WOULD YOU RECOGNIZE MUCOPOLYSACCHARIDOSIS TYPE I?

Mucopolysaccharidosis Type I (MPS I)

MPS I is a lysosomal storage disease that is caused by the deficiency of lysosomal enzyme alpha-L-iduronidase. Individuals with MPS I have a pathogenic variant in the *IDUA* gene that codes for the production of alpha-L-iduronidase. Alpha-L-iduronidase is needed to catabolize glycoaminoglycans (GAGs) in the lysosome. Reduced alpha-L-iduronidase activity results in the accumulation of GAGs, specifically heparan and dermatan sulfate.

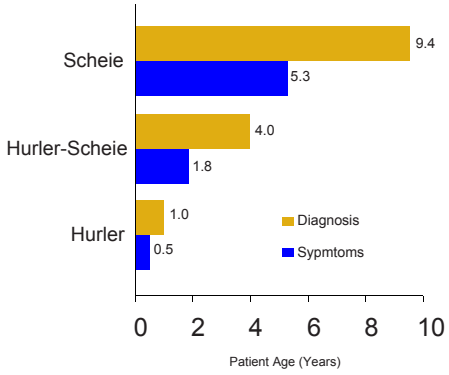
Inheritance and Epidemiology

- Autosomal recessive inheritance
- Estimated world-wide incidence: 1:100,000 births
- Pan-ethnic
- Prevalence varies in different populations
- The majority of recognized patients have the severe or Hurler phenotype instead of the attenuated Hurler-Scheie or Scheie phenotypes

Diagnostic Delays in MPS I

- Patients typically are referred to several specialists before they are correctly diagnosed
- Misdiagnoses and diagnostic delays are common, especially in attenuated MPS I

Median Age of Onset of Symptoms and Diagnosis



Beck et al. The natural history of MPS I: global perspectives from the MPS I Registry. Genet in Med online 27 March 2014.

MPS I spectrum of disease

	SEVERE		ATTENUATED
	Hurler	**Hurler-Scheie**	**Scheie**
Age at diagnosis	0.2 – 7 years	0.2 – 36 years	2 – 54 years
Effect on cognition	Pronounced mental delay with loss of acquired skills	No/mild mental delay; learning disabilities	No impairment
Mean life expectancy (without disease management)	7 years	Approximately 20 years	Adulthood
Phenotype distribution	~65%	~25%	~10%

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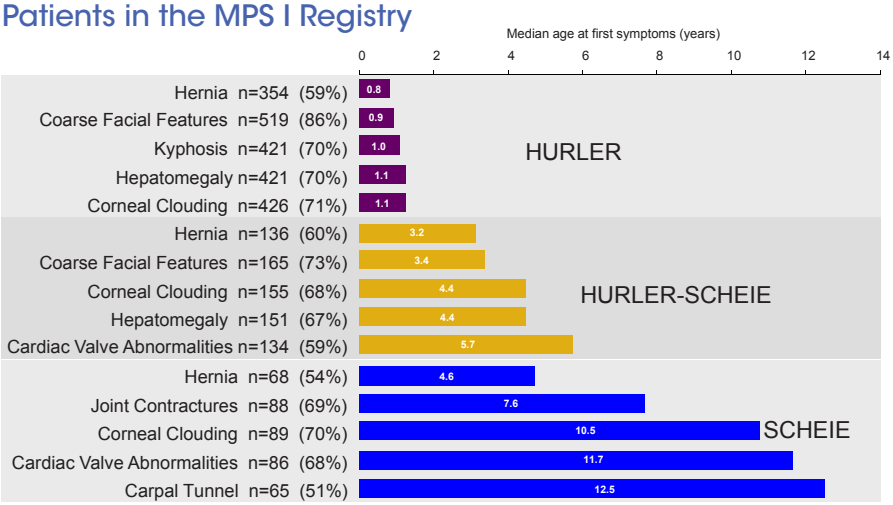
Clinical Manifestations of MPS I

PHENOTYPE	EAR, NOSE AND THROAT
Macrocephaly	Chronic rhinorrhea
Progressive coarse facial features	Recurrent otitis media
Macroglossia	Enlarged tonsils and adenoids
Corneal clouding	Obstructive sleep apnea
Hepatosplenomegaly	Hearing loss
Inguinal and umbilical hernias	**NEURODEVELOPMENTAL**
Toe walking	Developmental delay
Abnormal gait	Cognitive impairment
CARDIAC	Hydrocephalus
Cardiomyopathy	Carpal tunnel syndrome
Valvular disease	**ORTHOPEDIC/MUSCULOSKELETAL**
RESPIRATORY	Dysostosis multiplex
Recurrent lower respiratory tract infections	Lumbar kyphosis
Reactive airway disease	Joint contractures
	Short stature

Clinical presentation and organ involvement varies with phenotype and extend of disease progression.

Top 5 Presenting Symptoms by Phenotype Reported by Patients in the MPS I Registry



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Diagnosis

- Measuring alpha-L-iduronidase activity is the gold standard methodology for diagnosis
- Alpha-L-iduronidase activity can be measured in leukocytes, plasma, serum, or dried blood spots
- Diagnosis of MPS I can also be confirmed by molecular analysis of the *IDUA* gene
  - >100 disease-causing mutations have been identified in the *IDUA* gene
  - Nonsense alleles, when present singly in homozygotes or combined in compound heterozygotes, often predict a severe phenotype
  - Patients with missense mutations may present with a less severe phenotype
  - Determining genotype does not always help predict phenotype, as many mutations are unique ("private")
  - Pseudo-deficiency alleles in the *IDUA* gene have been reported
- Urinary GAG measurement can be a useful assessment (not diagnostic) negatives can occur

MPS I Registry (www.registrynxt.com)

- **Objectives of the MPS I Registry**
  - To enhance the understanding of the variability, progression, and natural history of MPS I
  - To assist the medical community caring for patients with MPS I by providing outcome reports and monitoring recommendations to optimize care
- **Initiated in April 2003, the MPS I Registry (clinicaltrials.gov, NCT00144794) is the *largest observational database of MPS I patients in the world***
  - All patients with a confirmed diagnosis of MPS I are eligible to participate
- **Rare disease registries, such as the MPS I Registry, provide an unparalleled resource for clinicians and scientists**
- **As of July 2018, contains data for 1131 patients worldwide**

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