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Mucopolysaccharidosis Type I

[*Alpha-L-Iduronidase Deficiency, IDUA Deficiency, MPS I. Includes: Hurler Syndrome (MPS I H), Hurler-Scheie Syndrome (MPS I H/S), Scheie Syndrome (MPS I S)*]

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Summary

Disease characteristics. Mucopolysaccharidosis type I (MPS I) is a progressive multisystem disorder with features ranging over a continuum from mild to severe. Traditionally, affected individuals have been classified as having one of three MPS I syndromes: Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome. As no clear clinical criteria to delineate these biochemically indistinguishable syndromes have been established, affected individuals are best described as having either severe MPS I or attenuated MPS I. Infants with severe MPS I appear normal at birth. Coarsening of the facial features becomes apparent within the first two years. Progressive skeletal dysplasia (dysostosis multiplex) involving all bones occurs in all individuals with severe MPS I. By age three years, linear growth ceases. Hearing loss is common. All develop progressive and profound mental retardation. Death, caused by cardiorespiratory failure, usually occurs within the first ten years of life. The greatest variability is observed in individuals with the attenuated MPS I phenotype. Onset is usually between ages three and ten years. Although pyschomotor development may be normal in early childhood, individuals with attenuated MPS I may have learning disabilities. The rate of disease progression and severity can range from serious life-threatening complications leading to death in the second to third decades to a normal life span with significant disability and discomfort from progressive severe restriction in range of motion of all joints. Hearing loss and cardiac valvular disease are common.

Diagnosis/testing. The diagnosis of MPS I relies on the demonstration of deficient activity of the lysosomal enzyme α-L-iduronidase in peripheral blood leukocytes, cultured fibroblasts, or plasma. Glycosaminoglycan (GAG) (heparan and dermatan sulphate) urinary excretion is a useful preliminary test. *IDUA* is the only gene currently known to be associated with MPS I. Sequence analysis is expected to identify both *IDUA* mutations in most individuals with MPS I.

Management. *Treatment of manifestations:* infant learning programs/special education for developmental delays; hats with visors/sunglasses to reduce glare; cardiac valve replacement as needed; physical therapy, orthopedic surgery as needed (joint replacement, atlanto-occipital stabilization, median nerve decompression for carpal tunnel syndrome); cerebrospinal fluid (CSF) shunting for hydrocephalus; tonsillectomy and adenoidectomy for eustachian tube dysfunction and/or upper airway obstruction; tracheostomy for sleep apnea, pulmonary hypertension, right heart failure; PE tubes; surgical intervention for cervical myelopathy; *Prevention of primary manifestations:* Hematopoietic stem cell transplantation (HSCT) in selected children with severe MPS 1 can increase survival, reduce facial coarseness and hepatosplenomegaly, improve hearing, and maintain normal heart function; HSCT does not

improve skeletal manifestations or corneal clouding; HSCT may slow the course of cognitive decline in those with mild, but not significant, cognitive impairment; HSCT morbidity/mortality is high. Enzyme replacement therapy (ERT) with Aldurazyme®, licensed for treatment of the non-CNS manifestations of MPS I, improved liver size, growth, joint mobility, breathing, and sleep apnea in those with attenuated disease. *Prevention of secondary complications:* bacterial endocarditis prophylaxis for those with cardiac involvement; special attention to anesthetic risks. *Surveillance:* early and continuous monitoring of head growth in infants and children; routine median nerve conduction velocity testing; educational assessment of children with attenuated disease prior to primary school entry; annual assessment by: orthopedic surgeon, neurologist (spinal cord involvement), ophthalmologist, cardiologist (including echocardiogram), audiologist, otolaryngologist. *Testing of relatives at risk:* Sibs of affected individuals should be evaluated either through assay of enzyme activity or *IDUA* molecular genetic testing (if both disease-causing mutations in the family are known) in order to begin 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 disease-causing mutation in the *IDUA* gene has a 25% chance of being affected with MPS I, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes are asymptomatic. When both disease-causing *IDUA* alleles have been identified in the family, carrier testing and prenatal testing diagnosis for at-risk pregnancies should be performed by molecular genetic testing.

Diagnosis

Clinical Diagnosis

The specific findings of mucopolysaccharidosis type I (MPS I) at presentation vary by disease severity. Clinical findings alone are not diagnostic.

MPS I is often suspected in individuals with the following:

- Coarse facial features
- Hepatosplenomegaly
- Characteristic skeletal and joint findings
- Characteristic ocular findings

Testing

For laboratories offering biochemical testing, see Testing.

Glycosaminoglycan (GAG) urinary excretion. Testing for mucopolysaccharidoses by analysis of urinary glycosaminoglycans (heparan and dermatan sulphate) is a useful preliminary test. Measurement of urinary GAGs may be quantitative (measurement of total urinary uronic acid) or qualitative (GAG electrophoresis).

- Neither method can diagnose a specific lysosomal enzyme deficiency, including MPS I; however, an abnormality of either or both indicates the likely presence of an MPS disorder.
- Both methods have somewhat reduced sensitivity, particularly when urine is dilute.
- GAG electrophoresis can exclude and include certain MPS disorders; definitive diagnosis requires specific enzyme determination.

Alpha-L-iduronidase enzyme assay

Affected individuals. The diagnosis of MPS I in an affected individual relies on the demonstration of deficient activity of the lysosomal enzymeα-L-iduronidase, a glycosidase that removes non-reducing terminal α-L-iduronide residues during the lysosomal degradation of the glycosaminoglycans heparan sulphate and dermatan sulphate. Alpha-L-iduronidase enzyme activity can be measured in most tissues; typically, peripheral blood leukocytes, cultured fibroblasts, or plasma are used.

- Almost all individuals with MPS I have no detectable enzyme.
- Although not yet confirmed by rigorous testing, as little as 0.13% of normal α-L-iduronidase protein appears to be sufficient to produce a mild phenotype [Ashton et al 1992].

Carrier testing by enzyme analysis alone can be problematic.

- **Relatives of a proband.** When only one or neither *IDUA* mutation is known, carrier testing of immediate family members of affected individuals requires testing of obligate carriers within the family first in order to determine if their levels of IDUA enzyme activity are clearly distinguishable from normal. If so, the same analysis can be applied to other family members at risk of being carriers.
- **General population**
  - The interpretation of α-L-iduronidase enzyme activity for carrier testing of individuals within the general population is difficult because considerable overlap exists between the lower end of the normal range ofα-L-iduronidase enzyme activity and the upper end of the heterozygous range [Neufeld & Muenzer 2001].
  - The presence of 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. Such studies are complex and not performed in most diagnostic laboratories. The molecular basis and frequency of pseudodeficiency are unknown.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *IDUA* is the only gene currently known to be associated with MPS I.

Clinical testing.

Sequence analysis. In a study involving 85 families with MPS I, a combination of targeted mutation analysis and mutation scanning identified both *IDUA* mutations in 81 (95%) families, one *IDUA* mutation in three (3.5%) families, and none in one (1.1%) family, with an overall mutation detection rate of 97% for mutant alleles [Beesley et al 2001].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in MPS I

Test Method	Mutations Detected	Mutation Detection Frequency [1, 2]	Test Availability
Sequence analysis	Common and private *IDUA* mutations	Unknown, but should be ~100%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by test method
2. Although no published data are available for mutation detection frequency using sequence analysis, Beesley et al (2001) determined that both mutations could be identified in >95% of affected individuals using a combination of targeted mutation analysis for the most common mutations and mutation scanning.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband. When MPS is clinically suspected, a combination of initial clinical evaluation and laboratory testing should enable definitive diagnosis of MPS I and distinction of MPS II, III, VI, and VII.

- **Clinical evaluation**
  - Ophthalmologic examination to evaluate for corneal clouding
  - Skeletal survey to evaluate for dysostosis multiplex
- **Laboratory evaluation**
  - Urinary GAG screening followed by urine GAG electrophoresis to determine the specific species of GAG excreted
  - Assay of α-L-iduronidase enzyme activity in white blood cells, plasma, or fibroblasts

Carrier testing for at-risk relatives

- **Molecular genetic testing.** Carrier testing is best performed using molecular genetic testing if both disease-causing alleles have been identified in an affected family member.
- **Alpha-L-iduronidase enzyme activity.** When only one or neither *IDUA* mutation is known, carrier testing of immediate family members of affected individuals requires testing of obligate carriers within the family first in order to determine if their levels of α-L-iduronidase enzyme activity are clearly distinguishable from normal. If so, the same analysis can be applied to other family members at risk of being carriers.

Prognostication. Alpha-L-iduronidase enzyme activity alone cannot predict the severity of MPS I. If molecular testing of an affected individual identifies two recurrent mutant alleles known to be associated with a particular clinical course, prognostication of severe versus attenuated phenotype may be possible. As many non-recurrent alleles have been identified, the ability to accurately predict phenotype based on results of molecular genetic testing may be difficult, particularly early in the course of disease.

Prenatal diagnosis for at-risk pregnancies should be performed by molecular genetic testing when both mutant *IDUA* alleles have been identified in the family because assay of α-L-iduronidase enzyme activity can be problematic, particularly in laboratories with limited experience.

Preimplantation genetic diagnosis (PGD) for at-risk pregnancies requires prior identification of both *IDUA* disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *IDUA*.

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

Clinical Description

Natural History

Mucopolysaccharidosis type I (MPS I), a progressive multisystem disorder with features ranging over a wide continuum, is considered the prototypic lysosomal storage disease. Traditionally, individuals with α-L-iduronidase deficiency have been classified as having one of three MPS I syndromes: Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome. As no clear clinical criteria have been established to delineate the three syndromes, particularly Hurler-Scheie and Scheie, affected individuals are best described as having either severe MPS I or attenuated MPS I. The greatest variability is observed in individuals exhibiting the attenuated MPS I phenotype. The clinical phenotypes are biochemically indistinguishable [Muenzer 2004].

An accurate determination of the proportion of individuals with the severe or attenuated phenotype has not been published. Conservative estimates suggest that at least 80% of individuals fall within the severe end of the spectrum; however, individuals with attenuated disease make up a larger fraction of the prevalent population because of their increased longevity.

Severe MPS I (Hurler Syndrome)—Individuals with severe MPS I have a chronic and progressive disease course involving multiple organs and tissues [reviewed in Clarke 1997, Neufeld & Muenzer 2001]. 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 nine months; most individuals are diagnosed before age 18 months. Death, caused by cardiorespiratory failure, usually occurs within the first ten years of life.

Craniofacial and physical appearance. Coarsening of the facial features, caused by storage of GAGS in the soft tissues of the orofacial region and underlying 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.

Ophthalmologic. Corneal clouding occurs in all individuals with MPS I. Progression can lead to severe visual impairment. Open-angle glaucoma may occur [Clarke 1997, Neufeld & Muenzer 2001]. 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.

Cardiovascular. Cardiac involvement is seen in all individuals with 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, 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 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.

Skeletal. Progressive skeletal dysplasia (dysostosis multiplex) involving all bones is seen in all individuals with severe MPS I. Severely affected children have severe early bone involvement. Mild dysostosis, particularly within the hip, as well as thickening of the ribs, can be detected on radiographs at birth [Clarke 1997, Neufeld & Muenzer 2001]. Gibbus deformity (dorsolumbar kyphosis) often becomes clinically apparent within the first 14 months.

By age three years linear growth ceases. 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. Typically, the pelvis is poorly formed. The femoral heads are small and coxa valga is common. Involvement of the femoral head leads to progressive and debilitating hip deformity. Progressive arthropathy leading to severe joint deformity is universal. 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 [Clarke 1997, Neufeld & Muenzer 2001]. Carpal tunnel syndrome is often missed because its onset is insidious and it often presents with few symptoms or signs other than thenar atrophy.

Auditory system. Hearing loss is common in severe MPS I and is correlated to the severity of somatic disease. The most important contributing factors include frequent middle ear infection from Eustachian tube dysfunction caused by storage of GAGs within the oro-pharynx, dysostosis of the ossicles of the middle ear, scarring of the tympanic membrane, and damage to the eighth nerve [Clarke 1997, Neufeld & Muenzer 2001].

ENT (otolaryngologic). Chronic recurrent rhinitis and persistent copious nasal discharge without obvious infection are common. Storage of GAGs within the oro-pharynx with associated enlargement of the tonsils and adenoids can contribute to upper airway complications [Clarke 1997, Neufeld & Muenzer 2001], 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 is a main component of obstructive sleep apnea, a common complication particularly in the later stages of disease. CNS involvement can also contribute to sleep apnea.

Individuals may have a deep, gravelly voice.

Intellect. In contrast to individuals with attenuated disease, those with severe MPS I suffer from progressive and profound mental retardation. Although early development may be normal, delay in development is usually suspected by age 12 months [Clarke 1997]. Thereafter, progressive deterioration ensues and developmental delay is usually obvious by age 18 months. Subsequently, most individuals do not progress developmentally but plateau for a number of years, then slowly decline in intellectual capabilities. By the time of death at age eight to ten years, most individuals are severely mentally retarded.

Children with severe MPS I develop only limited language skills, likely related to the triad of developmental delay, chronic hearing loss, and enlarged tongue [Neufeld & Muenzer 2001].

In contrast to MPS II and MPS III, the severe developmental effects in individuals with MPS I are associated with placid rather than aggressive behavior. Seizures appear to be uncommon even at the end stages of disease [Clarke 1997].

Heparan sulphate is found in abundance in the brain as part of the extracellular matrix. Deficiency of α-L-iduronidase in individuals with MPS I results in glycosaminoglycan accumulation in the lysosomes of neurons, leading to secondary accumulation of glycolipids that form zebra bodies. The glycosaminoglycan storage and secondary glycolipid storage presumably lead to severe mental retardation and hydrocephalus.

Hydrocephaly. Communicating high-pressure hydrocephalus is common in individuals with severe MPS I. Impaired resorption of CSF causes an increase in intracranial pressure, leading to brain compression. Rapid 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 individuals with severe MPS I is unknown.

Gastrointestional system. Protuberance of the abdomen caused by progressive hepatosplenomegaly is common [Clarke 1997]. Although organ size may be massive, storage of glycosaminoglycans in the liver and spleen does not lead to organ dysfunction.

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 problems [Clarke & MacFarland 2001]. Wegrzyn et al (2005) suggested that atypical gastrointestinal microbial infections may underlie gastrointestinal disturbance in the MPSs. The prevalence of such infections is unknown.

Attenuated MPS I (Hurler-Scheie Syndromel Scheie Syndrome)—If development is normal at age 24 months and if moderate somatic involvement is evident, an individual should be classified as having attenuated MPS I. Onset of disease in individuals with attenuated MPS I is variable, usually occurring between ages three and ten years. The rate of disease progression can range from serious life-threatening disease complications leading to death in the second to third decades to a normal life span with significant disease morbidity.

Although development may be normal in early childhood, individuals with attenuated MPS I may have detectable learning disabilities. No correlation between the degree of somatic disease and intellectual deficits in attenuated MPS I has been observed [Vijay & Wraith 2005].

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

Individuals with attenuated MPS I have variable degrees of growth retardation.

Ophthalmologic. Corneal clouding is exhibited by all individuals with MPS I and can lead to significant visual disability. Glaucoma, retinal degeneration, and optic atrophy can occur.

Cardiovascular. 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 individuals exhibiting attenuated MPS I than in those with severe MPS I [Neufeld & Muenzer 2001]; however, in some individuals, all valves are affected.

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

Skeletal. Skeletal and joint manifestations represent the most significant source of disability and discomfort for individuals with attenuated disease [Clarke 1997, Vijay & Wraith 2005]. Attended individuals may have severe bone involvement with no cognitive impairment.

Kyphosis, scoliosis, and severe back pain are common in individuals with mild MPS I. Spondylolisthesis of the lower spine leading to spinal cord compression can occur in individuals with intermediate disease.

Progressive arthropathy affecting all joints and eventually leading to loss of or severe restriction in range of motion is universal. Poor hand function as a result of the characteristic claw hand deformity, carpal tunnel syndrome, and interphalangeal joint stiffness is often observed. Most individuals do not have the classic early symptoms of carpal tunnel syndrome and thus nerve conduction studies should be used to identify persons early in the course of disease at a time when surgical release may be most beneficial (see Management).

Gastrointestinal system. A variable degree of hepatomegaly is seen in individuals with mild attenuated MPS I.

Hernias occur in individuals with attenuated disease perhaps less frequently than in those with severe disease. However, many have umbilical hernia during infancy, which often requires repeated surgical correction.

Auditory system. Moderate to severe hearing loss develops in many individuals with attenuated MPS I, particularly in 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.

Respiratory system. Rhinorrhea is common.

Sleep apnea as a result of obstructive airway disease and possibly CNS involvement occurs in attenuated MPS I.

Progressive pulmonary disease may manifest as abnormalities of forced vital capacity.

Central nervous system (CNS). In attenuated MPS I intellect may be normal or nearly normal. If intellectual abilities decline, the course is more protracted than in individuals with severe disease.

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

Arachnoid cysts may develop. The predictive power of changes noted on MRI does not seem to be significant in individuals with attenuated MPS I [Neufeld & Muenzer 2001, Matheus et al 2004].

Cervical myelopathy. 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 [Neufeld & Muenzer 2001].

Genotype-Phenotype Correlations

Enzyme assay alone is unable to predict the severity of MPS I.

Up to 70% of mutations are recurrent and thus may be helpful in phenotype prediction; however, because many non-recurrent alleles have been identified, the ability to accurately predict phenotype based on genotype may be limited.

Genotype-phenotype correlations in individuals with MPS I are complex and further research is required before they can be useful clinically. A 2003 comprehensive review of genotype-phenotype correlations illustrates the limitations related to the frequency of private mutations at this locus [Terlato & Cox 2003]. Rempel et al (2005) proposed a crystal structure of human α-L-iduronidase protein and suggested that mapping mutations onto this proposed crystal structure may be helpful in predicting possible effects of missense mutations onα-L-iduronidase processing and function.

In general, any combination of two severe alleles leads to severe MPS I.

Note: A severe allele is one that produces the severe phenotype either in the homozygous state or compound heterozygous state with a previously characterized severe allele.

Attenuated MPS I is usually associated with one severe allele and another allele that permits production of some residual enzyme activity. Other combinations are possible.

Earlier predictions [McKusick et al 1972] suggested that a series of mutations, present in the homozygous state, would confer either a severe (Hurler syndrome) or a mild (Scheie syndrome) phenotype, whereas compound state would confer an intermediate phenotype. This has proven to be highly unlikely.

- For example, two common severe mutations (p.Trp402X and p.Gln70X) always confer a severe phenotype whether present in a homozygous state or in a compound heterozygous state. Additional mutations (474-2A>G, p.Ala327Pro, p.Pro533Arg, p.Ala75Thr, and p.Leu218Pro), accounting for a smaller number of alleles, are also associated with severe disease.
- Two alleles (678-7A>G and p.Arg89Gln) confer a phenotype representative of the most attenuated disease; together they account for only 31% of the mutations associated with attenuated disease and often occur in combination with a severe allele.

Most individuals in whom the disease phenotype fits between the two extremes of attenuated and severe MPS I have one well-recognized severe allele compound with a private missense mutation.

Penetrance

Disease penetrance is complete.

Nomenclature

The use of a binary classification of severe and attenuated disease is now generally accepted and more accurately reflects the molecular and biochemical basis of the disease than previous naming systems, which referred to the attenuated form as intermediate and mild.

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].

The frequencies of specific mutations vary by population.

- The frequency of the p.Trp402X allele is estimated at 11% in Italy and 55% in Australasia.
- The frequency of the p.Gln70X allele is 7% in Britain and 65% in Scandinavia.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Lysosomal storage disease. Findings in individuals with mucopolysaccharidosis type I (MPS I) overlap those of other lysosomal diseases, particularly other mucopolysaccharide diseases including multiple sulfatase deficiency. Clinical findings and biochemical testing distinguish them.

Note that deficient α-L-iduronidase enzyme activity may be observed in I-cell disease (mucolipidosis II) and pseudo-Hurler polydystrophy (mucolipidosis III). 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 et al 2006]. Careful clinical evaluation for other manifestations of MPS I, as well as the pattern of joint involvement, should enable identification of individuals with attenuated MPS I presenting with noninflammatory arthritis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with mucopolysaccharidosis type I (MPS I), the following evaluations are recommended:

- Developmental assessment
- Ophthalmologic examination with measurement of visual acuity and intraocular pressure, slit lamp examination of the cornea, and assessment of retinal function by electroretinography and visual field testing
- Cardiac evaluation with echocardiography to assess ventricular size and function
- Skeletal survey to determine the involvement of the spine and degree and extent of joint involvement
- Cranial imaging, preferentially MRI, including assessment of possible hydrocephalus
- Assessment of spinal cord and peripheral nerve involvement
- Consideration of sleep study
- ENT assessment and consideration of venting tubes for recurrent infections

Treatment of Manifestations

Supportive or symptomatic management can improve the quality of life for affected individuals and their families. Follow-up of affected individuals to anticipate possible complications and to provide early intervention maximizes outcome.

Infants with severe MPS I require a stimulating environment to promote early learning, as some skills may be retained during the period of general deterioration.

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].

Cardiac valve replacement should be considered early.

Physical therapy and its benefits in individuals with MPS I deserve further research [Neufeld & Muenzer 2001]. 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; physical therapy may minimize further limitation.

Various orthopedic approaches can be undertaken, particularly in individuals with attenuated disease. Joint replacement is appropriate. 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.

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

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.

Tonsillectomy and adenoidectomy correct eustachian tube dysfunction and decrease upper airway obstruction. Early placement of grommets and ventilating tubes is recommended in severely affected individuals.

Carpal tunnel syndrome should be treated especially in individuals with attenuated MPS I and individuals with severe MPS I who have had hematopoietic stem cell transplantation (HSCT). Most individuals lack typical symptoms (pain, tingling, or numbness) until severe compression occurs [Haddad et al 1997, van Heest et al 1998]. 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 [Neufeld & Muenzer 2001].

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.

Inguinal hernias should be repaired surgically with the expectation that they may recur. Umbilical hernias are generally not treated unless they are exceedingly large and cause problems.

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.

Prevention of Primary Manifestations

Hematopoietic stem cell transplantation (HSCT). The beneficial effect of HSCT is thought to result from the replacement of deficient macrophages by marrow-derived donor macrophages (Kupffer cells; pulmonary, splenic, nodal, tonsilar, and peritoneal macrophages; and microglial cells) that constitute an ongoing source of normal enzyme capable of gaining access to the various sites of storage [Guffon et al 1998].

Although HSCT may modify disease progression and improve survival in some children, it is not curative. HSCT should be used only in carefully selected children with extensive pretransplantation clinical assessment and counseling in whom systematic long-term monitoring of the results will be possible [Neufeld & Muenzer 2001].

In general, the clinical outcome of children undergoing HSCT is varied and depends on the degree of clinical involvement and the age of the child at the time of transplantation. Adults have not undergone HSCT. Failure to achieve stable engraftment and graft-versus-host disease represent significant barriers to successful HSCT for many children [Peters et al 1996; Peters, Shapiro, Anderson et al 1998; Peters, Shapiro, Krivit 1998]; thus, the procedure carries a high risk of morbidity and mortality [Neufeld & Muenzer 2001]. Pulmonary and cardiac complications post-HSCT appear to be significant [Gassas et al 2003].

The use of enzyme replacement therapy (ERT) in the peri-HSCT period should be considered. In 26 patients [Cox-Brinkman et al 2006], ERT used during this time period neither increased nor decreased the frequency of engraftment or survival. Whether ERT begun prior to transplantation and continued in the peri-transplantation period reduces the frequency of these complications is yet to be systematically reviewed. It is reasonable to suggest that the use of ERT prior to HSCT may alleviate disease manifestations, thus reducing complications during HSCT.

HSCT has been successful in reducing the progression of some findings in children with severe MPS I [Vellodi et al 1997, Guffon et al 1998, reviewed in Neufeld & Muenzer 2001, Souillet et al 2003, Staba et al 2004]. Although the heterogeniety of the disease makes interpretation of the outcomes of HSCT somewhat difficult, available data show that successful HSCT increases survival, reduces facial coarseness, as well as hepatosplenomegaly, improves hearing, and maintains normal heart function. In a series of individuals predicted to have severe MPS I based on the presence of known severe mutations, use of HSCT resulted in stabilization and improvement of cardiac function with regression of hypertrophy and normalization of chamber dimensions. In that cohort, HSCT did not appear to show significant effects on the presence and progression of valvular involvement [Braunlin et al 2003].

In contrast, the skeletal manifestations and corneal clouding continued to progress at the same rate in children treated with HSCT as in untreated individuals [Weisstein et al 2004].

Neuropsychological responses to HSCT vary and are related to the age and intellectual capacity of the child at the time of the engraftment. In children undergoing HSCT before evidence of significant developmental delay (i.e., usually between ages 12 and 18 months), HSCT appears to slow the course of cognitive decline. Children showing significant cognitive impairment prior to undergoing HSCT do not appear to benefit developmentally.

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 (reviewed in Neufeld & Muenzer 2001). As a result, various orthopedic procedures intended to maintain function and gait have been performed post-HSCT [Masterson et al 1996, Tandon et al 1996].

Enzyme replacement therapy (ERT). Aldurazyme® is currently licensed in the US, Europe, and Canada for use in treating non-CNS manifestations of MPS I. The current dose regime involves premedication with an anti-inflammatory and antihistamine drugs and intravenous weekly infusion of 100 U/kg of Aldurazyme® over four hours.

The potential effect of Aldurazyme® on the progression of disease symptoms and, more importantly, the effect that Aldurazyme® may have when started very early in the treatment of an individual with attenuated disease remain to be answered. The latter is particularly important as early diagnosis is critical. Aldurazyme® does not cross the blood-brain barrier and thus is not expected to influence the CNS disease in severely affected individuals.

Biochemical characterization of MPS I revealed that mildly affected individuals appear to have as little as 0.13% of normal enzyme activity when tested with complex substrates, leading Ashton et al (1992) to suggest that ERT would be effective if as little as 3% of normal enzyme activity could be achieved. The effectiveness of ERT depends on the ability of recombinant enzymes (supplied intravenously) to enter cells and to localize to the lysosome, the appropriate intracellular site [Russell & Clarke 1999].

The phase I open label study included ten individuals with attenuated MPS I treated with human α-L-iduronidase and studied over one year. This study showed improvement in liver size, growth, joint mobility, breathing, and sleep apnea. Increased ability to perform daily functions was reported [Kakkis et al 2001]. A six-year follow-up of five of the treated individuals showed sustained improvements in joint range of motion and sleep apnea and no progression of heart disease, but evidence of progression of valvular involvement [Sifuentes et al 2007].

The phase III double-blind placebo-controlled study included 45 individuals with attenuated MPS I treated for 52 weeks with a 26-week placebo phase [Wraith et al 2005]. This study showed statistically significant improvements in pulmonary function and a six-minute walk test and clear biologic effect with reduction in urinary GAG excretion and liver volume. Patients who had significant sleep apnea at the start of the study improved significantly.

Other case reports representing smaller numbers of treated patients show variable responsiveness to treatment. The heterogeneity of treated patients published to date complicates any conclusions that can be drawn. It appears that the ability of ERT to reverse disease symptoms in individuals with attenuated disease relates closely to the burden of disease prior to commencement of treatment.

All published reports indicate that ERT is well tolerated. Although most individuals treated in either clinical trial developed IgG antibodies, no apparent clinical effects have been reported. Follow-up of individuals who were part of the phase I and phase III studies indicates that immune tolerance is eventually reached [Kakavanos et al 2003, Wraith et al 2005].

Further investigation is needed to determine the effects of ERT on individuals with more severe disease and the outcome of ERT initiated at earlier stages of disease.

Prevention of Secondary Complications

Bacterial endocarditis prophylaxis is advised for individuals with cardiac abnormalities [Neufeld & Muenzer 2001].

Individuals with MPS I present major anesthetic risks [Moores et al 1996], including death. It is appropriate for affected individuals to undergo general anesthesia in centers staffed with

anesthesiologists with experience managing individuals with a mucopolysaccharidosis [Neufeld & Muenzer 2001]. The following are 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 fiber-optic laryngoscopy.
- Recovery from anesthesia may be slow and postoperative airway obstruction is a common problem.

Surveillance

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.

- Early and continuous monitoring of head growth by measuring occipito-frontal circumference (OFC) in infants and children
  - Cranial ultrasound examination and other brain imaging studies are recommended if a rapid increase in OFC occurs.
  - MRI can show ventriculomegaly, but imaging studies often cannot reliably distinguish between brain atrophy and brain compression.
  - Lumbar puncture with measurement of opening pressure of CSF is a preferred method for assessing the degree of pressure elevation [Neufeld & Muenzer 2001].
- Aggressive orthopedic management for all patients regardless of treatment choices and disease severity; yearly or more frequent assessment by an experienced orthopedic surgeon is recommended.
- Annual assessment of spinal cord involvement by neurologic examination with consideration of spinal MRI studies when indicated
- Annual ophthalmologic assessment with assessment of corneal status and retinal function
- Cardiac assessment including annual echocardiogram
- Annual assessment by an audiologist as well as by an otolaryngologist to determine the degree and cause of hearing impairment
- Routine median nerve conduction velocity testing because of the high incidence of carpal tunnel syndrome [van Heest et al 1998]
- Developmental assessment in all patients; consideration of psycho-educational assessment of children with attenuated disease prior to primary school entry

Testing of Relatives at Risk

Sibs of affected individuals should be identified either through assay of enzyme activity or molecular genetic testing of *IDUA* if both disease-causing mutations in the family are known in order to initiate therapy as early in the course of disease as possible.

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

Therapies Under Investigation

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

Combined ERT and HSCT. Whether long-term combined ERT and HSCT may improve the outcome of a severely affected individual is of interest.

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 now underway in patients who have evidence of spinal cord involvement.

Stabilization of mutant 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 point mutations underlying lysosome enzyme deficiencies lead to disease by virtue of the fact that the point mutation alters the folding of the protein after translation. The resultant misfolded protein is unable to be transported to the lysosome. Small molecule substrate analogs have been shown to stabilize mutant lysosomal proteins in tissue culture and thus enable transport of these enzymes to the lysosome. Once in the lysosome, these mutant enzymes are likely able to metabolize enough substrate to alter the disease course. As most individuals with intermediate MPS I have at least one *IDUA* allele containing a missense mutation, the development of substrate analogs for *IDUA* 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].

Gene-/cell-based therapy. Advances in both gene- and stem cell-based therapies for genetic diseases could potentially influence treatment of MPS I [Punnett et al 2004, Di Domenico et al 2005].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Each parent of an affected child is an obligate heterozygote and therefore carries a single copy of a disease-causing mutation in the *IDUA* gene.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual 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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with MPS I are obligate heterozygotes (carriers) for a disease-causing mutation in the *IDUA* gene. Individuals with severe disease do not reproduce.

Other family members. Each sib of an obligate heterozygote is at a 50% risk of being a carrier.

Carrier Detection

Measurement of α-L-iduronidase enzyme activity in leukocytes is not a reliable method of carrier determination (see Carrier testing).

Molecular genetic testing of *IDUA* is clinically available and can be used to identify carriers among at-risk family members when both mutations have been identified in an affected family member.

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* mutation, carrier testing using molecular genetic techniques would be available to that parent's family members.

Molecular genetic testing is also available on a clinical basis for carrier testing in the unrelated reproductive partners of individuals known to have an *IDUA* mutation. Normal molecular genetic test results in an individual at a general population risk can reduce but not eliminate the probability of his/her being a carrier.

Related Genetic Counseling Issues

See Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being carriers.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

In cases in which the molecular basis of MPS I is known, prenatal diagnosis 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. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles in the family must be identified before prenatal testing can be performed.

Biochemical genetic testing. Prenatal testing is available for pregnancies at increased risk for MPS I by measuring α-L-iduronidase enzyme activity in cultured cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or CVS at about ten to 12 weeks' gestation.

(1) Difficulty with prenatal diagnosis for MPS I may result from the low α-L-iduronidase enzyme activity in normal chorionic villi [Young 1992]; however, difficulties in interpreting borderline low α-L-iduronidase enzyme activity can be overcome by assaying enzyme activity in cultured rather than uncultured CVS cells [Neufeld & Muenzer 2001], provided analysis for possible maternal contamination is performed. (2) Measurement of glycosaminoglycans or α-L-iduronidase enzyme activity in amniotic fluid is complicated by the high glycosaminoglycan excretion of the fetuses and is thus not useful for prenatal testing. (3) Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Carrier status documented in only one parent. When one parent is a known heterozygote and the other parent has inconclusive enzymatic activity and no disease-causing *IDUA* mutation has been identified by DNA analysis, 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.

Preimplantation genetic diagnosis (PGD) by polar body analysis for MPS I has been reported [Tomi et al 2006] and may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Mucopolysaccharidosis Type I

Gene Symbol	Chromosomal Locus	Protein Name
IDUA	4p16.3	Alpha-L-iduronidase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Mucopolysaccharidosis Type I

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

Table C. Genomic Databases for Mucopolysaccharidosis Type I

Gene Symbol	Entrez Gene	HGMD
IDUA	3425 (MIM No. 252800)	IDUA

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *IDUA* gene is approximately 19 kb with 14 exons; the cDNA open reading frame (ORF) is about 2 kb [Scott et al 1995]. An Alu repetitive sequence and a highly polymorphic VNTR have both been reported in intron 2 [Scott et al 1991, Scott et al 1992].

Pathologic allelic variants: The Human Gene Mutation database currently lists 108 mutations in the *IDUA* gene. Known mutations include nonsense exonic, missense, splice site, deletion, and insertion mutations. It is expected that more mutations that are null and lead to severe disease will be discovered; mutations causing attenuated (i.e., mild or intermediate) MPS I are expected to be limited [Neufeld & Muenzer 2001].

Normal gene product: Alpha-L-iduronidase is a glycosidase that removes non-reducing terminal α-L-iduronide residues during the lysosomal degradation of heparan sulphate and dermatan sulphate, which are glycosaminoglycans in mammalian cells [Neufeld & Muenzer 2001]. The enzyme cDNA represents an ORF that encodes a peptide of 653 amino acids. The protein sequence is thought to contain six N-glycosylation sites [Zhao et al 1997].

Abnormal gene product: Most of the alleles leading to attenuated MPS I are missense mutations. Exceptions are p.Tyr343Lys, a premature stop codon that is used as an acceptor splice site, thereby generating an in-frame deletion [Lee-Chen & Wang 1997] and p.X654Gly, which predicts an extension of α-L-iduronidase at its carboxyl end that may effect a change in the enyzme's conformation and/or stability. A base substitution in p.Arg89Gln may change the ability of α-L-iduronidase to effect catalysis; its deleterious effect appears to be potentiated by a polymorphism, p.Ala361Thr. An interesting mutation that results in mild MPS I is a base substitution in intron 5 (678-7A>G) that creates a new splice site and produces a frameshift; however, because the old splice site is not obliterated, some of the normal enzyme is produced.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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National Mucopolysaccharidoses/Mucolipidoses Society (MPS), Inc
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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Ashton LJ, Brooks DA, McCourt PA, Muller VJ, Clements PR, Hopwood JJ. Immunoquantification and enzyme kinetics of alpha-L-iduronidase in cultured fibroblasts from normal controls and mucopolysaccharidosis type I patients. Am J Hum Genet. 1992;50:787–94. [PubMed: 1550122]

Beesley CE, Meaney CA, Greenland G, Adams V, Vellodi A, Young EP, Winchester BG. Mutational analysis of 85 mucopolysaccharidosis type I families: frequency of known mutations, identification of 17 novel mutations and in vitro expression of missense mutations. Hum Genet. 2001;109:503–11. [PubMed: 11735025]

Braunlin EA, Stauffer NR, Peters CH, Bass JL, Berry JM, Hopwood JJ, Krivit W. Usefulness of bone marrow transplantation in the Hurler syndrome. Am J Cardiol. 2003;92:882–6. [PubMed: 14516901]

Cimaz R, Vijay S, Haase C, Coppa GV, Bruni S, Wraith E, Guffon N. Attenuated type I mucopolysaccharidosis in the differential diagnosis of juvenile idiopathic arthritis: a series of 13 patients with Scheie syndrome. Clin Exp Rheumatol. 2006;24:196–202. [PubMed: 16762159]

Clarke LA. Clinical diagnosis of lysosomal storage diseases. In: Applegarth DA, Dimmick JE, Hall JG (eds) Organelle Diseases. Clinical Features, Diagnosis, Pathogenesis and Management. Chapman and Hall Medical, London, p 37. 1997

Clarke LA, MacFarland J. Mucopolysaccharidosis-I (MPS-I). Clarke LA, Kaweski C, Di Ilio L, Hahn S (eds) The Canadian Society for Mucopolysaccharide and Related Diseases, Inc. Ticky Graphics and Printing, Vancouver. 2001

Cox TM, Aerts JM, Andria G, Beck M, Belmatoug N, Bembi B, Chertkoff R, Vom Dahl S, Elstein D, Erikson A, Giralt M, Heitner R, Hollak C, Hrebicek M, Lewis S, Mehta A, Pastores GM, Rolfs A, Miranda MC, Zimran A. The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease: a position statement. J Inherit Metab Dis. 2003;26:513–26. [PubMed: 14605497]

Cox-Brinkman J, Boelens JJ, Wraith JE, O'meara A, Veys P, Wijburg FA, Wulffraat N, Wynn RF. Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. Bone Marrow Transplant. 2006;38:17–21. [PubMed: 16715104]

Di Domenico C, Villani GR, Di Napoli D, Reyero EG, Lombardo A, Naldini L, Di Natale P. Gene therapy for a mucopolysaccharidosis type I murine model with lentiviral-IDUA vector. Hum Gene Ther. 2005;16:81–90. [PubMed: 15703491]

Gassas A, Sung L, Doyle JJ, Clarke JT, Saunders EF. Life-threatening pulmonary hemorrhages post bone marrow transplantation in Hurler syndrome. Report of three cases and review of the literature. Bone Marrow Transplant. 2003;32:213–5. [PubMed: 12838287]

Guffon N, Souillet G, Maire I, Straczek J, Guibaud P. Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. J Pediatr. 1998;133:119–25. [PubMed: 9672523]

Haddad FS, Jones DH, Vellodi A, Kane N, Pitt MC. Carpal tunnel syndrome in the mucopolysaccharidoses and mucolipidoses. J Bone Joint Surg Br. 1997;79:576–82. [PubMed: 9250742]

Kakavanos R, Turner CT, Hopwood JJ, Kakkis ED, Brooks DA. Immune tolerance after long-term enzyme-replacement therapy among patients who have mucopolysaccharidosis I. Lancet. 2003;361:1608–13. [PubMed: 12747881]

Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M, Izykowski B, Phillips J, Doroshow R, Walot I, Hoft R, Neufeld EF. Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl J Med. 2001;344:182–8. [PubMed: 11172140]

Lee-Chen GJ, Wang TR. Mucopolysaccharidosis type I: identification of novel mutations that cause Hurler/Scheie syndrome in Chinese families. J Med Genet. 1997;34:939–41. [PubMed: 9391892]

Lowry RB, Applegarth DA, Toone JR, MacDonald E, Thunem NY. An update on the frequency of mucopolysaccharide syndromes in British Columbia. Hum Genet. 1990;85:389–90. [PubMed: 2118475]

Masterson EL, Murphy PG, O'Meara A, Moore DP, Dowling FE, Fogarty EE. Hip dysplasia in Hurler's syndrome: orthopaedic management after bone marrow transplantation. J Pediatr Orthop. 1996;16:731–3. [PubMed: 8906643]

Matheus MG, Castillo M, Smith JK, Armao D, Towle D, Muenzer J. Brain MRI findings in patients with mucopolysaccharidosis types I and II and mild clinical presentation. Neuroradiology. 2004;46:666–72. [PubMed: 15205860]

McKusick VA, Howell RR, Hussels IE, Neufeld EF, Stevenson RE. Allelism, non-allelism, and genetic compounds among the mucopolysaccharidoses. Lancet. 1972;1:993–6. [PubMed: 4112371]

Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999;281:249–54. [PubMed: 9918480]

Moores C, Rogers JG, McKenzie IM, Brown TC. Anaesthesia for children with mucopolysaccharidoses. Anaesth Intensive Care. 1996;24:459–63. [PubMed: 8862643]

Muenzer J. The mucopolysaccharidoses: a heterogeneous group of disorders with variable pediatric presentations. J Pediatr. 2004;144:S27–34. [PubMed: 15126981]

Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B (eds) The Metabolic and Molecular Basis of Inherited Disease, 8 ed, Vol III. McGraw-Hill, Medical Publishing Division, p 3421. 2001

Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD, Henslee-Downey J, Trigg ME, Cowan MJ, Sanders J, Bunin N, Weinstein H, Lenarsky C, Falk P, Harris R, Bowen T, Williams TE, Grayson GH, Warkentin P, Sender L, Cool VA, Crittenden M, Packman S, Kaplan P, Lockman LA, et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. Blood. 1996;87:4894–902. [PubMed: 8639864]

Peters C, Shapiro EG, Anderson J, Henslee-Downey PJ, Klemperer MR, Cowan MJ, Saunders EF, deAlarcon PA, Twist C, Nachman JB, Hale GA, Harris RE, Rozans MK, Kurtzberg J, Grayson GH, Williams TE, Lenarsky C, Wagner JE, Krivit W. Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty- four children. The Storage Disease Collaborative Study Group. Blood. 1998;91:2601–8. [PubMed: 9516162]

Peters C, Shapiro EG, Krivit W. Hurler syndrome: past, present, and future. J Pediatr. 1998;133:7–9. [PubMed: 9672503]

Piotrowska E, Jakobkiewicz-Banecka J, Baranska S, Tylki-Szymanska A, Czartoryska B, Wegrzyn A, Wegrzyn G. Genistein-mediated inhibition of glycosaminoglycan synthesis as a basis for gene expression-targeted isoflavone therapy for mucopolysaccharidoses. Eur J Hum Genet. 2006;14:846–52. [PubMed: 16670689]

Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, Niezen-Koning KE, van Diggelen OP. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet. 1999;105:151–6. [PubMed: 10480370]

Punnett A, Bliss B, Dupuis LL, Abdolell M, Doyle J, Sung L. Ototoxicity following pediatric hematopoietic stem cell transplantation: a prospective cohort study. Pediatr Blood Cancer. 2004;42:598–603. [PubMed: 15127414]

Rempel BP, Clarke LA, Withers SG. A homology model for human alpha-l-iduronidase: insights into human disease. Mol Genet Metab. 2005;85:28–37. [PubMed: 15862278]

Russell CS, Clarke LA. Recombinant proteins for genetic disease. Clin Genet. 1999;55:389–94. [PubMed: 10450855]

Scott HS, Anson DS, Orsborn AM, Nelson PV, Clements PR, Morris CP, Hopwood JJ. Human alpha-L-iduronidase: cDNA isolation and expression. Proc Natl Acad Sci U S A. 1991;88:9695–9. [PubMed: 1946389]

Scott HS, Bunge S, Gal A, Clarke LA, Morris CP, Hopwood JJ. Molecular genetics of mucopolysaccharidosis type I: diagnostic, clinical, and biological implications. Hum Mutat. 1995;6:288–302. [PubMed: 8680403]

Scott HS, Guo XH, Hopwood JJ, Morris CP. Structure and sequence of the human alpha-L-iduronidase gene. Genomics. 1992;13:1311–3. [PubMed: 1505961]

Sifuentes M, Doroshow R, Hoft R, Mason G, Walot I, Diament M, Okazaki S, Huff K, Cox GF, Swiedler SJ, Kakkis ED. A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. Mol Genet Metab. 2007;90:171–80. [PubMed: 17011223]

Souillet G, Guffon N, Maire I, Pujol M, Taylor P, Sevin F, Bleyzac N, Mulier C, Durin A, Kebaili K, Galambrun C, Bertrand Y, Froissart R, Dorche C, Gebuhrer L, Garin C, Berard J, Guibaud P.

Outcome of 27 patients with Hurler's syndrome transplanted from either related or unrelated haematopoietic stem cell sources. Bone Marrow Transplant. 2003;31:1105–17. [PubMed: 12796790]

Staba SL, Escolar ML, Poe M, Kim Y, Martin PL, Szabolcs P, Allison-Thacker J, Wood S, Wenger DA, Rubinstein P, Hopwood JJ, Krivit W, Kurtzberg J. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. N Engl J Med. 2004;350:1960–9. [PubMed: 15128896]

Tandon V, Williamson JB, Cowie RA, Wraith JE. Spinal problems in mucopolysaccharidosis I (Hurler syndrome). J Bone Joint Surg Br. 1996;78:938–44. [PubMed: 8951011]

Terlato NJ, Cox GF. Can mucopolysaccharidosis type I disease severity be predicted based on a patient's genotype? A comprehensive review of the literature. Genet Med. 2003;5:286–94. [PubMed: 12865757]

Tomi D, Schultze-Mosgau A, Eckhold J, Schopper B, Al-Hasani S, Steglich C, Gal A, Axt-Fliedner R, Schwinger E, Diedrich K, Griesinger G. First pregnancy and life after preimplantation genetic diagnosis by polar body analysis for mucopolysaccharidosis type I. Reprod Biomed Online. 2006;12:215–20. [PubMed: 16478590]

Van Heest AE, House J, Krivit W, Walker K. Surgical treatment of carpal tunnel syndrome and trigger digits in children with mucopolysaccharide storage disorders. J Hand Surg [Am]. 1998;23:236–43. [PubMed: 9556262]

Vellodi A, Young EP, Cooper A, Wraith JE, Winchester B, Meaney C, Ramaswami U, Will A. Bone marrow transplantation for mucopolysaccharidosis type I: experience of two British centres. Arch Dis Child. 1997;76:92–9. [PubMed: 9068295]

Vijay S, Wraith JE. Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I. Acta Paediatr. 2005;94:872–7. [PubMed: 16188808]

Wegrzyn G, Kurlenda J, Liberek A, Tylki-Szymanska A, Czartoryska B, Piotrowska E, Jakobkiewicz-Banecka J, Wegrzyn A. Atypical microbial infections of digestive tract may contribute to diarrhea in mucopolysaccharidosis patients: a MPS I case study. BMC Pediatr. 2005;5:9. [PubMed: 15882450]

Weisstein JS, Delgado E, Steinbach LS, Hart K, Packman S. Musculoskeletal manifestations of Hurler syndrome: long-term follow-up after bone marrow transplantation. J Pediatr Orthop. 2004;24:97–101. [PubMed: 14676543]

Wraith EJ, Hopwood JJ, Fuller M, Meikle PJ, Brooks DA. Laronidase treatment of mucopolysaccharidosis I. BioDrugs. 2005;19:1–7. [PubMed: 15691212]

Young EP. Prenatal diagnosis of Hurler disease by analysis of alpha-iduronidase in chorionic villi. J Inherit Metab Dis. 1992;15:224–30. [PubMed: 1527990]

Zhao KW, Faull KF, Kakkis ED, Neufeld EF. Carbohydrate structures of recombinant human alpha-L-iduronidase secreted by Chinese hamster ovary cells. J Biol Chem. 1997;272:22758–65. [PubMed: 9278435]

Suggested Readings

Boelens JJ. Trends in haematopoietic cell transplantation for inborn errors of metabolism. J Inherit Metab Dis. 2006;29:413–20. [PubMed: 16763911]

Desnick RJ. Enzyme replacement and enhancement therapies for lysosomal diseases. J Inherit Metab Dis. 2004;27:385–410. [PubMed: 15190196]

Hoffmann B, Mayatepek E. Neurological manifestations in lysosomal storage disor Neuropediatrics. 2005;36:285–9. [PubMed: 16217702]

Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 136. www.ommbid.com. revised 2002

Chapter Notes

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