
Mucopolysaccharidosis Type 1 (MPS 1)

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Background of MPS 1

- Lysosomal storage disorder
 - Lysosome: a part within each cell that is responsible for breakdown and clean-up of old or extra cell components
 - In Edinburgh, in the early 20th century, a child presented with the first characteristics of what would be MPS 1
 - In 1917, Dr. Hurler noted a patient with “coarse features, an enlarged liver and spleen, clawing of the hands, and bony deformities” (13)
 - Treatment in the past has been only palliative care and symptom-based interventions but has since progressed
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Spectrum of MPS 1

- Categorized into 3 different diseases based on severity of the enzyme deficiency:
 - Hurler syndrome: first described in 1917, most severe with early onset symptoms (immediately following birth)
 - Scheie syndrome: first described in 1962, least severe symptoms and a later onset
 - Hurler-Scheie syndrome: somewhat in the middle on the severity scale
- Due to the similarity in the symptoms and biochemical features, the three were combined into MPS 1 in 1972 but are still on a spectrum of severity



Severe

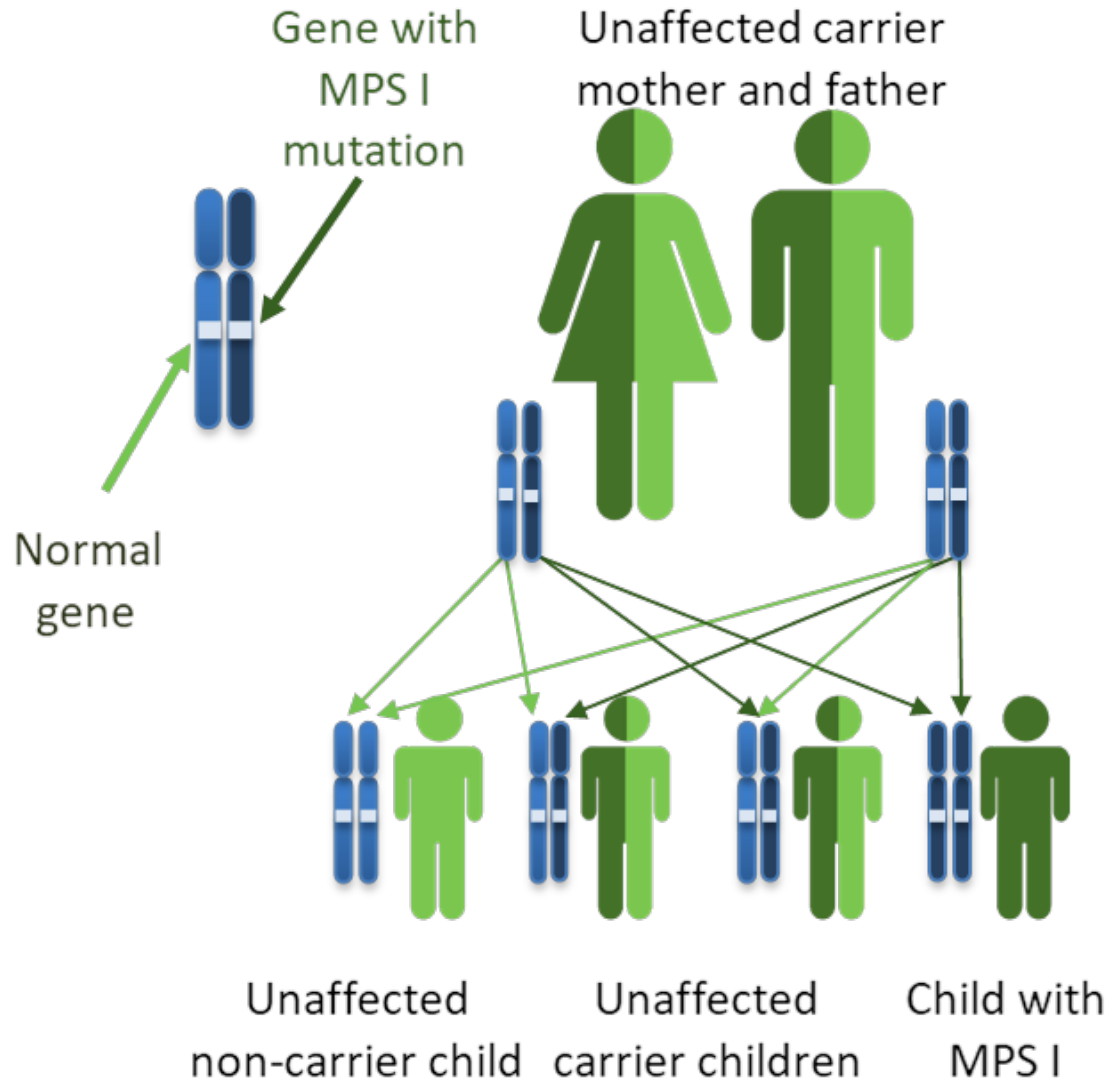
- Can have life threatening effects
- Historically called Hurler syndrome

Attenuated

- Almost normal life expectancy, but still a significant disability
- What was historically referred to as Hurler-Scheie and Scheie syndromes

Frequency of MPS I

- 1 in every 100,000 live births in the U.S. have the more severe form of the disease
 - 1 in every 500,000 live births in the U.S. have the less severe form of the disease
 - The disease affects males and females equally
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Genetics

- MPS 1 is an inherited, autosomal recessive disease, which requires two copies (one from each parent) of the mutated alpha-L-iduronidase (IDUA) gene to show symptoms
- If both parents are carriers for the gene, there is a 25% chance with each pregnancy that the child could inherit both copies of the mutated gene and show signs of MPS 1
- It is likely that 1 out of every 160 people are carriers of this gene in all populations

Genetics of autosomal recessive disorders

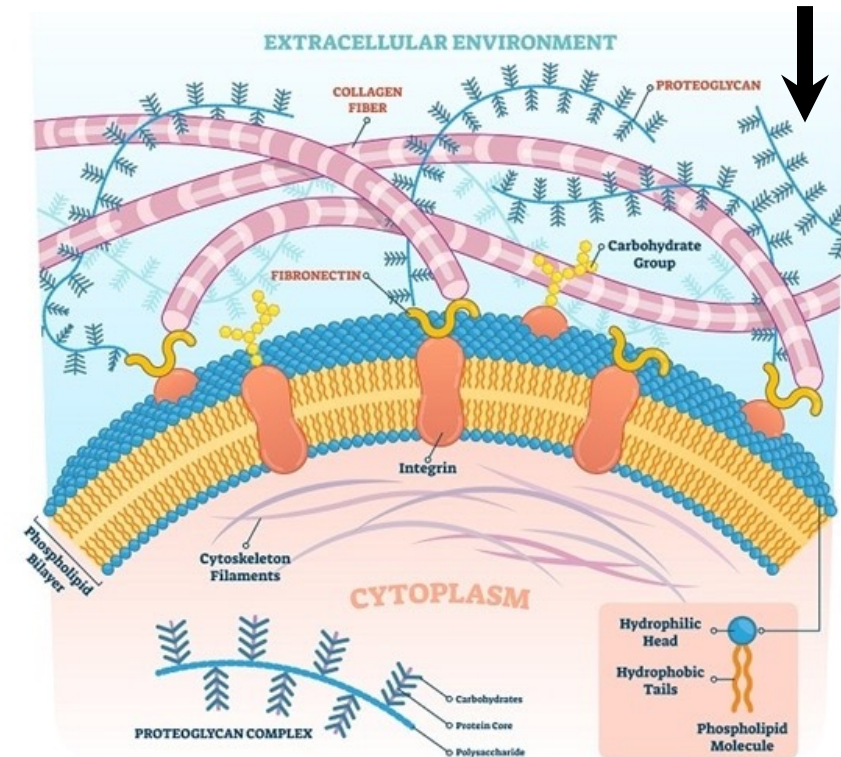


Digital video retrieved April 13, 2021 from
<https://www.youtube.com/watch?v=Nv6qUsKYodA>

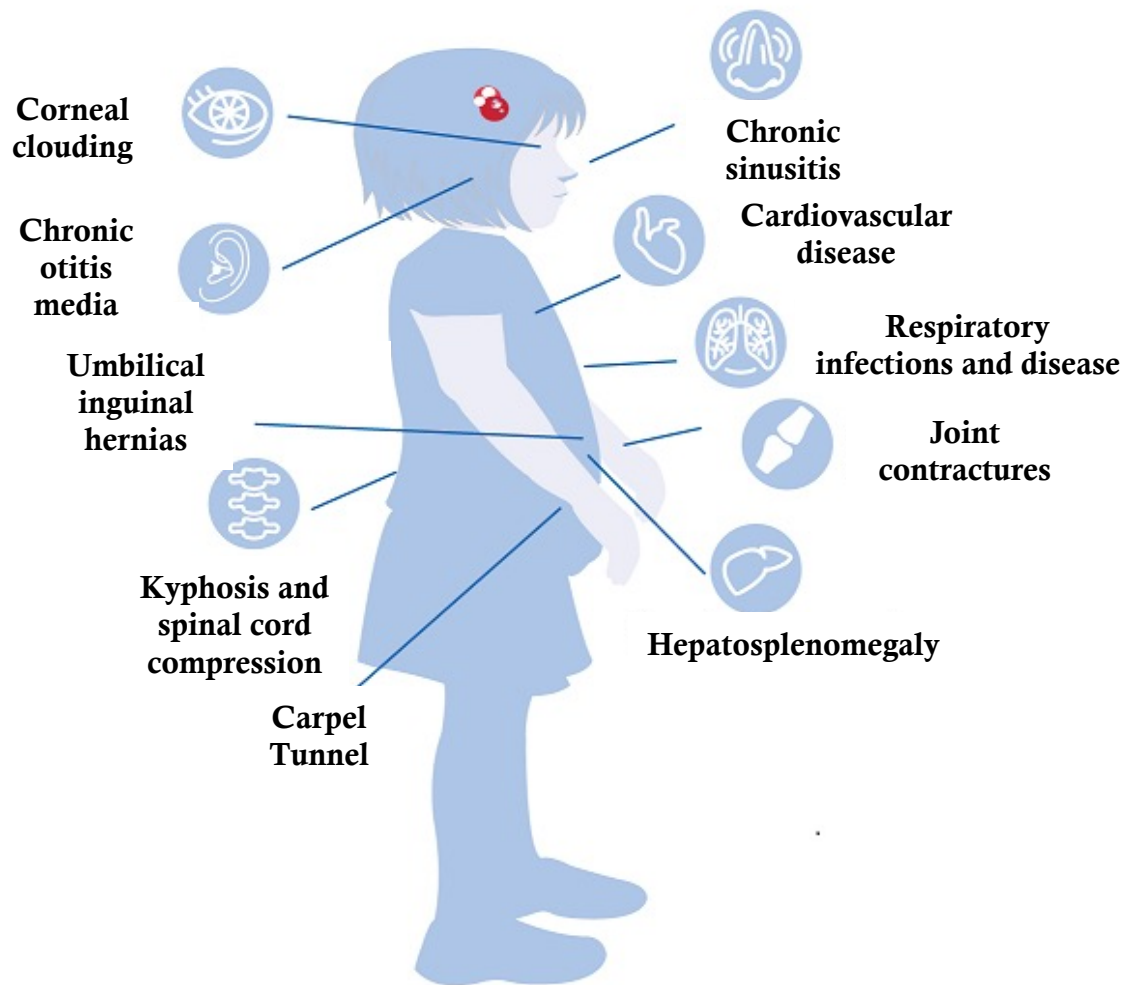
Biochemical features

- The lysosome is a locale for nutrient digestion in the cell, housing enzymes that break down larger molecules (i.e., complex sugars) into smaller parts so they can be used for either generating energy or supporting new biosynthesis
- Mutation of the IDUA gene causes a deficiency of the IDUA enzyme involved in degradation of proteoglycans, which act as a lubricant in the extracellular matrix
- These undigested biomolecules accumulate in the lysosome, causing cellular dysfunction and inflammation of organs

Proteoglycans in the extracellular matrix



Digital image retrieved March 29, 2021 from <https://www.news-medical.net/life-sciences/Structure-and-Function-of-Proteoglycans.aspx>



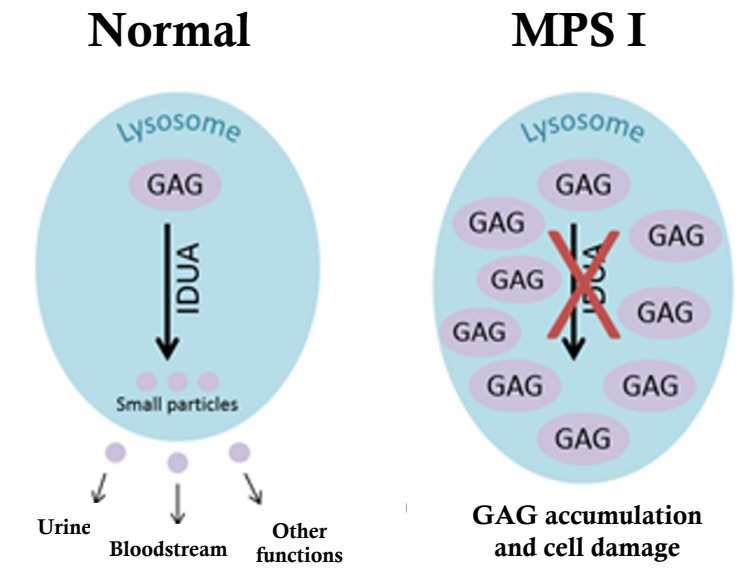
Symptoms

- Those with **severe** MPS 1 usually show signs within the **first year** of life, while those with attenuated MPS 1 tend to show signs in late childhood
- **Symptoms include**, but not limited to, the following:
 - A large head
 - Coarse facial features
 - A large tongue
 - Enlarged vocal cords resulting in a deep, hoarse voice
 - Clouding over the cornea of the eye/vision loss
- **Severe MPS 1:** multiple **skeletal abnormalities**, referred to as dystosis multiplex, that can be seen by x-ray analysis and a decline in intellectual function that is usually present by one year of age

Digital image retrieved October 21, 2020 from
<http://www.sanofimedicalaffairs.com/rarediseases/index.php/mps-i/signs-and-symptoms>.

Diagnosis

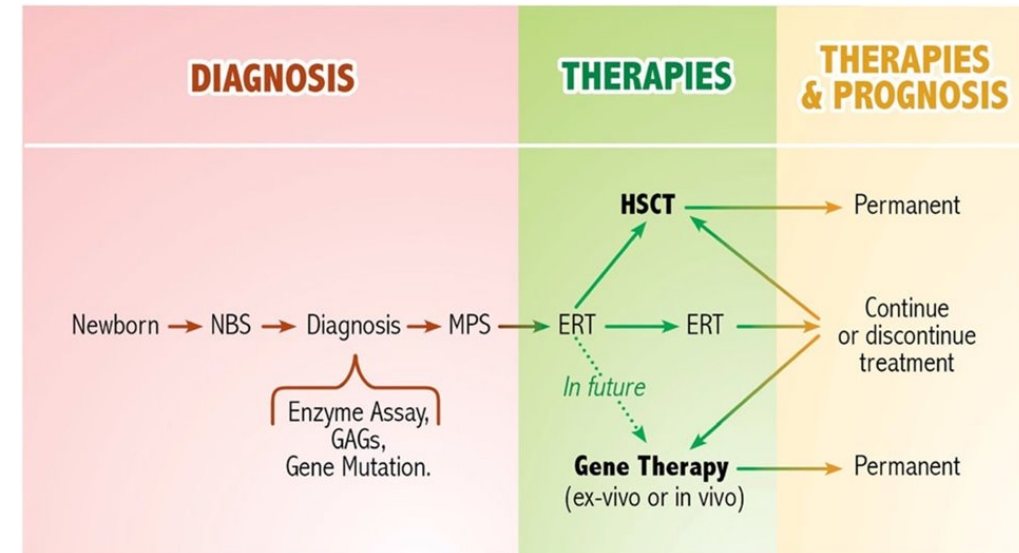
- **Blood tests** are conducted as part of the newborn screening process to analyze the activity of the **IDUA enzyme**; an individual with MPS1 will show low IDUA enzyme activity
- **Urine tests** are used to detect if mucopolysaccharides (proteoglycans) are at **elevated levels**
- Prenatal diagnosis can be done by **amniocentesis** and **chorionic villus sampling**
 - **Amniocentesis**: fluid around the fetus that contains the fetus's DNA is removed and analyzed for the presence of the mutated IDUA gene
 - **Chorionic villus sampling**: tissues are removed from placenta to analyze DNA
- **Genetic testing** of parents to test for recessive alleles
- Characteristics such as **collapsed nose bridge** and other **skeletal malformations** can further provide clinical evidence to diagnosis of MPS1



Digital Image retrieved April 7, 2021
from <https://www.newbornscreening.info/mps-i-mucopolysaccharidosis-type-i/>

Therapy

- **Enzyme Replacement Therapy (ERT)** is suitable for the entire spectrum of MPS 1; used only when moderate-to-severe complications are present. ERT (~\$200,000/patient/year) only increases amount of missing enzyme with intravenous solution.
- **Allogeneic hematopoietic stem cell transplantation (HSCT)** - frontline defense for patients <2 years of age to permit intellectual development (the earlier the better); ~\$150,000/patient/year
 - Requires suitable donor
 - Does not help to prevent osteoarticular deformities (dysostosis multiplex or scoliosis)
 - Risks of the procedure include infections and graft versus host disease
- Both ERT and HSCT treatments decrease symptoms but do not cure the disease
- Before newborn screening was implemented, patient diagnosis was often much later and therefore delayed therapy
 - Patients with Hurler disease: typically diagnosed within 2-3 months
 - Patients with Scheie and Hurler-Scheie can go undiagnosed for years



Digital image retrieved April 7, 2021
from <https://onlinelibrary.wiley.com/doi/full/10.1007/s10545-015-9900-2>

Prognosis

- Life expectancy varies
 - Depends on severity of MPS 1 in individuals
- Without treatment:
 - Hurler side of spectrum: patients rarely live more than 10 years
 - Hurler-Scheie: patients live until teenage years
 - Scheie side of spectrum: patients often live into adulthood
- When the deficient IDUA is replaced (for example, by ERT), the new enzyme can make it to the lysosome and resume its role in degrading proteoglycans to alleviate the MPS I symptoms



Resources

- For information, advice & support regarding inherited genetic diseases: <https://www.metabolicsupportuk.org/> and <http://www.geneticalliance.org/>
 - For information specifically regarding MPS: <https://mpssociety.org/> and <http://ryanfoundation.org/who-we-are/>
 - For information regarding using cord blood for stem cell therapy: <https://sites.duke.edu/ccbb/>
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Works cited

1. Beck, M., Arn, P., Giugliani, R., Muenzer, J., Okuyama, T., Taylor, J., & Fallet, S. (2014). The natural history of MPS I: global perspectives from the MPS I Registry. *Genetics in medicine : official journal of the American College of Medical Genetics*, 16(10), 759–765.
 2. *Genetics and MPS I*. (2017). MPS I. <https://www.mps1disease.com/healthcare/about-mps1/genetics>
 3. *Mucopolysaccharidosis type I | Genetic and Rare Diseases Information Center (GARD)*. (2016). National Institutes of Health. <https://rarediseases.info.nih.gov/diseases/10335/mucopolysaccharidosis-type-i>
 4. *Mucopolysaccharidosis type I: MedlinePlus Genetics*. (n.d.). Medlineplus.gov. Retrieved October 21, 2020, from <https://medlineplus.gov/genetics/condition/mucopolysaccharidosis-type-i/#inheritance>
 5. Marsden, D. (2017, June 23). *Mucopolysaccharidoses*. NORD (National Organization for Rare Disorders). <https://rarediseases.org/rare-diseases/mucopolysaccharidoses/>.
 6. Muenzer, J. (2011). Overview of the mucopolysaccharidoses. *Rheumatology*, 50(suppl_5), v4-v12.
 7. Genzyme Corporation. (2019). *What are the signs and symptoms of MPS I?* <https://www.mps1disease.com/patients/about/signs-and-symptoms>.
 8. Bie, H., Yin, J., He, X., Kermodé, A.R., Goddard-Borger, E.D., Withers, S.G., James, M.N.G. (2013). Human Iduronidase Apo Structure P21 Form. [Photograph]. *Protein Data Bank*. <https://www.rcsb.org/structure/4MJ4>.
 9. National Organization for Rare Disorders. (2017). *Mucopolysaccharidoses Fact Sheet*. <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Mucopolysaccharidoses-Fact-Sheet>.
 10. Jones, S., MD, & Wynn, R., MD. (2020). UpToDate. Retrieved October 26, 2020, from <https://www.uptodate.com/contents/mucopolysaccharidoses-treatment>
 11. ERT. (2018, March 22). Retrieved October 26, 2020, from <https://mpssociety.org/learn/treatments/ert/>
 12. Parini, R., Deodato, F., Di Rocco, M., Lanino, E., Locatelli, F., Messina, C., . . . Scarpa, M. (2017, June 15). Open issues in Mucopolysaccharidosis type I-Hurler. Retrieved October 26, 2020, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5472858/>
 13. History of MPS. (2019). Retrieved November 10, 2020, from <https://www.mpssociety.ca/education/history-of-mps/>
 14. *MPS I Signs and Symptoms*. (n.d.). Sanofi. <http://www.sanofimedicalaffairs.com/rarediseases/index.php/mps-i/signs-and-symptoms>.
 15. Pan, C., Nelson, M. S., Reyes, M., Koodie, L., Brazil, J. J., Stephenson, E. J., Zhao, R. C., Peters, C., Selleck, S. B., Stringer, S. E., & Gupta, P. (2005). Functional abnormalities of heparan sulfate in mucopolysaccharidosis-I are associated with defective biologic activity of FGF-2 on human multipotent progenitor cells. *Blood*, 106(6), 1956–1964. <https://doi.org/10.1182/blood-2005-02-0657>
 16. Goetsch, A. (2016). Hurler Syndrome (MPS 1). Retrieved December 05, 2020, from <https://oncofertility.msu.edu/resources/hurler-syndrome-mps-i>
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Contributions

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| Kate Gromofsky | Background, frequency, and resources |
| Anna Tsai | Genetics |
| Ilays Aden | Biochemical features |
| Kobey Rawlins | Symptoms |
| Sarabeth Anderson | Diagnosis |
| Patrick Scheatzle | Therapy |
| Josh Marcum | Biochemical features |
