# Lysosomal disorders

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**Abstract**

Lysosomal storage disorders (LSDs) are a group of over 50 distinct genetic disorders, each one resulting from a deficiency of a lysosomal enzyme/protein activity, or in some cases, from lysosomal activities that are involved in lysosomal biogenesis or protein maturation. Most LSDs are progressive, the majority have a neurodegenerative component and are mostly life-limiting. The lysosome and its constituent parts are referred to as the greater lysosomal system and form a major metabolic regulatory network in eukaryotic cells. The lysosomes are therefore not "end organelles" but a "central metabolic co-ordinator" with a key role in highly complex regulatory and recycling mechanisms that are essential for normal cell function. New treatment strategies are in preclinical and clinical trial stages. This review briefly discusses the pathophysiology, offers a clinical overview of the categories of LSDs based on the accumulating substrate, and reviews treatment modalities available and those on the near horizon.

**Keywords** Fabry; Gaucher; lysosomal storage disorders; Niemann Pick; oligosaccharidosis; Pompe; sphingolipidosis

## Lysosomes

Since their discovery in the 1950s by Christian De Duve, lysosomes have been studied intensively. Lysosomes are membrane-bound organelles which maintain a specialized biochemical environment within the cell. They possess a number of lysosomal membrane proteins, including proton pumps, which actively maintain an acidic pH which is the optimum working environment for a number of hydrolytic enzymes found within the lysosome. These break down a variety of different, mostly large, molecules, hence lysosomes have historically been thought of as the "recycling centres" of the cell. This simple concept, though helpful in some ways to understand the lysosomal storage disorders (LSDs), considerably understates the complexity of the cellular processes that the lysosomes are involved with. New functions and properties of the lysosomes continue to be discovered each year including calcium storage, intracellular trafficking, paracrine functions and the regulation of autophagy. The lysosome and its constituent parts make up the greater lysosomal system and form a major metabolic regulatory network. Lysosomes are not simply "end organelles" but a central metabolic co-ordinator in highly complex regulatory and recycling mechanisms essential for normal cell function.

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LSDs can occur due to:

- A deficiency of one of the hydrolytic enzymes contained in the lysosomes.
- A deficiency of one of the lysosomal membrane proteins (e.g. transporters).
- Defective intracellular trafficking.
- Defective activation of lysosomal enzymes.

The effects of these deficiencies are dependent on the processes affected and the accumulating chemical(s). In most LSDs, it is not the storage itself, which is necessarily the cause of the disease symptoms but more the secondary effects of lysosomal dysfunction – including inflammation and disturbed autophagy. This may explain why many groups of lysosomal disorders have very similar clinical features despite the accumulating molecule(s) being different.

Recently, the role of the transcription factor EB (TFEB), a master regulator of lysosomal biogenesis and function, in modulating lysosomal proteostasis in LSDs has been investigated. TFEB activation has shown to result in enhanced folding, trafficking and rescues lysosomal activity of severely destabilised mutant lysosomal enzymes, and hence may prove to be an effective therapeutic option in lysosomal disorders.

## Mucopolysaccharidoses

The mucopolysaccharidoses arise due to the deficiency of enzymes involved in the degradation of complex glycoproteins called glycosaminoglycans (GAG). The best screening test for the mucopolysaccharidoses is a fresh urine sample for GAG electrophoresis, followed by specific enzyme testing in white blood cells (WBC)/plasma and/or DNA testing. A more thorough discussion of these conditions will not be undertaken here because of limitations of space but they are summarized in Table 1 and the interested reader is directed to the further reading section of this article.

## Oligosaccharidoses

Many proteins, especially membrane surface or secreted proteins, are glycosylated by the addition of a specialized oligosaccharide side chain. These glycoproteins are recycled through the lysosomes, using a number of enzymes which break the chain at specific carbohydrate units Figure 1 illustrates where these enzymes act on the oligosaccharide side chain structure.

The clinical features of these oligosaccharidoses overlap with the mucopolysaccharidoses (summarized in Table 2). The best screening test for the oligosaccharidoses is a fresh urine sample for oligosaccharide chromatography, followed by specific enzyme testing in WBC/plasma and/or DNA testing.

## Sphingolipidoses

Just as many proteins are glycosylated, so are a number of complex lipids. The sphingolipids and glycosphingolipids (GSL) are important components of the cell membrane. Whilst sphingolipidoses can be categorized according to where the enzymes involved act in the breakdown of these complex molecules (Figure 2), from a clinical perspective the main distinction is between those disorders where there is progressive neurological deterioration and those without prominent CNS involvement. The

## Mucopolysaccharidoses

| MPS | Eponym | Enzyme | Gene | Substrate | Clinical features |
|---|---|---|---|---|---|
| I-H | Hurler | Alpha-iduronidase (severe deficiency) | *IDUA*<br>4p16.3 | Dermatan Sulphate<br>Heparan Sulphate | Coarse facial features<br>Corneal clouding<br>Dysostosis multiplex<br>Cardiomyopathy<br>Hepatosplenomegaly<br>Neurodegeneration |
| I-HS | Hurler-Scheie | Alpha-iduronidase (attenuated deficiency) | | | Dysostosis multiplex<br>Cardiomyopathy<br>Hepatosplenomegaly |
| I-S | Scheie | Alpha-iduronidase (attenuated deficiency) | | | Dysostosis multiplex |
| II | Hunter | Iduronate-2-Sulphatase | *IDS*<br>Xq27-28 | | Coarse facial features<br>Dysostosis multiplex<br>Cardiomyopathy<br>Hepatosplenomegaly<br>Neurodegeneration |
| III-A | Sanfilippo | Sulphamidase | *SGSH*<br>17q25.3 | Heparan Sulphate | Neurodegeneration<br>Behaviour problems |
| III-B | | N-acetyl glucosaminidase | *NAGLU*<br>17q21.1 | | Coarse facial features<br>(subtle) |
| III-C | | Acetyl CoA Glucosamine N-acetyl transferase | *HGSNAT*<br>8pcen | | Cardiomyopathy<br>Hepatosplenomegaly |
| III-D | | N-acetyl glucosamine-6-sulphatase | *GNS*<br>12q14 | | (mild) |
| IV-A | Morquio | N-acetyl galactosamine-6-sulphatase | *GALNS*<br>16q24 | Keratan Sulphate | Dysostosis multiplex<br>Cardiomyopathy |
| IV-B | | Beta-galactosidase | *GLB1*<br>3p22.3 | | Hepatosplenomegaly<br>(mild) |
| VI | Maroteaux-Lamy | N-acetyl galactosamine-4-sulphatase<br>(Arylsulphatase B) | *ARSB*<br>5q14.1 | Dermatan Sulphate | Coarse facial features<br>Corneal clouding<br>Dysostosis multiplex<br>Cardiomyopathy<br>Hepatosplenomegaly |
| VII | Sly | Beta-glucuronidase | *GUSB*<br>7q11.21 | Dermatan Sulphate<br>Heparan Sulphate | Coarse facial features<br>Corneal clouding<br>Dysostosis multiplex<br>Cardiomyopathy<br>Hepatosplenomegaly<br>Neurodegeneration<br>Fetal Hydrops |
| IX | Natowicz | Hyaluronidase | *HYAL1*<br>3p21.31 | Hyaluronic Acid | Skeletal dysplasia<br>Subcutaneous nodules<br>Dysmorphism (mild) |

**Table 1**

sphingolipidoses can be diagnosed by specific enzyme testing in WBC or DNA testing.

## Non-neurodegenerative sphingolipidoses

### Non-neuronopathic Gaucher disease

Gaucher disease (GD) is caused by deficiency of the glucocerebrosidase enzyme and is the commonest LSD worldwide with an incidence of around 1:50 000. The most common form, particularly in Ashkenazi Jews where the carrier frequency can reach 1 in 18, is the non-neuronopathic or Type 1 subtype which is characterized by significant splenomegaly, hepatomegaly and bone marrow involvement with pancytopenia, painful bone crises and progressive skeletal deformity (usually in adults). Unlike haematological malignancies, the degree of anaemia and thrombocytopenia usually outweigh the degree of leucopenia and this can be a useful indicator of GD. Symptoms may be relatively subtle in children and many patients are only diagnosed in adulthood, though in retrospect symptoms have usually been present in childhood.