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Mucopolysaccharidosis Type II

[*Hunter Syndrome, Iduronate 2-Sulfatase Deficiency, MPS II, I2S Deficiency*]

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Summary

Disease characteristics. Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is a multisystem disorder characterized by glycosaminoglycans (GAG) accumulation. Age of onset, disease severity, and rate of progression vary significantly. In those with severe disease, CNS involvement, manifest primarily by progressive cognitive deterioration, and progressive airway disease and cardiac disease usually result in death in the first or second decade of life. In those with attenuated disease, the CNS is not (or is minimally) affected, although the effect of GAG accumulation on other organ systems may be just as severe as in those who have progressive cognitive decline. Survival into the early adult years with normal intelligence is common in the attenuated form of the disease. Additional findings in both forms of MPS II include: short stature; macrocephaly with or without communicating hydrocephalus; macroglossia; hoarse voice; conductive and sensorineural hearing loss; hepatomegaly and/or splenomegaly; dysostosis multiplex and joint contractures including ankylosis of the temporomandibular joint; spinal stenosis; and carpal tunnel syndrome.

Diagnosis/testing. Urine GAGs and skeletal survey can establish the presence of an MPS condition but are not specific to MPS II. The gold standard for diagnosis of MPS II in a male proband is assay of I2S enzyme activity in white cells or serum. Molecular genetic testing of *IDS*, the only gene known to be associated with MPS II, is used to confirm the diagnosis in a male proband with an unusual phenotype or a phenotype that does not match the results of GAG testing.

Management. *Treatment of manifestations:* Interventions commonly include: developmental, occupational, and physical therapy; shunting for hydrocephalus; tonsillectomy and adenoidectomy; positive pressure ventilation (CPAP or tracheostomy); carpal tunnel release; cardiac valve replacement; inguinal hernia repair; hip replacement. *Prevention of primary manifestations:* Enzyme replacement therapy (ERT) with idursulfase (Elaprase®), a recombinant form of human iduronate 2-sulfatase called idursulfase, has recently been approved in the United States and the European Union. Because only individuals with the attenuated form of the disease were studied, no information is yet available on the outcome of ERT in children younger than age five years or individuals with severe pulmonary compromise or severe CNS disease. Elaprase® does not cross the blood-brain barrier; thus, no effect on CNS disease is anticipated. *Prevention of secondary complications:* attention to risks associated with general anesthesia. *Surveillance:* Depends on organ system and disease severity and usually includes annual: cardiac evaluation and echocardiogram; pulmonary evaluation including pulmonary function testing; audiogram; eye examination; developmental assessment; neurologic examination. Additional studies may include: sleep study for obstructive apnea; nerve conduction velocity (NCV) for carpal tunnel syndrome; evaluation for hydrocephalus; orthopedic evaluation to monitor hip disease. *Testing of relatives at risk:* Whether the potential benefits of early initiation of ERT justify early diagnosis either by newborn screening or by testing of at-risk male relatives is at present unclear. *Other:* Although

hematopoietic stem cell transplantation (HSCT) (using umbilical cord blood or bone marrow) could provide sufficient enzyme activity to slow or stop the progression of the disease, anecdotal case reports to date have been disappointing.

Genetic counseling. Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is inherited in an X-linked manner. The risk to sibs depends on the carrier status of the mother. If the mother of the proband has the disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers. Germline mosaicism has been observed. Affected males pass the disease-causing mutation to all of their daughters and none of their sons. Prenatal testing for pregnancies at increased risk is possible when the disease-causing mutation in the family is known; molecular genetic testing is preferred over assay of enzyme activity which is more difficult.

Diagnosis

Clinical Diagnosis

The diagnosis of mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) cannot be made on clinical findings alone. The physical findings vary widely, depending on disease severity.

- The diagnosis is often suspected in male children age two to four years with short stature, hepatosplenomegaly, joint contractures, and coarse facies; subtle early signs and symptoms such as frequent ear/sinus infections and umbilical hernia are often present.
- A skeletal survey may show skeletal anomalies known collectively as dysostosis multiplex; however, these findings may not be present in early life and are not specific to MPS II.

Testing

Urine glycosaminoglycans (GAGs). GAG quantitative and qualitative analysis is useful as a preliminary test to help establish that the person has an MPS condition. In MPS II, GAG analysis shows large concentrations of the GAGs dermatan sulphate and heparan sulphate. The profile is similar to that seen in MPS I.

Iduronate 2-sulfatase (I2S) enzyme activity. Confirmation of the diagnosis of MPS II is made by demonstrating a deficient I2S enzyme activity in leukocytes, fibroblasts, or serum. Most affected males have no detectable activity using the artificial substrate.

Absence or reduced levels of I2S enzyme activity decreases the amount of the sulfate moiety released from the glycosaminoglycans (GAGs) dermatan sulphate and heparan sulphate during their degradation.

Note: Documentation of normal enzymatic activity of at least one other sulfatase is critical, as low levels of I2S enzyme activity are present in multiple sulfatase deficiency, which can share some common clinical features with MPS II.

Carrier testing. Measurement of I2S enzyme activity is not reliable for detection of carrier females as a carrier may have normal I2S enzyme activity resulting from X-chromosome inactivation that may be non-random.

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. *IDS* is the only gene known to be associated with MPS II. A pseudogene *(IDS2*) is located 20 kb telomeric to the *IDS* gene.

Clinical testing. Three general types of *IDS* mutations are observed in persons with MPS II: mutations within the gene, exonic and whole gene deletions, and gross alterations resulting from recombination with the nearby *IDS* pseudogene, *IDS2*.

- **Sequence analysis** of the entire *IDS* coding region detects 82% of mutations in both males and females [Froissart et al 2007]. The following two types of mutations are detected by sequence analysis:
  - Single nucleotide changes and splicing mutations, which together account for 65% of all mutations
  - Small (i.e., intra-exonic) deletions and insertions, which account for 17% of all mutations

  Note: (1) Sequence analysis may be reported as normal in individuals (males or females) who have the most common pseudogene recombination. Therefore, Southern blot analysis should also be performed. (2) Sequence analysis of the entire *IDS* coding region also detects in males (but not females) the 9% of mutations that are exonic and whole gene deletions. (3) Sequence analysis of the mRNA is available and can detect promoter mutations and intronic mutations affecting splicing that would be missed by other methods. This analysis is accurate in males, but may not be accurate in females.
- **Deletion testing for exonic and whole gene deletions.** Multiplex dosing assays are used to detect large deletions in males and females that account for 9% of mutations [Froissart et al 2007].
- **Southern blot analysis** is used to detect complex rearrangements resulting from recombination with the pseudogene and accounting for 9% of all mutations [Froissart et al 2007].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in MPS II (Hunter Syndrome)

Test Method	Mutations Detected	Mutation Detection Frequency [1]		Test Availability
		Males	Females	
Sequence analysis	*IDS* sequence variants, splicing mutations, small (i.e., intra-exonic) deletions and insertions	82%	82%	Clinical Testing
	IDS exonic and whole gene deletions	9%	0% [2]	
Deletion testing	*IDS* exonic and whole gene deletions	Not necessary [3]	9%	
Southern blot analysis	*IDS* complex rearrangements involving the *IDS2* pseudogene	9%		

1. Proportion of affected individuals with a mutation(s) as classified by gender and/or test method
2. Exonic and whole gene deletions on the X chromosome cannot be detected in females using sequence analysis.
3. Exonic and whole gene deletions on the X chromosome can be detected in males using sequence analysis.

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

Testing Strategy

To confirm the diagnosis in a male proband

- Urine GAGs and skeletal survey are useful in establishing that the individual being tested has an MPS condition, but are not specific to MPS II.
- The gold standard for diagnosis of MPS II in a male proband is assay of I2S enzyme activity in white cells or serum.
- Molecular genetic testing of *IDS* to confirm the diagnosis in a male proband may be useful in cases with an unusual phenotype or a phenotype that does not match the results of GAG testing.

Identification of female carriers requires **one** of the following:

- Testing for the family-specific mutation that has been identified in an affected male relative
- If an affected male is not available for testing:
  1. Molecular genetic testing of the female by sequence analysis
  2. If no mutation is identified, use of deletion testing methods to detect intragenic and exonic gene deletions
  3. If no mutation is identified, use of Southern blot analysis to detect gene rearrangements between *IDS* and the *IDS2* pseudogene

Note: Carriers are heterozygotes for this X-linked disorder and are not expected to be symptomatic.

Prenatal diagnosis and preimplantation diagnosis for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Deletions extending beyond the *IDS* locus result in symptoms atypical of MPS II. These deletions cause a more severe central nervous system (CNS) phenotype and may be associated with other atypical features such as ptosis and seizures.

Clinical Description

Natural History

Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) has multisystem involvement with significant variability in both age of onset and rate of progression.

CNS involvement, the most significant feature in the group of children often labeled with "severe" disease, manifests primarily by progressive cognitive deterioration. Such cognitive decline, combined with the progressive airway and cardiac disease, usually results in death in the first or second decade of life.

In individuals with the attenuated form of the disease, the CNS is minimally affected, if at all, yet the effect of GAG accumulation on other organ systems may be just as severe as in those who have progressive cognitive decline. Survival into the early adult years with normal intelligence is common in this group.

GAG accumulation in virtually all organs occurs in MPS II, but specific body systems are more affected than others. The clinical presentations of the organ systems most severely affected in this disease are the following:

- **General.** The appearance of newborns with MPS II is normal. Coarsening of facial features — the result of macroglossia, prominent supraorbital ridges, a broad nose, a broad nasal bridge, and deposition of GAG in the soft tissues of the face resulting in large rounded cheeks and thick lips — generally manifests between ages two and four years.

  Growth in the first five years of life is above average for most boys with MPS II; after that growth falls behind and short stature is the norm. Macrocephaly is universal.

- **Eye**. In contrast to MPS I, corneal clouding is not a feature of MPS II. However, discrete corneal lesions that do not affect vision may be discovered by slit-lamp examination. Electroretinography may reveal retinal dysfunction and field of vision loss can occur.

- **Ear, nose, throat.** Common oral findings in boys with MPS II include macroglossia, hypertrophic adenoids and tonsils, and ankylosis of the temporomandibular joint, which limits opening of the mouth. GAG deposition in the larynx typically results in a characteristic hoarse voice.

  Teeth are often irregularly shaped and gingival tissue is overgrown.

  Conductive and sensorineural hearing loss, complicated by recurrent ear infections, occurs in most affected individuals.

- **Joints/skeletal.** Joint contractures, particularly of the phalangeal joints, are universal. The contractures cause significant loss of joint mobility and are one of the earliest noteworthy diagnostic clues.

  The skeletal abnormalities in MPS II are comparable regardless of the severity of the cognitive phenotype but are not specific to MPS II. Termed dysostosis multiplex, these radiographic findings are found in all MPS disorders and manifest as a generalized thickening of most long bones, particularly the ribs, with irregular epiphyseal ossification centers in many areas. Notching of the vertebral bodies is common.

  Hip dysplasia is the most common long-term orthopedic problem and can become a significant disability with early-onset arthritis if not treated.

- **Respiratory.** Frequent upper respiratory infections are one of the earliest findings in MPS II. The airway progressively narrows as GAGs accumulate in the tongue, soft tissue of the oropharynx, and the trachea, eventually leading to airway obstruction. Complicating this obstruction is thickening of respiratory secretions, stiffness of the chest wall, and hepatosplenomegaly which can reduce thoracic volume. The progression of airway obstruction is relentless and usually results in sleep apnea, and the need for positive pressure assistance and eventual tracheostomy.

- **Cardiovascular.** The heart is abnormal in the majority of boys with MPS II and is a major cause of morbidity and mortality. The most common effect of cardiac GAG

deposition is valvular disease leading to right and left ventricular hypertrophy and heart failure.

- **Gastrointestinal.** Hepatomegaly and/or splenomegaly occur in most affected individuals. Umbilical/inguinal hernia is also a frequent finding. In persons with severe MPS II, chronic diarrhea is a common complaint.
- **Nervous system.** Delay in global developmental milestones is typically the first clue of brain involvement in children with the CNS form of MPS II. As is the case for the other organ systems, progression of the CNS manifestations is inexorable, usually resulting in developmental regression between ages six and eight years.

  Chronic communicating hydrocephalus may complicate the clinical picture, especially on the background of deteriorating cognitive ability. Seizures may also occur.

  The decline of cognitive function, combined with progression of severe pulmonary and cardiac disease, generally heralds the terminal phase of the disease, with death in the first or second decade of life.

  Males who do not have the progressive CNS form of the disease have normal or nearly normal intelligence. However, while deteriorating cognitive abilities and seizures are not common in males with this attenuated form of MPS II, chronic communicating hydrocephalus may still occur.

  Carpal tunnel syndrome (CTS) is often an overlooked complication of MPS II. Unlike adults with CTS, most children with MPS II do not complain of the typical symptoms. Nonetheless, nerve conduction studies are abnormal; hand function improves after surgical correction.

  Another nervous system complication that must be monitored is narrowing of the spinal canal (spinal stenosis), particularly in the cervical region, with spinal cord compression.

Genotype-Phenotype Correlations

Genotype-phenotype correlations for point mutations, most of which are private, are not reliable for MPS II [Vafiadaki et al 1998, Li et al 1999, Moreira da Silva et al 2001].

At least two sibships have been reported in which one brother has the severe phenotype while the other brother shows an attenuated phenotype [Yatziv et al 1977].

On the other hand, boys with complete absence of functional enzyme as a result of gene deletion or complex gene rearrangements (~17% of affected individuals) invariably manifest the severe CNS presentation of the disease. Outside of this group, however, neither the amount of I2S protein nor its enzyme activity can be correlated with phenotypic severity.

Penetrance

Penetrance of MPS II in males is complete; however, it is anticipated that if newborn screening becomes available for MPS II, much milder presentations would be documented.

Nomenclature

The modifier terms "mild" and "severe" are often used to describe the phenotypic variability of the condition but it is clear that, as for all MPS disorders, the range of severity is wide. The term "attenuated" MPS II (Hunter syndrome) has been suggested as a replacement for the word

"mild" to describe those individuals with the non-CNS form of the disease since this group often has somatic presentations just as debilitating as those found in the "severe" CNS group.

Prevalence

Several surveys suggest an incidence between 1:100,000 and 1:170,000 male births [Nelson et al 2003, Baehner et al 2005].

The severe CNS phenotype may be more than twice as prevalent as the attenuated form of the disease; however, accurate prevalence rates are not available.

Differential Diagnosis

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

The differential diagnosis for mucopolysaccharidosis type II (MPS II, or Hunter syndrome) essentially includes all of the other MPS disorders, given the significant overlap of clinical presentation and radiologic findings (see MPS I).

Multiple sulfatase deficiency and mucolipidosis types II and III may also present with findings similar to MPS II.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome), the following evaluations are recommended:

- Echocardiogram
- Pulmonary function testing
- Sleep study if sleep apnea is a potential concern
- Hearing test
- Nerve conduction velocity (NCV) study to assess for carpal tunnel syndrome
- Head MRI and/or opening pressure on lumbar puncture to assess for hydrocephalus
- Eye examination
- Developmental assessment

Note: Many of these assessments are age dependent. For example, pulmonary function and sleep studies would not be appropriate in a two-year-old.

Treatment of Manifestations

At this time, treatment of complications in MPS II is symptomatic.

The involvement of specialists for each affected organ system is required to monitor and treat specific problems (see Natural History). Commonly required interventions include the following:

- Shunting for hydrocephalus
- Tonsillectomy and adenoidectomy
- Positive pressure ventilation (CPAP or tracheostomy)

- Carpal tunnel release
- Cardiac valve replacement
- Inguinal hernia repair
- Hip replacement

Developmental, occupational, and physical therapy are often necessary.

Enzyme replacement therapy (ERT) (see Prevention of Primary Manifestations) is now available for MPS II. No data are yet available as to any long-term benefits of such treatment.

Prevention of Primary Manifestations

Bone marrow transplantation (BMT). Hematopoietic stem cell transplantation (HSCT) using umbilical cord blood or bone marrow is a potential way of providing sufficient enzyme activity to slow or stop the progression of the disease. The anecdotal case reports published to date have been disappointing, quite unlike the reports of BMT in Hurler syndrome (MPS I), in which early treatment (age ≤2 years) has met with good success.

Enzyme replacement therapy (ERT). Idursulfase (Elaprase®) is a recombinant form of human iduronate 2-sulfatase that has recently been approved in the United States and the European Union for the treatment of MPS II [FDA Consumer 2006a, 2006b].

Clinical efficacy of ERT was shown in a double-blinded placebo-controlled study of 96 patients [Muenzer et al 2006]. After one year of treatment, persons in the weekly idursulfase group compared to the placebo group demonstrated statistically significant improvement of the primary endpoint, a composite consisting of distance walked in six minutes and the percentage of predicted forced vital capacity based on the sum of ranks of change from baseline. Based on the larger clinical response in the weekly compared to the every other week group, idursulfase was approved for the treatment of MPS II in both the US and European Union at a dose of 0.5 mg/kg weekly.

Because of the trial design, the study only included individuals with the attenuated form of the disease. Despite Elaprase ® being approved for treatment of MPS II, no information is yet available on the outcome of using the drug for individuals who are younger than age five years or have severe pulmonary compromise or severe CNS disease. Elaprase® does not cross the blood-brain barrier, and thus no effect on CNS disease is anticipated.

Infusion reactions were generally mild, easy to manage, and consistent with reactions reported in other ERT therapies for lysosomal storage diseases.

Prevention of Secondary Complications

ERT. Infusion-related reactions that may occur with use of Elaprase® ERT are comparable to similar reactions seen with other ERT products used in treatment of lysosomal storage disease and with other infused proteins such as monoclonal antibodies (e.g., infliximab). The etiology of the more severe forms of these non-allergic reactions, referred to as anaphylactoid, is unknown. Current evidence suggests that anaphylactoid (as opposed to anaphylactic) reactions are not immune mediated [Mayer & Young 2006].

Most infusion-related reactions are mild, manifest as brief, insignificant decreases or increases in heart rate, blood pressure, or respiratory rate. Other mild reactions are itching, rash, flushing, and headache. Mild reactions can usually be managed by slowing the infusion rate for several treatments and then slowly returning to the prior rate.

Pretreatment with anti-inflammatory drugs or antihistamines, as is often done for ERT in other conditions, is not suggested on the label for Elaprase®; however, if mild or moderate infusion reactions (e.g., dyspnea, urticaria, or systolic blood pressure changes of ≤20 mm Hg) cannot be ameliorated by slowing the infusion rate, the addition of treatment one hour before infusion with diphenhydramine and acetaminophen (or ibuprofen) to the regimen usually resolves the problem. Pretreatment can typically be discontinued after six to ten weeks.

Severe non-allergic anaphylactoid reactions such as major changes in blood pressure, wheezing, stridor, rigors, or drop in oxygen saturations should be immediately addressed by stopping the infusion and giving appropriate doses of subcutaneous (SQ) epinephrine, intravenous (IV) diphenhydramine, and hydrocortisone or methylpredinsolone. Subsequent infusions should then be given at a significantly reduced rate with pretreatment with prednisone 24 hours and eight hours before the infusion, diphenhydramine and acetaminophen or ibuprofen orally one hour before the infusion, and IV methylpredinsolone just before beginning the infusion.

Patients with relatively attenuated forms of Hunter syndrome were studied in the clinical trial leading to FDA approval of Elaprase®; thus, it is not known at this time whether the incidence or severity of infusion-related reactions is different for patients younger than age five years with severe respiratory compromise or with severe CNS disease.

General anesthesia. Risks associated with general anesthesia are significant in MPS II:

- Ankylosis of the temporomandibular (TM) joint can restrict oral access to the airway.
- Visualization of the vocal cords is compromised by the large tongue, GAG-infiltrated soft tissues, and large tonsils and adenoids.
- Care must be taken to avoid hyperextension of the neck secondary to atlantoaxial instability and cervicomedullary compression which may be present.

Nasopharyngeal intubation is often necessary. Anesthesia is best administered in centers familiar with the complications inherent in MPS disorders.

Surveillance

Modes of surveillance for complications over time depend, like treatment, on organ system and disease severity. Because all persons with MPS II face the same organ failure issues, with the time of failure being dependent on severity, when and how often to monitor for change cannot be generalized. However, the following studies/evaluations are appropriate at the time of diagnosis and will likely be necessary on at least a yearly basis beginning in early to mid-childhood:

- Cardiology visit with echocardiogram
- Pulmonary clinic visit with pulmonary function testing
- Audiogram
- Eye examination, including examination through a dilated pupil to view the optic disc
- Developmental assessment
- Neurologic examination

The following are appropriate at baseline and/or when symptoms/age dictates:

- Sleep study for obstructive sleep apnea
- NCV study for evidence of carpal tunnel syndrome

- Head/neck MRI to document ventricular size and cervicomedullary narrowing
- Opening pressure on lumbar puncture
- Orthopedic evaluation to monitor hip disease

Testing of Relatives at Risk

It is unclear at present whether early diagnosis, either by newborn screening or testing of at-risk male relatives, is beneficial from the aspect of early initiation of ERT. No data are available on whether early ERT improves the outcome of the somatic disease in MPS II. No effect of ERT on children with the CNS form of the disease is anticipated.

Certainly for hematopoietic stem cell transplantation (HSCT) to have any significant effect on CNS development, it should be done prior to age two years, preferably earlier. However, the efficacy of HSCT in treating MPS II has yet to be proven.

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

Therapies Under Investigation

A number of interventions are being evaluated for potential use in MPS II. These include direct delivery of enzyme into the CNS, higher peripheral dosing regimens, small molecule therapies such as chaperone and substrate reduction and, of course, gene therapy.

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

Other

The results of bone marrow transplantation (BMT) in MPS II, compared to results seen in Hurler syndrome, have not been encouraging. However, the efficacy of BMT for MPS II cannot be determined with accuracy until a reasonable series of persons with MPS II younger than age two years with known or probable severe CNS disease undergoes transplantation, along with documentation of long-term follow-up.

Genetics clinics are a source of 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 (below) may include disease-specific and/or umbrella support organizations.

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 II (MPS II; also known as Hunter syndrome) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If a woman has more than one affected son and the disease-causing mutation cannot be detected in DNA extracted from her leukocytes, she has germline mosaicism.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* gene mutation, in which case the mother is not a carrier.
- When an affected male is the only affected individual in the family, several possibilities regarding his mother's carrier status need to be considered:
  - He has a *de novo* disease-causing mutation in the *IDS* gene and his mother is not a carrier.
  - His mother has a *de novo* disease-causing mutation in the *IDS* gene, either a) as a "germline mutation" (i.e., present at the time of her conception and therefore in every cell of her body); or b) as "germline mosaicism" (i.e., present in some of her germ cells only).
  - His mother has a disease-causing mutation that she inherited from a maternal female ancestor.

Sibs of a proband

- The risk to sibs depends upon the carrier status of the mother.
- If the mother of the proband has the disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers.
- Germline mosaicism has been observed in this condition [Froissart et al 2007]. Thus, even if the disease-causing mutation has not been identified in the mother's DNA, sibs of the proband are still at increased risk of inheriting the disease-causing mutation.

Offspring of a proband. Affected males will pass the disease-causing mutation to all of their daughters and none of their sons.

Other family members of a proband. The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending upon their gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carrier testing of at-risk female relatives is available on a clinical basis if the mutation has been identified in the family.

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 the 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 Testing for a list of laboratories offering DNA banking.

Prenatal Testing

In families in which the molecular basis of MPS II is known, prenatal diagnosis should be performed by molecular genetic testing, as assay of enzyme activity is more difficult.

Molecular genetic testing. Prenatal testing using molecular testing is the preferred method of diagnosis for pregnancies of women who are carriers of an *IDS* mutation previously identified in a family member. The usual procedure is to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation or by amniocentesis usually performed at approximately 15-18 weeks' gestation. If the karyotype is 46,XY, DNA from fetal cells can be analyzed for the known disease-causing mutation.

Biochemical genetic testing. Prenatal testing is technically feasible for pregnancies at increased risk for MPS II by measuring I2S enzyme activity in cultured cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. However, this service is not readily available.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) 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 II

Gene Symbol	Chromosomal Locus	Protein Name
IDS	Xq28	Iduronate 2-sulfatase

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 II

309900	MUCOPOLYSACCHARIDOSIS TYPE II

Table C. Genomic Databases for Mucopolysaccharidosis Type II

Gene Symbol	Entrez Gene	HGMD
IDS	3423 (MIM No. 309900)	IDS

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Mutations in the *IDS* gene result in minimal to absent lysosomal I2S enzyme activity, depending on the mutation. Lack of enzyme activity causes heparan and dermatan sulphate (two forms of glysosaminoglycans, or GAGs) to accumulate in the lysosomes of the cell, disrupting their function and causing disease.

Normal allelic variants: The *IDS* gene spans 24 kb with nine exons. An *IDS* pseudogene, *IDS2*, is also recognized about 20 kb away in the telomeric direction.

Pathologic allelic variants: Over 300 mutations have been described, the majority being point mutations or small deletions [Froissart et al 2007]. However, up to 25% of MPS II cases are the result of large intragenic deletions and/or chromosomal rearrangements, typically associated with the severe phenotype. The presence of homologous regions in the nearby *IDS* pseudogene predisposes to unequal recombination events, leading to these large deletions.

Normal gene product: Iduronate 2-sulfatase (I2S), a 550-amino acid protein, catalyzes the release of sulfate from the iduronate sulfate residues of heparan sulphate and dermatan sulphate [Neufeld & Muenzer 2001].

Abnormal gene product: Missense point mutations make up the majority of gene mutations in *IDS*, resulting in variable expression of I2S enzyme activity and disease severity. Genotype-phenotype predictions are not reliable in these cases. In males with large deletions and intragenic rearrangements, no enzyme is produced and these individuals typically have the severe phenotype.

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.

Canadian Society for Mucopolysaccharide and Related Diseases, Inc
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Medline Plus
Hunter syndrome

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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.

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Suggested Readings

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Chapter Notes

Revision History

- 6 November 2007 (me) Review posted to live Web site
- 8 June 2007 (rm) Original submission