

Inherited Metabolic Disorders



What are inherited metabolic disorders?

While inherited metabolic disorders are individually rare, they are collectively common. Single gene defects result in abnormalities in the synthesis or degradation of proteins, carbohydrates, or fats. Most are due to a defect in an enzyme or in a transport protein, resulting in a block in the way the compounds are processed by the body. Severe effects are due to the toxic accumulations of molecular debris.

Nearly every metabolic disease has several forms that vary in age of onset, clinical severity and, often, in the way they are passed on through the generations. The mode of inheritance

determines the male-to-female ratio of affected individuals. Many inherited metabolic disorders have multiple forms that differ in their mode of inheritance. For disorders caused by chromosomal changes leading to autosomal dominant and autosomal recessive inheritance the male-to-female ratio is 1:1. It is also 1:1 for chromosome X-linked dominant inheritance if transmission is from mother to child.

The diseases can affect any organ and usually affect more than one. Symptoms often tend to be non-specific and usually relate to major organ dysfunction or failure. Inherited metabolic disorders vary from acute life-threatening disease to less dangerous degenerative disorders. Their onset and severity may be exacerbated by environmental factors, such as diet and concurrent illness.

Who do inherited metabolic disorders affect?

They can occur at any time, even in adulthood. In the EU, the incidence is estimated to be 1 in 5,000 live births. The frequency for individual diseases varies based on the ethnic composition of the population, and most are very rare. The diseases can be divided into disorders of protein metabolism, into disorders of carbohydrate metabolism, and others. They tend to occur immediately after birth or in early infancy and tend to be rapidly progressive. Less severe variants usually present later in infancy or childhood and tend to be episodic. Their subtle neurological or psychiatric features often go undiagnosed until adulthood.

In this review, it is not possible to give an exhaustive summary of all disease variations. The overview concentrates on areas where there has been recent significant therapeutic progress.

Pompe's disease is a hereditary, life-threatening condition affecting between 5,000 and 10,000 people worldwide. Most affected babies die in their first year of life.

Pompe's disease belongs to the class of lysosomal storage disorders, due to deficiency of the enzyme acid maltase (an alpha-glucosidase), and causes severe muscle degeneration that affects motor skills and functions of the heart and the lung. Other examples of lysosomal storage disorders include Type B **Niemann-Pick disease** (with an extremely rare prevalence; here the enzyme defect is with acid sphingomyelinase) with spleen and liver malfunction and muscle degeneration, Gaucher's disease, Fabry's disease and mucopolysaccharidoses of various types.

Approximately 1 in 60,000 people have **Gaucher's disease**. However, among Jews of Eastern European (Ashkenazi) descent, one in 450 people will have the disorder, and the carrier rate is approximately 1 in 14. Carrier status can be detected through a simple blood test. All three types of the disease result from the deficiency of an enzyme called glucocerebrosidase, which is necessary for the breakdown of a particular fatty substance, glucocerebroside. This compound is stored abnormally, primarily in unique cells in the bone marrow, spleen and liver. Gaucher's cells in the bone marrow cause bone and joint pain and fractures. Accumulation in the spleen and liver causes enlargement of these organs as well as anaemia, easy bruising and impaired blood clotting. In a small number of patients, glucocerebroside also accumulates in the central nervous system, leading to neurological damage.

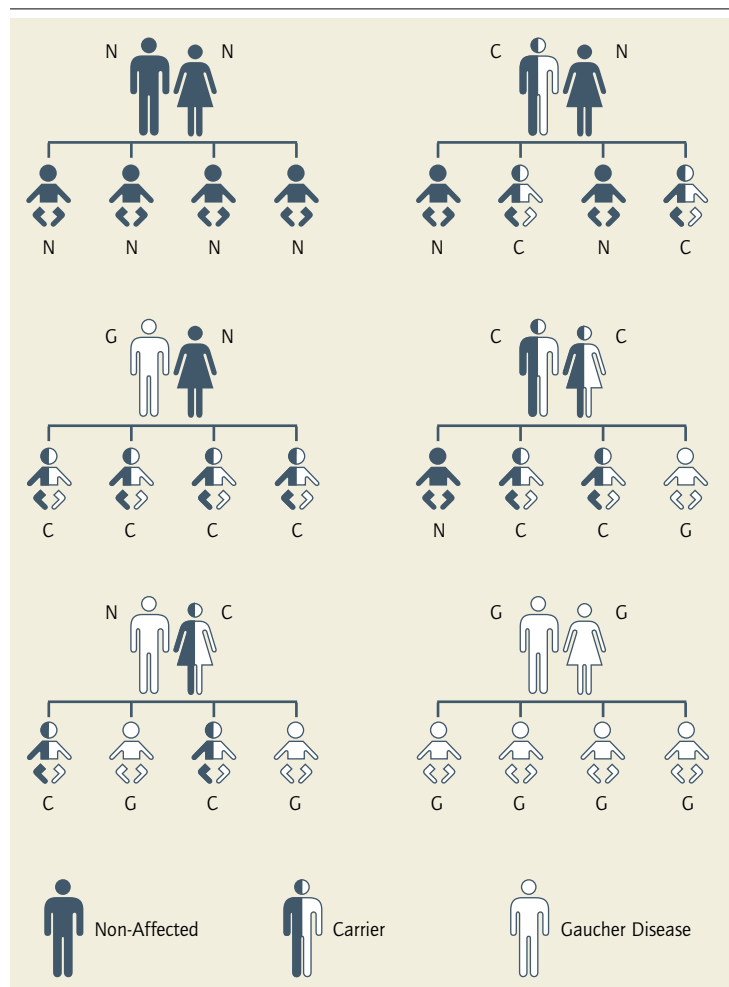
Fabry's disease is estimated to occur in 1:40,000 births and affects around 5,000 people worldwide. It results from a deficiency of the enzyme alpha-galactosidase A, which leads to the progressive accumulation of lipids within the kidney, heart and other organs. Symptoms include kidney failure, stroke, heart disease and pain. The average lifespan for patients with the disease is 50 years.

The rare inherited condition of **type 1 mucopolysaccharidosis** affects between 3,000 and 4,000 people worldwide. It is a debilitating disease caused by a deficiency of the enzyme alpha-L-iduronidase. Symptoms include progressive damage to the heart, lungs, liver and kidneys and in some cases decreased mental functions. The most severe Hurler form leads to severe mental retardation, obstructive respiratory disease and death occurs before the age of ten. Children with the less severe Scheie form have normal intelligence, less progressive physical problems but experience corneal clouding, joint stiffness and heart disease. Life expectancy in such cases lies between 20 and 30 years. Most patients are diagnosed between birth and two to three years of age.

Duchenne muscular dystrophy (DMD) is another example of a disease with a genetic defect which results in the absence of the protein dystrophin in muscle cells. The disease affects only males, with rare exceptions. Unless a boy with DMD is known to be at risk because of his family history, he is unlikely to be diagnosed before the age of two or three years. Concern may also arise because of mental retardation. Although intellectual handicap affects only a minority of patients with DMD, it is more frequent than in other children.

In the human body, the urea cycle is the metabolic pathway allowing the transformation of ammonia into urea. In children with **N-acetylglutamate synthetase**

Inherited metabolic disorders are a range of diseases caused by defective genes. Though rare, they can have devastating consequences for patients and their families. Research by the pharmaceutical industry has led to many specialised treatments. However, further improvements are still urgently needed.



Gaucher disease: heredity pattern

(NAGS) deficiency, the disorder leads to a build up of ammonia in the blood which can cause irreversible brain damage or death. The exact incidence of NAGS deficiency is unknown. Its inheritance is autosomal recessive, i.e. each parent contributes a defective gene to the child.

Present treatments:

The treatment of **Gaucher's disease** via once-weekly infusions with recombinant imiglucerase was the first therapy available for an inherited metabolic disorder. Since 2003, a glucosylceramide synthetase inhibitor has been available in the EU for the treatment of patients with mild to moderate type 1 Gaucher's disease for whom enzyme replacement therapy with imiglucerase (cerebrosidase) is unsuitable. It is the first oral therapy for the disease.

Since August 2001, an enzyme replacement therapy is also available for **Fabry's disease**. It consists of weekly infusions of agalsidase beta.

Since February 2003, the recombinant infusion product laronidase is available in the EU to treat patients with **type 1 mucopolysaccharidosis**. It has been shown that the new compound has a significant effect on pulmonary function and endurance. In patients with mucopolysaccharidosis VI, enzyme replacement therapy by weekly infusions of arylsulfatase B has been shown to offer continued benefit.

In patients with **NAGS deficiency**, carbamyl glutamate has been shown to be effective in normalising ammonia. Since 2004, it is available in Europe to treat children with NAGS deficiency.

What's in the development pipeline?

Thanks to recent achievements in understanding the causes of inherited metabolic disorders, new therapeutic approaches with recombinant compounds are being investigated. Multicentre clinical trials of enzyme replacement therapy for Pompe's disease are continuing. This involves intravenous infusions of alpha glucosidase, the enzyme missing in people with the disease.

A glucosylceramide synthetase inhibitor is also planned to be investigated in the treatment of type 3 Gaucher's disease, Niemann-Pick type C and another disorder, late-onset Tay-Sachs disease.

Researchers recently found that the protein utrophin can substitute for dystrophin, the protein implicated in Duchenne muscular dystrophy, and this avenue is being explored further.

The longer-term future:

Enzyme replacement therapy with human recombinant preparations will become available also for other rare inherited metabolic disorders. A more general approach in the long run will be the isolation of primordial cells with the potential to turn into various kinds of tissue. This would include inserting genes capable of correcting the inherited disorder to make the cell capable of producing the compound missing in the disease and transfer it to the patient.

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Chromosome 12: phenylketonuria
(metabolic disorder resulting in organ damage)