in the determination of phenotype.

## Management

*Treatment of manifestations:* An essential component of management is the determination of whether the proband has severe or attenuated MPS I. This requires detailed clinical and laboratory assessment and can be challenging in very young individuals.

*Targeted therapies:* Hematopoietic stem cell transplantation (HSCT) is considered the standard of care for children with severe MPS I. Outcome is significantly influenced by disease burden at the time of diagnosis (and thus, by the age of the individual). HSCT can improve cognitive outcomes, increase survival, improve growth, reduce facial coarseness and hepatosplenomegaly, improve hearing, prevent hydrocephalus, and alter the natural history of cardiac and respiratory symptomatology. HSCT has lesser effects on the skeletal and joint manifestations, corneal clouding, and cardiac involvement. HSCT alters the course of cognitive decline in children with severe MPS I; cognitive outcome is greatly influenced by the degree of cognitive impairment at the time of transplantation. Due to the morbidity and mortality associated with HSCT, it is currently recommended primarily for children with severe MPS I.

Enzyme replacement therapy (ERT) with laronidase (Aldurazyme®), licensed for treatment of the non-CNS manifestations of MPS I, improves liver size, linear growth, and mobility and joint range of motion; slows progression of respiratory disease; and improves sleep apnea in persons with attenuated disease. The age of initiation of ERT influences the outcome.

*Supportive care*: Infant learning programs/special education for developmental delay; physical therapy, orthopedic surgery as needed, joint replacement for progressive arthropathy, atlanto-occipital stabilization; spinal cord decompression for cervical myelopathy; cerebrospinal fluid shunting for hydrocephalus; early median nerve decompression for carpal tunnel syndrome based on nerve conduction studies before clinical manifestations develop; special attention to anesthetic risks; hats with visors/sunglasses to reduce glare, corneal transplantation for ophthalmologic involvement; cardiac valve replacement as needed and bacterial endocarditis prophylaxis for those with cardiac involvement; tonsillectomy and adenoidectomy for eustachian tube dysfunction and/or upper airway obstruction; ventilating tubes; hearing aids as needed; CPAP for sleep apnea; gastrointestinal management for diarrhea and constipation.

*Surveillance:* Annual assessment by a team of physicians with knowledge of the multisystem nature of MPS I. Specialists and assessments: orthopedic surgery including annual assessment of median nerve conduction velocity; ophthalmology, cardiology (including echocardiography), respiratory with assessment of pulmonary function and sleep studies, audiology, and otolaryngology. Assessment for constipation and/or hernias as needed. Early and continuous monitoring of head growth in infants and children with imaging as needed; assessment for evidence of spinal cord compression by neurologic examination; developmental assessment annually; and psycho-educational assessment of children with attenuated disease prior to primary school entry.

*Evaluation of relatives at risk:* Early diagnosis prior to significant disease manifestations is warranted in relatives at risk in order to initiate therapy as early in the course of disease as possible.

## Genetic counseling

MPS I is inherited in an autosomal recessive manner. At conception, each child of a couple in which both parents are heterozygous for a *IDUA* pathogenic variant has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if both disease-causing *IDUA* variants have been identified in the family.

# *GeneReview* Scope

| Mucopolysaccharidosis Type I: Included Phenotypes |
| --- |
| • Severe MPS I (Hurler syndrome)<br>• Attenuated MPS I (Hurler-Scheie syndrome / Scheie syndrome) |

For synonyms and outdated names see Nomenclature.

# Diagnosis

## Suggestive Findings

### Scenario 1 – Abnormal Newborn Screening (NBS) Result

Note: The approach to NBS for mucopolysaccharidosis type I (MPS I) is currently in evolution. Although single-tier α-L-iduronidase (IDUA) enzyme activity measurement was the original and remains the most common approach taken in the United States, the potential adoption of a second tier involving measurement of dried blood spot glycosaminoglycans is currently under way by some centers. The addition of the second tier greatly increases the positive predictive value of NBS for MPS I [Clarke et al 2020].

- Single-tier NBS for mucopolysaccharidosis type I (MPS I) is primarily based on quantification of IDUA enzyme activity on dried blood spots.
- IDUA enzyme activity values below the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing and clinical evaluation. Follow-up biochemical testing includes confirmation of deficiency of IDUA enzyme activity in blood as well as demonstration of elevation in urinary glycosaminoglycan levels.
- Positive NBS results should be reviewed by a clinical specialist with experience in MPS I to ensure that the appropriate additional laboratory testing and clinical assessment is performed and correctly interpreted to determine whether this a true positive NBS result and to definitively establish the diagnosis of MPS I.

### Scenario 2 – Symptomatic Individual

A symptomatic individual who has findings associated with either attenuated MPS I or severe untreated MPS I (Hurler syndrome) may present because of any of the following: NBS not performed, false negative NBS result, and/or caregivers not adherent with the recommended assessment plan following a positive NBS result.

Supportive (particularly when multiple findings are present) but nonspecific clinical findings and preliminary laboratory findings can include the following.

**Clinical findings**

- Coarse facial features
- Early frequent upper respiratory infections including otitis media
- Inguinal or umbilical hernia
- Hepatosplenomegaly

- Characteristic skeletal findings (gibbus deformity, limitation of joint range of motion)
- Noninflammatory arthropathy
- Characteristic ocular findings (corneal clouding)
- Hydrocephalus
- Developmental delay

Note: Clinical findings vary by disease severity. Clinical findings alone are not diagnostic.

**Preliminary laboratory findings.** Analysis of urine glycosaminoglycans (GAG) (i.e., heparan and dermatan sulfate) may be quantitative (measurement of total urinary GAGs or specific GAG disaccharides) or qualitative (GAG electrophoresis to analyze the specific GAGs excreted).

- Neither the quantitative nor the qualitative method can diagnose a specific lysosomal enzyme deficiency, including MPS I; however, an abnormality detected by either or both methods indicates the likely presence of an MPS disorder.
- GAG electrophoresis can exclude and include certain MPS disorders; however, definitive diagnosis requires additional testing (see Establishing the Diagnosis).
- Both methods have reduced sensitivity, particularly when urine is dilute.

**Family history** is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of MPS I **is established** in a proband with the suggestive clinical AND laboratory findings above and detection of deficient IDUA enzyme activity or identification of biallelic pathogenic (or likely pathogenic) variants in *IDUA* on molecular genetic testing (see Table 1).

Note: (1) Due to the presence of IDUA pseudodeficiency, the establishment of the diagnosis of MPS I requires the demonstration of BOTH deficiency of IDUA enzyme activity AND elevation of urine GAGs. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (3) Identification of biallelic *IDUA* variants of uncertain significance (or of one known *IDUA* pathogenic variant and one *IDUA* variant of uncertain significance) does not establish or rule out the diagnosis.

### Molecular Testing

When NBS results and/or clinical and preliminary laboratory findings suggest the diagnosis of MPS I, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *IDUA* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. Typically, if only one or 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 only rarely been reported.
- **An MPS multigene panel** that includes *IDUA* 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.

**Table 1.** Molecular Genetic Testing Used in Mucopolysaccharidosis Type I

| Gene [1] | Method | Proportion of Disease-Causing Variants [2] Identified by Method |
|---|---|---|
| *IDUA* | Sequence analysis [3] | 97% [4] |
| | Gene-targeted deletion/duplication analysis [5] | Rare [6] |

*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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*4.* The detection rate for two pathogenic variants detectable by sequence analysis in 556 patients was 97% [Clarke 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.
*6.* Whole-gene deletions and intragenic deletions of exons 1-2 and exon 14 have been reported [Breen et al 2016, Jahic et al 2019].

### IDUA Enzyme Activity

IDUA enzyme activity can be measured in most tissues; typically, peripheral blood leukocytes, plasma, or cultured fibroblasts are used.

- All individuals with MPS I have no or very little IDUA enzyme activity detected by the standard methods used for diagnostics.
- Detailed studies using fibroblasts from individuals with MPS I have revealed that as little as 0.13% of normal IDUA enzyme activity appears to be sufficient to produce a mild phenotype [Ashton et al 1992, Oussoren et al 2013]. The overlapping range of residual IDUA enzyme activity noted in fibroblasts of individuals with severe and attenuated disease precludes this measure from being clinically useful.
- The presence of pseudodeficiency alleles also renders interpretation of IDUA enzyme activity difficult. Pseudodeficiency relates to the finding of reduced or undetectable IDUA enzyme activity with the use of artificial substrates, but no evidence of altered glycosaminoglycan metabolism with the use of radiolabeled (35S) GAG [Aronovich et al 1996].

# Clinical Characteristics

## Clinical Description

Mucopolysaccharidosis type I (MPS I), a progressive multisystem disorder with features ranging over a wide continuum, is considered the prototypic lysosomal storage disease. While affected individuals have traditionally been classified as having one of three MPS I syndromes (Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome), no easily measurable biochemical differences have been identified [Muenzer 2004] and the clinical findings overlap; thus, affected individuals are best described as having either severe or attenuated MPS I, a

distinction that influences therapeutic options. The greatest variability is observed in individuals with attenuated MPS I.

An accurate determination of the proportion of individuals with severe or attenuated MPS I has not been published. Data from the international MPS I Registry available in 2011 showed that of the 891 individuals included in the registry, 57% were classified as having Hurler syndrome, 23.5% as having Hurler-Scheie syndrome, and 10% as having Scheie syndrome; 8.6% were classified as either unknown or indeterminate. The potential ascertainment bias of registry data and the lack of a clear definition of phenotypic features for each of the subcategories should be considered in interpretation of the data [D'Aco et al 2012].

**Table 2.** Mucopolysaccharidosis Type I: Comparison of Phenotypes by Select Features

| Feature | % of Persons w/Feature [1] | |
|---|---|---|
| | Severe MPS I | Attenuated MPS I |
| Course facial features | 100% | 10% |
| Macrocephaly | 50% | 20% |
| Hepatosplenomegaly | 100% | 80% |
| Dysostosis multiplex | 100% | 100% |
| Ophthalmologic issues | 100% | 100% |
| Cardiac involvement | 100% | 100% |
| Hearing loss | 100% | 50% |
| Upper airway involvement | 100% | 80% |
| Hydrocephalus | 25% | 5% |
| Intellectual disability | 100% | 10% |

*1.* The age of the affected individual considerably affects the phenotypic features.

## Severe MPS I (Hurler Syndrome)

Severe MPS I is characterized by a chronic and progressive disease course involving multiple organs and tissues [Neufeld & Muenzer 2001, Muenzer et al 2009]. Infants with severe MPS I appear normal at birth but may have inguinal or umbilical hernias. The mean age of diagnosis for severe MPS I is approximately ten months; most affected children are diagnosed before age 18 months [Giugliani et al 2021]. In untreated individuals, death due to cardiorespiratory failure usually occurs within the first ten years of life.

**Craniofacial and physical appearance.** Coarsening of the facial features, caused by storage of glycosaminoglycans (GAGs) in the soft tissues of the orofacial region and facial bone dysostosis, becomes apparent within the first two years. Thickening of the alae nasi, lips, ear lobules, and tongue becomes progressively more evident. Thickening of the calvarium results in macrocephaly. Scaphocephaly is common. Facial and body hypertrichosis are often seen by age 24 months, at which time the scalp hair is coarse, straight, and thatch-like.

**Hepatosplenomegaly.** Protuberance of the abdomen caused by progressive hepatosplenomegaly is common. Although organ size may be massive, storage of GAGs in the liver and spleen does not lead to organ dysfunction.

**Skeletal.** Progressive skeletal dysplasia (dysostosis multiplex) involving all bones is seen in all individuals with severe MPS I. Children have significant early bone involvement. Mild dysostosis, particularly of the hip, as well as thickening of the ribs, can be detected on radiographs soon after birth but findings may be interpreted as within normal limits at this early age. Gibbus deformity (dorsolumbar kyphosis) often becomes clinically apparent within the first ten months; it has been reported as early as age six months [Mundada & D'Souza 2009].

MPS I registry data show that by age six months the median growth for individuals with severe MPS I begins to deviate from normal, falling below the third percentile of normal by age four years [Viskochil et al 2019]. Defective ossification centers of the vertebral bodies lead to flattened and beaked vertebrae and subsequent spinal deformity. Complications may include spinal nerve entrapment, acute spinal injury, and atlanto-occipital instability.

The clavicles are short, thickened, and irregular. Long bones are short with wide shafts; the knees are prone to valgus and varus deformities. Endochondral growth plates are thickened and disordered. Typically, the pelvis is poorly formed. The femoral heads are small and coxa valga is common. Involvement of the femoral heads and acetabula leads to progressive and debilitating hip deformity. Progressive arthropathy leading to severe joint deformity is universal; significant and functionally impactful joint stiffness is common by age two years.

Phalangeal dysostosis and synovial thickening lead to a characteristic claw hand deformity. Carpal tunnel syndrome and interphalangeal joint involvement commonly lead to poor hand function. Carpal tunnel syndrome is often missed because of its insidious onset; it often presents with few symptoms or signs other than thenar atrophy.

**Ophthalmologic.** Corneal clouding occurs in all individuals with MPS I. Progression can lead to severe visual impairment. Open-angle glaucoma may occur. Retinal degeneration resulting in decreased peripheral vision and night blindness is common. Blindness can result from a combination of retinal degeneration, optic nerve compression and atrophy, and cortical damage from hydrocephalus.

**Cardiovascular.** Cardiac involvement is seen in all individuals with severe MPS I. Cardiac involvement is evident by echocardiography much earlier than observed clinically. Progressive thickening and stiffening of the valve leaflets can lead to mitral and aortic regurgitation and stenosis, which may become hemodynamically significant in the later stages of disease. Mitral valve regurgitation is the more common valvular disease in individuals with severe MPS I [Neufeld & Muenzer 2001]. As lysosomal storage continues in the heart, cardiomyopathy, sudden death from arrhythmia, coronary artery disease, and cardiovascular collapse may occur. A small subset of individuals with severe MPS I have an early-onset fatal endocardiofibroelastosis.

**Hearing loss.** Hearing loss, which is common in severe MPS I, is correlated to the severity of somatic disease. Hearing loss results from frequent middle-ear infection, from eustachian tube dysfunction caused by storage of GAGs within the oropharynx, dysostosis of the ossicles of the middle ear, scarring of the tympanic membrane, and damage to the eighth nerve.

**ENT (otolaryngologic).** Chronic recurrent rhinitis and persistent copious nasal discharge without obvious infection are common. Storage of GAGs within the oropharynx with associated enlargement of the tonsils and adenoids can contribute to upper airway complications, along with narrowed trachea, thickened vocal cords, redundant tissue in the upper airway, and an enlarged tongue. This upper airway involvement leads to noisy breathing (particularly at night) and a deep and gravelly voice, and is a main component of obstructive sleep apnea, a common complication of MPS I. CNS involvement can also contribute to sleep apnea.

**Gastrointestinal system.** Inguinal hernias should be repaired surgically with the expectation that they may recur. Umbilical hernias are generally not treated unless they are exceedingly large.

For unknown reasons, many children with severe MPS I periodically experience loose stools and diarrhea, sometimes alternating with periods of severe constipation. These problems may or may not diminish with age; they are exacerbated by muscle weakness and physical inactivity, as well as antibiotic use for other medical complications.

**Hydrocephaly.** Communicating high-pressure hydrocephalus is common in individuals with severe MPS I. Impaired resorption of cerebrospinal fluid causes an increase in intracranial pressure, leading to brain compression. Increase in intracranial pressure can cause rapid cognitive decline in some individuals. Symptoms

may be difficult to assess and progression insidious. The degree to which hydrocephalus contributes to the neurologic deterioration in children with severe MPS I is unknown.

**Intellect.** Although early psychomotor development may be normal, developmental delay is usually obvious by age 18 months. A measurable decrease in intellectual capacity occurs monthly thereafter (as graded by the Bayley Mental Development Index) [Shapiro et al 2018]. Subsequently, most children do not progress developmentally but plateau for a number of years, followed by a slow decline in intellectual capabilities. By the time of death at age eight to ten years, most children are severely intellectually disabled.

Children with severe MPS I develop only limited language skills, likely related to the triad of developmental delay, chronic hearing loss, and enlarged tongue.

In contrast to MPS II and MPS III, the severe developmental effects in children with MPS I are associated with placid rather than aggressive behavior. Seizures appear to be uncommon even at the end stages of disease.

**Pathophysiology.** The metabolic and physiologic bases of the various symptoms in MPS I are complex and involve the direct cellular effect of lysosomal storage of GAGs, inflammatory pathway activation, alteration of extracellular matrix composition and function, interference of other lysosomal and endosomal pathways, cell signaling, and alteration of autophagy.

## Attenuated MPS I (Hurler-Scheie Syndrome / Scheie Syndrome)

If development is normal by age 24 months and if moderate somatic involvement is evident (e.g., mild hepatomegaly, relatively normal joint range of motion, mild dysostosis on skeletal radiographs, mild corneal clouding), an individual should be classified as having attenuated MPS I.

**Onset** of disease in children with attenuated MPS I is variable, usually occurring between ages three and ten years, but recognition of the diagnosis may be delayed [Giugliani et al 2021].

**Craniofacial and physical appearance.** The physical appearance of individuals with attenuated MPS I varies. Coarseness of facial features is less obvious than in individuals with severe MPS I. Findings can include a short neck, wide mouth, and square jaw.

Children with attenuated MPS I have variable growth restriction that may not be apparent until later childhood [Viskochil et al 2019].

**Hepatosplenomegaly** is variable in individuals with attenuated MPS I.

**Skeletal.** Skeletal and joint manifestations are the most significant source of disability and discomfort for individuals with attenuated disease, who may have severe bone involvement but no cognitive impairment [Vijay & Wraith 2005]. The MPS I Registry showed that more than 85% of persons with attenuated MPS I have dysostosis, primarily in the vertebrae and femur [Thomas et al 2010]. Kyphosis, scoliosis, and severe back pain are common. Spondylolisthesis of the lower spine leading to spinal cord compression can occur.

Progressive arthropathy affecting all joints and eventually leading to loss of or severe restriction in range of motion is universal. Carpal tunnel syndrome was present at a median age of nine years 11 months in 138 individuals with attenuated MPS I included in the MPS I Registry [Viskochil et al 2017]. Poor hand function resulting from the characteristic claw hand deformity, carpal tunnel syndrome, and interphalangeal joint stiffness is often observed. Most individuals do not have the characteristic early symptoms of carpal tunnel syndrome (see Management).

**Ophthalmologic.** Corneal clouding, exhibited by approximately 82% of children with attenuated MPS I, was identified at a median age of 9.1 years [Thomas et al 2010]. Corneal clouding can lead to significant visual disability. Glaucoma, retinal degeneration, and optic atrophy can occur.

**Cardiovascular.** Significant cardiac involvement is estimated to occur in approximately 88% of children with attenuated MPS I at a median age of 11.7 years [Thomas et al 2010]. Virtually all individuals with MPS I will have evidence of cardiac valvular thickening. Cardiac involvement can present as progressive disease of the mitral and aortic valves with regurgitation and/or stenosis, for which valve replacement may be necessary. Aortic valvular disease is more likely to occur in children with attenuated MPS I than in those with severe MPS I [Neufeld & Muenzer 2001]; however, in some individuals, all valves are affected. In a group of 78 persons with attenuated MPS I, 40% had involvement of one valve and 60% had involvement of two or more valves [Thomas et al 2010].

Coronary disease may also be a feature of attenuated MPS I.

**Hearing loss.** Moderate-to-severe hearing loss develops in many individuals with attenuated MPS I, particularly children with significant somatic disease. Hearing impairment, most commonly in the high frequency range, is likely caused by a combination of eustachian tube dysfunction, dysostosis of the ossicles of the middle ear, and eighth nerve involvement.

**ENT (otolaryngologic).** Rhinorrhea is common. Sleep apnea as a result of obstructive airway disease and possibly central nervous system involvement occurs in individuals with attenuated MPS I.

**Gastrointestinal system.** Hernias were present in approximately 65% of persons with attenuated MPS I included in the MPS I Registry [Thomas et al 2010]. Many have also had inguinal hernias during infancy, often requiring repeated surgical correction.

**Respiratory system.** Progressive pulmonary disease may manifest as abnormalities of forced vital capacity. Respiratory complications (and cardiac involvement) are among the leading causes of premature death.

**Hydrocephaly.** The risk of communicating hydrocephalus and its complications are lower in attenuated MPS I than severe MPS I. However, hydrocephalus may occur with insidious onset.

**Other neurologic findings.** Arachnoid cysts may develop. The predictive power of changes noted on MRI does not appear to be significant in individuals with attenuated MPS I [Neufeld & Muenzer 2001, Valayannopoulos et al 2010].

Progressive compression of the spinal cord with resulting cervical myelopathy caused by thickening of the dura (hypertrophic pachymeningitis cericalis) is common in individuals with attenuated MPS I. Cervical myelopathy may present initially as reduced activity or exercise intolerance and may not be recognized until the injury is irreversible.

**Intellect.** Although development may be normal in early childhood, children and adults with attenuated MPS I may have detectable learning disabilities. No correlation between the degree of multiorgan disease and intellectual deficits in attenuated MPS I has been observed [Shapiro et al 2015]. If intellectual abilities decline, the course is more protracted than in individuals with severe disease.

**Prognosis.** The rate of disease progression can range from serious life-threatening complications leading to death in the second to third decade, to a normal life span (albeit with significant disease morbidity).

## Genotype-Phenotype Correlations

There is a close correlation of genotype to phenotype in MPS I based on data from 538 individuals within the international MPS I registry [Clarke et al 2019]. Complete loss of IDUA enzyme activity, often due to homozygosity or compound heterozygosity of the common p.Gln70Ter or p.Trp402Ter pathogenic variants, is associated with severe MPS I. Any combination of two "severe" variants leads to severe MPS I. In individuals with severe MPS I, 68% (257/380) had two variants that would be predicted to severely disrupt gene

transcription or translation, 76 of the remaining 123 individuals (20%, 76/380) had recurrent variants, and 47 (12.4%, 47/380) had at least one unique variant.

Attenuated MPS I is usually associated with at least one missense variant; registry data showed that 95.6% (151/158) of individuals with attenuated MPS I had at least one missense variant. It is postulated that the missense variant permits some residual enzyme activity.

Exceptions include the following variants associated with attenuated MPS I:

- p.Tyr343Ter. A premature stop codon that is used as an acceptor splice site, thereby generating an in-frame deletion [Lee-Chen & Wang 1997]
- p.Ter654Gly predicts an extension of α-L-iduronidase at its carboxyl end that may change the conformation and/or stability of the enzyme.
- p.Ter654Arg predicts an extension of α-L-iduronidase at its carboxyl end that may change the conformation and/or stability of the enzyme.
- c.590-7G>A. A base substitution in intron 5 creates a new splice site and produces a frameshift; however, because the old splice site is not obliterated, some normal enzyme is produced.

## Nomenclature

While affected individuals have traditionally been classified as having one of three MPS I syndromes – Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome – no biochemical differences have been identified and the clinical findings overlap; thus, affected individuals are best described as having either severe (Hurler syndrome) or attenuated MPS I, a distinction that influences therapeutic options.

## Prevalence

MPS I is seen in all populations at a frequency of approximately 1:100,000 for the severe form and 1:500,000 for the attenuated form [Lowry et al 1990, Meikle et al 1999, Poorthuis et al 1999].

# Genetically Related (Allelic) Disorders

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

# Differential Diagnosis

**Lysosomal storage disease.** Findings in individuals with mucopolysaccharidosis type I (MPS I) overlap those of other lysosomal diseases, particularly other mucopolysaccharide disorders, including those summarized in Table 3. Clinical findings and biochemical testing can distinguish them.

**Table 3.** Genes and Disorders of Interest in the Differential Diagnosis of Mucopolysaccharidosis Type I

| Gene [1] | DiffDx Disorder | MOI | Clinical Findings | Biochemical Findings |
|---|---|---|---|---|
| *IDS* | MPS II | XL | Similar to MPS I but no corneal involvement | Deficiency of iduronate-2-sulfatase |
| *GUSB* | MPS VII | AR | Similar to MPS I | Deficiency of β-D-glucuronidase |
| *ARSB* | MPS VI | AR | Similar to MPS I | Deficiency of galactosamine-4-sulfatase |
| *GNPTAB* | ML II & ML IIIα/β (See *GNPTAB*-Related Disorders.) | AR | Similar to MPS I | ↑ α-L-iduronidase enzyme activity may be observed in ML II & ML IIIα/β. [2] |
| *MAN2B1* | Alpha-mannosidosis | AR | Mild dysostosis | Deficiency of alpha mannosidase |

*Table 3. continued from previous page.*

| Gene [1] | DiffDx Disorder | MOI | Clinical Findings | Biochemical Findings |
|---|---|---|---|---|
| *NEU1* | Mucolipidosis I (sialidosis type II) (OMIM 256550) | AR | Coarse features, myoclonus, seizures | Deficiency of neuraminidase |
| *SUMF1* | Multiple sulfatase deficiency | AR | Similar to MPS I | Formylglycine-generating enzyme |
| *GALNS* | MPS IVA | AR | Short stature, chest deformity | Deficiency of galactosamine-6-sulfatase |
| *GLB1* | MPS IVB | AR | Short stature, chest deformity | Deficiency of β-D-galactosidase |

AR = autosomal recessive; DiffDx = differential diagnosis; ML = mucolipidosis; MOI = mode of inheritance; MPS = mucopolysaccharidosis; XL = X-linked

*1.* See also Mucopolysaccharidoses: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

*2.* In these conditions, the enzyme α-L-iduronidase is synthesized in adequate amounts but is not transported to the lysosome because of a defect in the receptor-mediated lysosomal targeting process.

**Juvenile idiopathic arthritis.** Persons with attenuated MPS I may present with noninflammatory arthritis at any age; thus, MPS I should be considered in the differential diagnosis of juvenile idiopathic arthritis [Cimaz & Mauro 2015]. Clinical evaluation for the pattern of joint involvement and other manifestations of MPS I should permit identification of individuals with attenuated MPS I presenting with noninflammatory arthritis.

# Management

Guidelines for the management of mucopolysaccharidosis type I (MPS I) have been developed [Muenzer et al 2009].

## Evaluations Following Initial Diagnosis

To establish the extent of disease and determination of phenotype (i.e., severe or attenuated) in an individual diagnosed with MPS I, the evaluations summarized in Table 4 and Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 4.** Mucopolysaccharidosis Type I: Recommended Evaluations Following Initial Diagnosis in a Newborn

| Evaluation | Comment |
|---|---|
| Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian [1] | Referral to specialist center w/experience in mgmt of inherited metabolic/genetic diseases is strongly recommended. |
| Molecular genetic testing for *IDUA* variants | Genotype of affected person is an important component of determining phenotype. |
| Developmental assessment | • Consultation w/PT, OT, & speech therapist<br>• Consider referral to developmental pediatrician. Experience with the nuances of developmental assessment of children with MPS or other multisystem disorders is critical. |
| Consultation w/social worker | To ensure understanding of the diagnosis & assess parental / affected person's coping skills & resources |
| Genetic counseling by genetics professionals [2] | To inform affected persons & families re nature, MOI, & implications of MPS I to facilitate medical & personal decision making |

MOI = mode of inheritance; OT = occupational therapist; PT = physical therapist

*1.* After a new diagnosis of MPS I in a child, the closest hospital and local pediatrician should also be informed.

*2.* Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

**Table 5.** Mucopolysaccharidosis Type I: Recommended Evaluations in All Individuals

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Skeletal** | Complete skeletal survey to determine degree & extent of joint involvement & involvement of spine | Hip dysplasia as well as spinal compression are common. |
| **Ophthalmologic** | Ophthalmologic exam w/measurement of visual acuity & intraocular pressure, slit lamp exam of cornea, & assessment of retinal function by electroretinography & visual field testing if age allows | Corneal clouding is universal & older persons are at risk of glaucoma & retinal dysfunction. |
| **Cardiovascular** | Cardiac eval w/echocardiography to assess ventricular size, function, & valvular disease | Valvular dysfunction is common; young persons can exhibit cardiomyopathy. |
| **Hearing** | Hearing assessment | |
| **ENT (otolaryngologic)** | ENT assessment incl sleep study | Chronic otitis is common as is upper airway obstruction w/large tonsils & adenoids. |
| **Gastrointestinal** | Eval for hernias, stooling issues, & assessment of diet | |
| **Neurologic** | Cranial imaging, preferably MRI, incl assessment of possible hydrocephalus | Severely affected persons can have hydrocephalus early in life. |
| | Assessment of spinal cord & peripheral nerve involvement | Spinal cord compression can occur at any level, w/cervical compression most common. |
| | Assessment for carpal tunnel syndrome | Carpal tunnel compression is common & affected persons may not have primary symptoms. |
| **Development** | Developmental assessment | |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & families re nature, MOI, & implications of MPS I to facilitate medical & personal decision making |
| **Family support & resources** | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement for parental support;<br>• Home nursing referral. | |

MOI = mode of inheritance

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

## Treatment of Manifestations

There is no cure for MPS I.

A central component of management of MPS I is the initiation of treatment early in the natural history of disease, as symptoms and disease complications are difficult or impossible to reverse. It is essential to promptly determine whether the individual fits the phenotype of severe or attenuated MPS I, as the only therapeutic approach that has been demonstrated to alter the natural history of the central nervous system (CNS) manifestations characteristic of severe MPS I is hematopoietic stem cell transplantation (HSCT), and the age of initiation of HSCT directly influences the ultimate outcome of affected individuals. Additionally, the age of initiation of enzyme replacement therapy in individuals with attenuated MPS I influences the long-term outcome (see Table 6).

## Targeted Therapies

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure.* —ED

**Table 6.** Mucopolysaccharidosis Type I: Targeted Treatment

| Targeted Treatment | Indication/Dosage | Benefits | Consideration |
|---|---|---|---|
| **Hematopoietic stem cell transplantation (HSCT)** [1, 2] | Considered the standard of care for children w/MPS I & is generally recommended to be performed before age 2 years to maximize benefit | • Improved survival [3]<br>• Reduction in facial coarseness & hepatosplenomegaly, & improvement in hearing [4]<br>• Initial stabilization & improvement in myocardial function w/regression of hypertrophy & normalization of chamber dimensions; however, long-term follow up shows continued progression of valvular involvement [3] | • HSCT is the only therapeutic approach that alters the natural history of neurocognitive disease in MPS I. [5, 6]<br>HSCT has more limited impact on cardiac valvular, ocular, & skeletal manifestations. [7, 8]<br>Outcome from HSCT is significantly influenced by disease burden at time of diagnosis (& thus age of affected person). [9]<br>HSCT has been successful in ↓ rate of progression of some findings in children w/severe MPS I. |
| **Laronidase (Aldurazyme®) [10] enzyme replacement therapy (ERT)** | • Premedication w/anti-inflammatory & antihistamine drugs<br>• Intravenous weekly infusion of 100 U/kg of Aldurazyme® over 4 hours<br>• Package insert provides details that may differ by country. | Benefits have included: [11]<br>• ↓ & sustained urinary GAG levels [12]<br>• Normalization of hepatic & splenic volume<br>• Stabilization (but not improvement) in respiratory function<br>• Gradual ↑ in shoulder range of motion (typically w/in 1st 2 years, then plateauing)<br>• Improvements in mobility w/in 1st 2 years [13]<br>• Improvement in quality of life index | • Currently licensed widely for use in **treating non-CNS manifestations**<br>• Aldurazyme® does not cross blood-brain barrier & thus is not expected to influence CNS disease.<br>• The effect on rate of disease progression & effect when started very early in a person w/attenuated disease has not been comprehensively studied.<br>• ERT does not impact corneal involvement, cardiac valvular disease progression, progressive arthropathy of involved large joints & hands, & progressive spinal diseases w/cord compression. |

*Table 6. continued from previous page.*

| Targeted Treatment | Indication/Dosage | Benefits | Consideration |
|---|---|---|---|
| | | | • Carpal tunnel syndrome remains a potential complication. |

GAG = glycosaminoglycan
*1.* HSCT is not curative but does significantly alter the natural history of the disorder.
*2.* HSCT should be used only in carefully selected children with extensive pre-transplantation clinical assessment and counseling in whom systematic long-term monitoring will be possible [Aldenhoven et al 2015a, Aldenhoven et al 2015b]. Adults have not undergone HSCT.
*3.* Lum et al [2017]
*4.* van den Broek et al [2020a]
*5.* Aldenhoven et al [2015a], Aldenhoven et al [2015b], Shapiro et al [2015], Kunin-Batson et al [2016]
*6.* The degree to which HSCT relieves neurologic complications other than progressive intellectual decline is not clear. In children undergoing HSCT before evidence of significant developmental delay (i.e., usually age 12-18 months), HSCT appears to slow the course of cognitive decline. Children showing significant cognitive impairment prior to undergoing HSCT do not show correction of existing impairment.
*7.* In part because of increased longevity after HSCT, treated individuals develop increasing pain and stiffness of the hips and knees, carpal tunnel syndrome, spinal cord compression, and progressive thoracolumbar kyphosis. The age of HSCT appears to influence the age of onset of carpal tunnel syndrome and cervical compression.
*8.* The skeletal manifestations and corneal clouding continue to progress in children treated with HSCT and in untreated children [van den Broek et al 2020b].
*9.* Individuals who have received HSCT require continued multidisciplinary follow up and monitoring related to MPS I complications.
*10.* Comparative sib studies indicate improved outcomes when ERT is initiated early in the disease course.
*11.* Sifuentes et al [2007], Clarke et al [2009], Al-Sannaa et al [2015], Gabrielli et al [2016]
*12.* Response is usually within 12 weeks, with some individuals achieving normal values.
*13.* As measured by timed-walk measurements; after two years mobility may be variably affected by hip, knee, and spinal disease progression.

## Supportive Care

Due to the multisystem involvement and progressive nature of this disorder, treatment of affected individuals is complex and requires the support of a multidisciplinary team consisting of metabolic/genetic physicians, specialist physicians including orthopedics, general surgery, ophthalmology, ENT, cardiology, neurosurgery, pulmonary, and developmental pediatrics, as well as specialists in neuropsychology, physiotherapy, occupational therapy, genetic counseling, and social work.

**Skeletal.** Physical therapy is a critical aspect of MPS I therapy [Tylki-Szymanska et al 2010]. Range of motion exercises appear to offer some benefits in preserving joint function and should be started early. Once significant joint limitation has occurred, increased range of motion may not be achieved without HSCT.

Various orthopedic approaches can be undertaken, particularly in individuals with attenuated disease. Joint replacement and atlanto-occipital stabilization may be necessary. These procedures must be performed at appropriate times in the individual's clinical course and must take into account the presence of other disease complications.

Carpal tunnel syndrome should be treated especially in individuals with attenuated MPS I and individuals with severe MPS I who have had HSCT. Most individuals lack typical symptoms (pain, tingling, or numbness) until severe compression occurs [Van Heest et al 1998, Bahadir et al 2009, Viskochil et al 2017]; thus, nerve conduction studies should be used early in the course of disease to identify persons with carpal tunnel syndrome at a time when surgical release may be most beneficial. Surgical decompression of the median nerve results in variable restoration of motor hand activity [Van Heest et al 1998]. Intervention at an early stage, prior to severe nerve damage, optimizes outcome; repeated surgery may be required.

**Surgical management.** Individuals with MPS I present major anesthetic risks, including death [Moores et al 1996]. It is appropriate for affected individuals to undergo general anesthesia in centers staffed by anesthesiologists experienced in managing individuals with a mucopolysaccharidosis [Neufeld & Muenzer 2001]. Important considerations:

- Dysostosis multiplex can lead to instability of the spine, including the atlanto-axial joint. Careful positioning and avoidance of hyperextension of the neck are necessary.
- Induction of anesthesia for any purpose can be difficult because of the difficulty of maintaining an adequate airway. Smaller-than-anticipated endotracheal tubes may be required for endotracheal intubation because the trachea may be narrowed and the vocal cords thickened.
- Intubation may require fiberoptic laryngoscopy.
- Recovery from anesthesia may be slow and postoperative airway obstruction is a common problem.

**Ophthalmologic.** Wearing peaked caps or eye shades can help reduce glare resulting from corneal clouding. Corneal transplantation is successful for individuals with attenuated disease, although donor grafts eventually become cloudy. Individuals with clear grafts may still experience poor vision because of involvement of the retina and/or optic nerve [Neufeld & Muenzer 2001].

**Cardiovascular.** Cardiac valve replacement should be considered early. Bacterial endocarditis prophylaxis is advised for individuals with cardiac abnormalities [Neufeld & Muenzer 2001].

**Hearing loss.** Tonsillectomy and adenoidectomy correct eustachian tube dysfunction and decrease upper airway obstruction. Early placement of ventilating tubes is recommended in severely affected individuals. Hearing aids should also be considered.

**ENT (otolaryngologic).** Sleep apnea may require tracheotomy or high-pressure continuous positive airway pressure with supplemented oxygen. Tracheostomy is often required to maintain the airway and control pulmonary hypertension and right heart failure.

**Gastrointestinal system.** Some gastrointestinal symptoms (diarrhea and constipation) can be controlled by diet, including control of the amount of roughage. Increased roughage and the conservative use of laxatives may ease constipation.

**Hydrocephaly.** Cerebrospinal fluid (CSF) pressure and progressive ventricular enlargement indicate need for a shunting procedure. Ventriculoperitoneal shunting in individuals with MPS I who have moderate-to-severe hydrocephalus is generally palliative and improves quality of life.

**Other.** Progressive compression of the spinal cord with resulting cervical myelopathy should be aggressively and quickly evaluated in individuals with attenuated disease or those who have had HSCT. Early surgical intervention may prevent severe complications.

## Surveillance

The recommended minimal schedule of assessments is highlighted in Muenzer et al [2009].

Persons with MPS I, regardless of disease severity and mode of treatment, should be actively followed at a center that is experienced with the care of individuals with MPS disease.

**Table 7.** Mucopolysaccharidosis Type I: Recommended Surveillance

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Skeletal** | Assessment by experienced orthopedic surgeon | At least annually |
| | Median nerve conduction velocity testing to assess for carpal tunnel syndrome | Annually for 1st 10 yrs |

*Table 7. continued from previous page.*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Ophthalmologic** | Ophthalmologic assessment incl corneal status & retinal function | Annually |
| **Cardiac** | Cardiac assessment incl echocardiogram | |
| **Audiologic/ENT** | Assessment by audiologist & ENT physician to determine degree & cause of hearing impairment | |
| **Gastrointestinal** | Assessment for constipation &/or hernias | As needed |
| **Neurologic** | Monitor head growth by measuring OFC. | At each visit in infants & children |
| | • Cranial ultrasound exam & other brain imaging studies; MRI can show ventriculomegaly, but imaging studies often cannot reliably distinguish between brain atrophy & brain compression.<br>• Lumbar puncture w/measurement of opening pressure of CSF is preferred method to assess degree of pressure elevation [Neufeld & Muenzer 2001]. | If a rapid ↑ in OFC occurs |
| | Assessment for evidence of spinal cord compression by neurologic exam w/ consideration of spinal MRI studies when indicated | Annually |
| **Development** | Developmental assessment | At least annually |
| | In children w/attenuated disease: consider psycho-educational assessment. | Prior to primary school entry |

CSF = cerebrospinal fluid; OFC = occipitofrontal circumference

## Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted in order to initiate therapy as early in the course of disease as possible. For at-risk newborn sibs when prenatal testing was not performed: in parallel with newborn screening, either test for the familial *IDUA* pathogenic variants or measure IDUA enzyme activity and urinary GAG excretion.

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

## Pregnancy Management

Women with MPS I who become pregnant require assessment and frequent monitoring of cardiorespiratory and spinal cord involvement.

## Therapies Under Investigation

With the success of ERT for MPS I demonstrated by clinical trials, an increased effort is under way to improve responsiveness to ERT and to develop other forms of therapy directed at areas/organs that may not be responsive to ERT, such as skeletal and neurologic involvement.

**Combined ERT and HSCT.** There have been limited observational data on the outcome of individuals with severe MPS I treated with long-term combined ERT and HSCT. Polgreen et al [2020] report on ten individuals who received long-term ERT post HSCT; growth may have been improved in the younger individuals.

**Delivery of enzyme to the CNS.** Intravenous infusion of recombinant proteins does not lead to transfer of proteins across the blood-brain barrier. Various means to provide enzyme to the CNS are currently being researched. These approaches include CSF instillation of enzyme via direct injection, continuous pumps, microcapsule implants, and production of chimeric recombinant proteins, enabling passage across the blood-brain barrier.

A clinical trial of intrathecal ERT is currently under way in individuals who have evidence of spinal cord involvement. To date, this method has reduced CSF GAG levels and CSF pressure and has been found to be safe. The efficacy of intrathecal ERT is unclear [Munoz-Rojas et al 2008, Dickson et al 2015a, Dickson et al 2015b].

**Stabilization of mutated enzyme with substrate analogs.** It is now generally accepted that lysosomal enzymes must be processed through a complex intracellular sorting mechanism prior to transport to the lysosome. Many single-nucleotide variants underlying lysosome enzyme deficiencies lead to disease by altering the folding of the protein after translation, such that the misfolded protein cannot be transported to the lysosome. Small-molecule substrate analogs have been shown to stabilize mutated lysosomal proteins in tissue culture and thus enable transport of these enzymes to the lysosome. Once in the lysosome, these mutated enzymes are likely able to metabolize enough substrate to alter the disease course. As most individuals with attenuated MPS I have at least one *IDUA* pathogenic missense variant, the development of substrate analogs for α-L-iduronidase may lead to new forms of therapy for this disorder.

**Substrate deprivation.** Decreasing the quantity of stored substrate in lysosomal disorders is currently being investigated for the treatment of Gaucher disease [Cox et al 2003]. Potential use of similar molecules that may decrease the production of GAGs or other substances that are stored in MPS disease may have a future role in treatment [Piotrowska et al 2006]. These approaches are still in the animal model phase, with attempts including silencing of key GAG synthetic enzymes [Kaidonis et al 2010] to certain GAGs.

**Gene- and cell-based therapy.** Advances in both gene- and stem cell-based therapies for genetic diseases could potentially influence treatment of MPS I [Di Domenico et al 2005].

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

Mucopolysaccharidosis type 1 (MPS I) is inherited in an autosomal recessive manner.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *IDUA* pathogenic variant disease-causing variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *IDUA* disease-causing variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**

- If both parents are known to be heterozygous for an IDUA disease-causing variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Although MPS I is a heterogeneous disorder, affected sibs will have a clinical course similar to the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** The offspring of an individual with MPS I are obligate heterozygotes (carriers) for an *IDUA* disease-causing variant. Individuals with severe MPS I generally do not reproduce, but fertility is likely unaffected by the disease; thus, advances to treatments and improved outcomes may lead to pregnancies in the future.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *IDUA* disease-causing variant.

## Carrier Detection

**Molecular genetic testing**

- If both *IDUA* disease-causing variants have been identified in an affected family member, molecular genetic testing can be used to identify carriers among at-risk family members.
- Molecular genetic testing of *IDUA* to determine carrier status can be offered to both parents of an affected deceased child with MPS I in whom no molecular testing of *IDUA* was performed and for whom no DNA samples are available. If both parents are found to be carriers, the diagnosis of MPS I in the proband is confirmed and carrier testing can be offered to family members. If only one parent has an identifiable *IDUA* disease-causing variant, carrier testing using molecular genetic techniques would be available to the carrier parent's family members.

**Enzyme analysis.** Measurement of α-L-iduronidase enzyme activity in leukocytes is not a reliable method of carrier determination.

## 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, are carriers, or are at risk of being carriers.

**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

In families in which the molecular basis of MPS I is known, prenatal testing should be performed by molecular genetic testing, as enzyme activity measurements (particularly those performed by laboratories with limited experience) have potential inherent difficulties.

**Molecular genetic testing**

- **Both *IDUA* disease-causing variants identified in an affected family member.** Once both *IDUA* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MPS I are possible.
- **Carrier status documented in only one parent.** When one parent is a known heterozygote and the other parent has inconclusive enzymatic activity and no *IDUA* disease-causing variant on molecular genetic testing, or when the mother is a known heterozygote and the father is unknown and/or unavailable for testing, options for prenatal testing can be explored in the context of formal genetic counseling.

**Biochemical genetic testing.** Measurement of α-L-iduronidase enzyme activity in cultured cells obtained by amniocentesis or CVS was formerly used for prenatal diagnosis; however, the presence of IDUA pseudodeficiency as well as a lack of laboratories available to accurately perform this assay has led to the current use of molecular methods [Clarke 2021].

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.*

- **Canadian Society for Mucopolysaccharide and Related Diseases**
  Canada
  **Phone:** 800-667-1846
  **Email:** info@mpssociety.ca
  mpssociety.ca
- **Medical Home Portal**
  Mucopolysaccharidosis Type I (MPS 1)
- **MPS Society**
  United Kingdom
  **Phone:** 0345 389 9901
  **Email:** mps@mpssociety.org.uk
  mpssociety.org.uk
- **National MPS Society**
  **Phone:** 877-MPS-1001
  mpssociety.org

- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **RegistryNXT!**
  **Phone:** 888-404-4413
  **Email:** RegistryNXTHelpDesk@nof1health.com
  www.registrynxt.com

# 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.** Mucopolysaccharidosis Type I: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *IDUA* | 4p16.3 | Alpha-L-iduronidase | IDUA database | IDUA | IDUA |

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 Mucopolysaccharidosis Type I (View All in OMIM)

| | |
|---|---|
| 252800 | ALPHA-L-IDURONIDASE; IDUA |
| 607014 | HURLER SYNDROME |
| 607015 | HURLER-SCHEIE SYNDROME |
| 607016 | SCHEIE SYNDROME |

## Molecular Pathogenesis

*IDUA* encodes alpha-L-iduronidase, a glycosidase that removes nonreducing terminal α-L-iduronide residues during the lysosomal degradation of heparan sulfate and dermatan sulfate, which are glycosaminoglycans in mammalian cells [Neufeld & Muenzer 2001]. The protein sequence is thought to contain six N-glycosylation sites [Zhao et al 1997].

**Mechanism of disease causation.** Loss of function

***IDUA*-specific laboratory technical considerations.** The presence of rare pseudodeficiency alleles renders interpretation of α-L-iduronidase enzyme activity difficult. Pseudodeficiency relates to the finding of reduced or undetectable α-L-iduronidase enzymatic activity with the use of artificial substrates, but no evidence of altered glycosaminoglycan metabolism with the use of radiolabeled (35S) GAG [Aronovich et al 1996]. Pilot studies of newborn screening for MPS I have identified three additional *IDUA* pseudodeficiency variants: p.Ala79Thr, p.His82Gln, and p.Val322Glu [Pollard et al 2013].

It has been observed that *IDUA* contains an overlapping transcript coding for a putative sulfate transporter termed Sat-1 (*SLC26A6*). No pathogenic variants of *SLC26A6* have been reported in humans to date. It is conceivable that pathogenic variants could affect the function of both *IDUA* and *SLC26A6* and thus lead to a complex phenotype.

**Table 8.** Notable *IDUA* Variants

| Reference Sequences | DNA Nucleotide Change (Alias [1]) | Predicted Protein Change | Comment [Reference] [2] |
|---|---|---|---|
| NM_000203.3<br>NP_000194.2 | c.235G>A | p.Ala79Thr | Pseudodeficiency variants |
| | c.246C>G | p.His82Gln | |
| | c.667G>A | p.Asp223Asn | |
| | c.787A>T | p.Arg263Trp | |
| | c.965T>A | p.Val322Glu | |
| | c.1081G>A | p.Ala361Thr | |
| | c.1757C>T | p.Ser586Phe | |
| | c.152G>A | p.Gly51Asp | Common pathogenic variant in Italy |
| | c.208C>T | p.Gln70Ter | Common variant in Europe & Russia; assoc w/ severe MPS I |
| | c.266G>A | p.Arg89Gln | • Common pathogenic variant in Japan; causes attenuated MPS I<br>• May change ability of α-L-iduronidase to affect catalysis<br>• Deleterious effect appears to be potentiated by a polymorphism, p.Ala361Thr [Leroy 2003]. |
| | c.613_617dupTGCTC (704ins5) | p.Glu207AlafsTer29 | Common pathogenic variant in Japan |
| | c.590-7G>A | -- | Variant causes attenuated MPS I; creates alternate splice site, but (as old splice site is not obliterated) some normal enzyme is produced. |
| | c.979G>C | p.Ala327Pro | Common pathogenic variant in Europe |
| | c.1029C>A | p.Tyr343Ter | Variant causes attenuated MPS I; premature stop codon used as an acceptor splice site, generating an in-frame deletion [Lee-Chen & Wang 1997]. |
| | c.1205G>A | p.Trp402Ter | Common pathogenic variant in persons of European ancestry & Australasia |
| | c.1598C>G | p.Pro533Arg | Common pathogenic variant in Italy |
| | c.1960T>G | p.Ter654Gly | Variants cause attenuated MPS I; predict extension of α-L-iduronidase at the carboxyl end that may change conformation &/or stability of enzyme. |
| | c.1960T>C | p.Ter654Arg | |

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.

*1.* Variant designation that does not conform to current naming conventions

*2.* See Table 9 for common pathogenic variants by ethnic background and/or geographic location.

**Table 9.** Common Pathogenic Variants in Persons with Mucopolysaccharidosis Type I by Ethnic Background and/or Geographic Location

| Ethnic Background or Geographic Location | % of Persons w/MPS I in whom the Common Pathogenic Variant Was Identified | | # of Affected Persons or Families Studied | Other Pathogenic Alleles w/ Apparent High Frequencies (%) | Reference |
|---|---|---|---|---|---|
| | p.Gln70Ter | p.Trp402Ter | | | |
| European [1] | 35% | 37% | 46 | | Bunge et al [1994] |
| Italian | 13% | 11% | 27 | p.Pro533Arg (11%)<br>p.Gly51Asp (9.3%)<br>p.Ala327Pro (5.6%) | Gatti et al [1997] |
| North American & European ancestry [1] | 9% | 46% | | | Clarke et al [1994], Bertola et al [2011] |
| Czech & Slovak [2] | 17% | 30% | 19 | | Vazna et al [2009] |
| Russian | 44% | 4% | 25 | | Voskoboeva et al [1998] |
| Britain | 10% | 43% | 291 | | Ghosh et al [2017] |
| Japan | | | 19 | p.Arg89Gln (24%) [3]<br>c.613_617dupTGCTC (18%) [3] | Yamagishi et al [1996] |

*1.* The most common pathogenic alleles in individuals of European background with MPS I are p.Trp402Ter and p.Gln70Ter.
*2.* Includes persons from the Czech Republic and Slovakia
*3.* The p.Arg89Gln and c.613_617dupTGCTC alleles appear to be most frequent in the Japanese population, while the p.Trp402Ter and p.Gln70Ter alleles may be completely absent [Yamagishi et al 1996]; data, however, are limited.

# Chapter Notes

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