Sphingolipid Lysosomal Storage Diseases

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In 1881, Tay-Sachs disease was described as the first lysosomal storage disease. A description of Gaucher disease soon followed in 1882. Thus began the identification of a group of rare, inherited disorders that result in the accumulation of lipid compounds within the lysosome. More than 50 lysosomal storage disorders have now been identified. Most of these diseases are autosomal recessive, with a few that are X-linked recessive, and occur in about 1:8,000 cases.

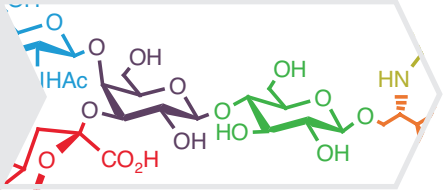
The lysosome is an organelle within the cell that is responsible for catabolizing and recycling many lipid compounds, as well as maintaining a proper balance of compounds in cells. Lysosomes have a low pH, and the enzymes present within lysosomes mostly function only in this acidic environment. Enzyme deficiencies within the lysosome result in the accumulation of various lipids, which are toxic at high concentrations.

Lysosomal storage diseases are classified according to the compounds accumulated in the lysosomes. This includes sphingolipidoses, oligosaccharidoses, mucolipidoses, mucopolysaccharidoses, lipoprotein storage disorders, lysosomal transport defects, and neuronal ceroid lipofuscinoses. Because the lysosome lacks sufficient enzyme activity to metabolize a particular lipid compound, substrates in lysosomes accumulate. Disease can also result from an inability to transport a particular lipid out of the lysosome. Both of these issues stem from specific mutations in an enzyme's gene code.

For many years, lysosomal storage diseases were untreatable, but now, with a clearer understanding of the mechanisms involved, several effective therapies have been developed. There are two approaches to treating these diseases: replacing the defective enzymes or inhibiting the synthesis of the accumulated lipid. The most promising and most common treatment is enzyme replacement therapy (ERT). However, this treatment is very expensive and requires the transport of enzymes across the blood-brain barrier. This limits the effectiveness of ERT in cases involving the central nervous system (CNS). Another treatment in development is stem cell transplantation, either on its own or along with ERT. However, bone marrow transplant has limited applications and cannot be applied to as many cases as ERT. A third treatment option, inhibiting the synthesis of the accumulated lipid, has seen some success in treating type I Gaucher disease by reducing the synthesis of glucosylceramide. However, this affects the synthesis of other downstream lipids, which are also critical for cellular functions. It appears that, due to the complexity of the diseases encountered, a combination of therapeutic approaches will be needed.

Sphingolipidoses (sphingolipid lysosomal storage disorders) result in an accumulation of various sphingolipids in the lysosome. Ten main sphingolipidoses affect the glycosphingolipid pathway: Farber's, Krabbe, Gaucher, Metachromatic Leukodystrophy, Fabry, Sandhoff, Niemann-Pick, Sialidosis, Tay-Sachs, and GM_1 gangliosidosis. All of these disorders are characterized by an accumulation of sphingolipids in the lysosome due to enzyme deficiency or ineffective transport of lipids from the lysosome.

Turn to the next page to view sphingolipidoses pathways detailing the enzymes associated with these disorders and the sphingolipid products they produce.



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LYSOSOMAL STORAGE DISEASE BIOMARKERS

Sphingosine and Ceramide Accumulation

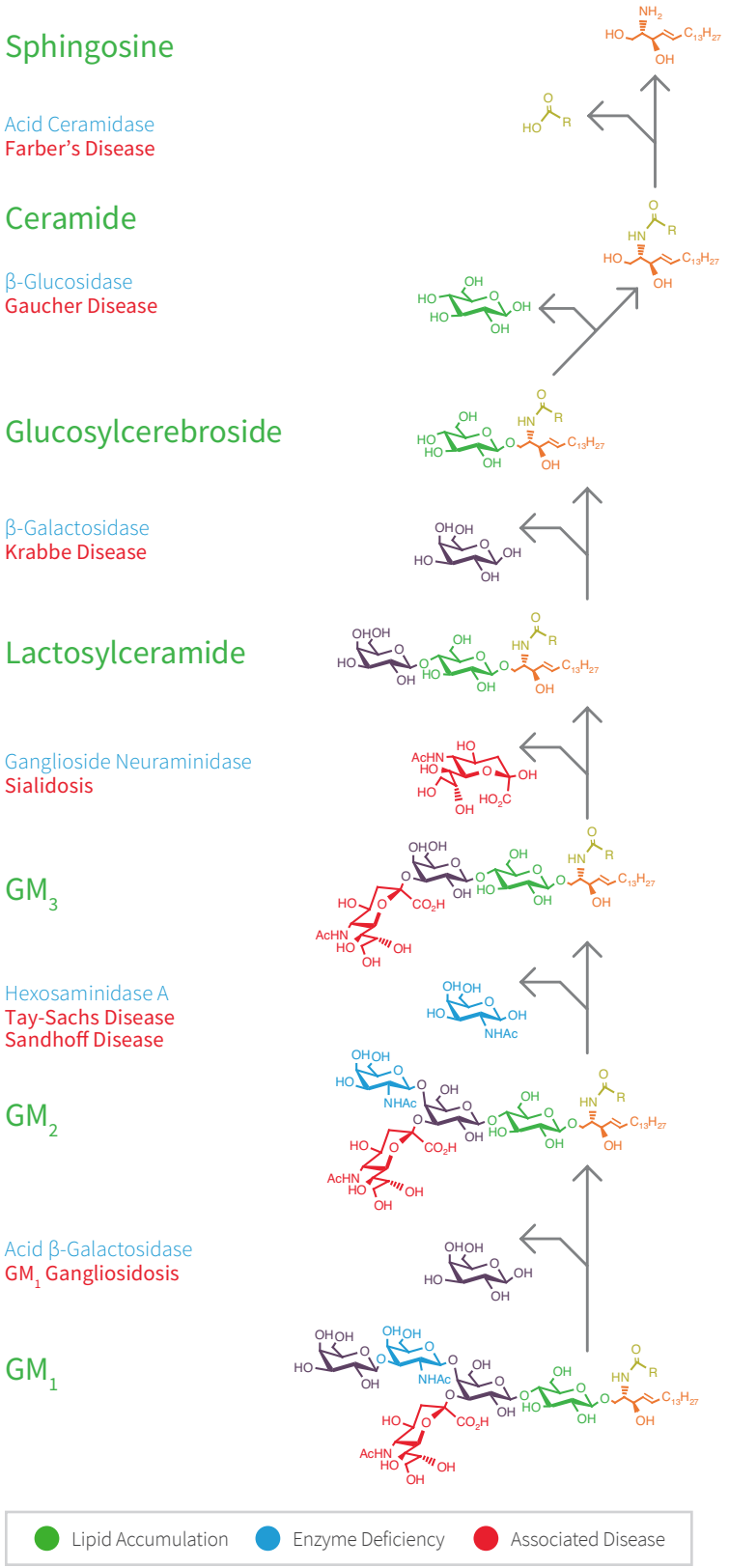
Catalog No.	Product Name
1802	D-*erythro*-Sphingosine
2079	D-*erythro*-Sphingosine, D_9
1618	N-Dodecanoyl-NBD-D-*erythro*-sphingosine
2038	N-Heptadecanoyl-D-*erythro*-sphingosine
2081	N-Hexanoyl-biotin-D-*erythro*-sphingosine
1841	N-Hexanoyl-NBD-D-*erythro*-sphingosine
2201	N-*omega*-CD_3-Octadecanoyl-D-*erythro*-sphingosine

Glucosylceramide Accumulation

Catalog No.	Product Name
1522	Glucocerebrosides, plant
1521	Glucocerebrosides, buttermilk
1057	Glucocerebrosides, Gaucher's spleen
1306	Glucosylsphingosine, buttermilk
1310	Glucosylsphingosine, plant
2086	Glucosylsphingosine, synthetic
1533	N-*omega*-CD_3-Hexadecanoyl-glucopsychosine
2085	N-Hexanoyl-biotin-glucosylceramide
1622	N-Hexanoyl-NBD-glucosylceramide
2089	N-Glycinated glucosylsphingosine

Galactosylceramide Accumulation

Catalog No.	Product Name
1050	Cerebrosides, bovine
1633	N-Dodecanoyl-NBD-galactosylceramide
2091	N-Glycinated galactosylsphingosine
2203	N-Hexanoyl-biotin-galactosylceramide
1621	N-Hexanoyl-NBD-galactosylceramide
1914	N-Octadecanoyl-D_{35}-psychosine, (perdeuterated, C18:0 fatty acid)
1335	N-Pentadecanoyl-psychosine
1305	Psychosine (free amine form)
2087	Psychosine, synthetic



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Lactosylceramide Accumulation

Catalog No.	Product Name
1500	Lactosylceramides, porcine RBC
1507	Lactosylceramides, bovine buttermilk
1517	*lyso*-Lactosylceramide (bovine buttermilk)
2088	*lyso*-Lactosylceramide, synthetic
2090	N-Glycinated lactosylsphingosine
2205	N-Hexanoyl-biotin-lactosylceramide
1534	N-*omega*-CD_3-Hexadecanoyl-lactosylceramide
1629	N-Hexanoyl-NBD-lactosylceramide
1630	N-Dodecanoyl-NBD-lactosylceramide

Ceramide Trihexoside (Globotriaosylceramide) Accumulation

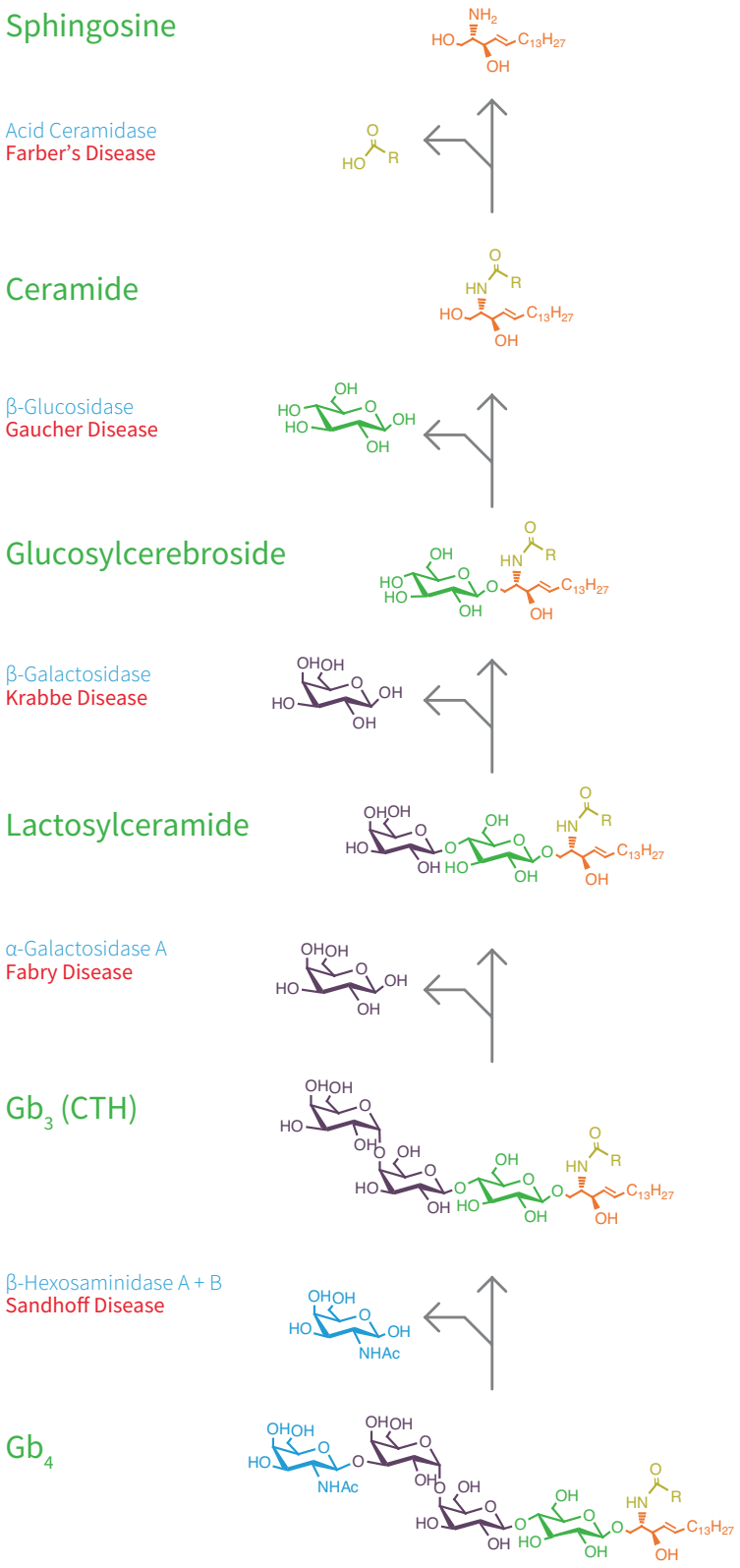
Catalog No.	Product Name
1067	Ceramide trihexosides; Gb_3 (porcine)
1520	*lyso*-Ceramide trihexoside
1631	N-Dodecanoyl-NBD-ceramide trihexoside
1530	N-Glycinated *lyso*-ceramide trihexoside
1523	N-Heptadecanoyl-ceramide trihexoside
1537	N-*omega*-CD_3-Octadecanoyl-ceramide trihexoside

Globoside Accumulation

Catalog No.	Product Name
1068	Globosides (porcine)

Ganglioside Accumulation

Catalog No.	Product Name
1061	Monosialoganglioside GM_1 (NH_4^+ salt)
1518	*lyso*-Monosialoganglioside GM_1 (NH_4^+ salt)
2050	N-*omega*-CD_3-Octadecanoyl monosialoganglioside GM_1 (NH_4^+ salt)
2053	N-Hexanoyl-biotin-monosialoganglioside GM_1
2051	N-*omega*-CD_3-Octadecanoyl monosialoganglioside GM_2 (NH_4^+ salt)
2052	N-*omega*-CD_3-Octadecanoyl monosialoganglioside GM_3 (NH_4^+ salt)
2054	N-*omega*-CD_3-Octadecanoyl disialoganglioside GD_3
2055	N-Hexanoyl-biotin-disialoganglioside GD_3



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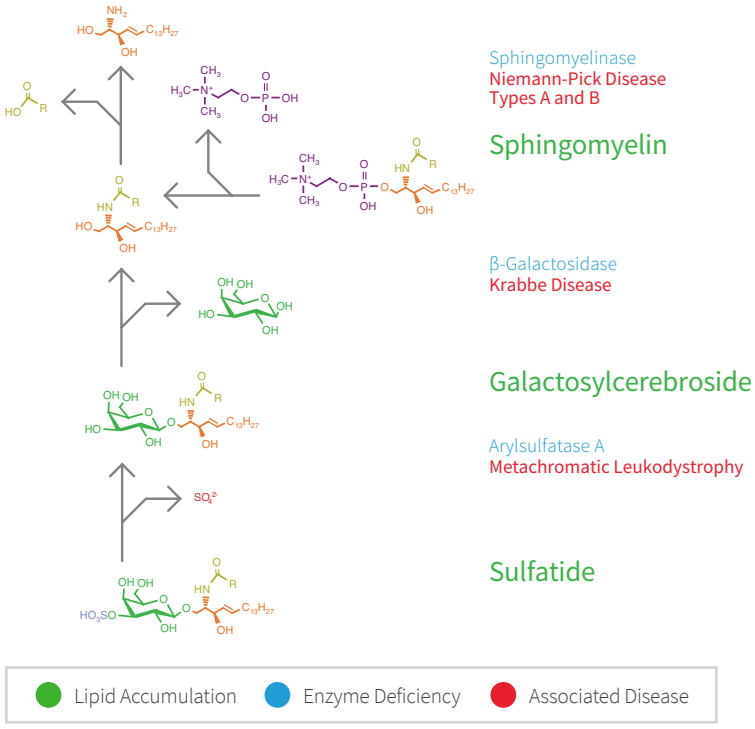
Sphingosylphosphorylcholine Accumulation

Catalog No.	Product Name
1318	D-*erythro*-Sphingosylphosphorylcholine
1619	N-Dodecanoyl-NBD-sphingosylphosphorylcholine
1890	N-Heptadecanoyl-sphingosylphosphorylcholine
2200	N-1-^{13}C-Hexadecanoyl-D-*erythro*-sphingosylphosphorylcholine
1912	N-Hexanoyl-NBD-sphingosylphosphorylcholine

Sulfatide Accumulation

Catalog No.	Product Name
1049	Sulfatides (bovine)
1904	*lyso*-Sulfatide (NH_4^+ salt)
1632	N-Dodecanoyl-NBD-sulfatide
2092	N-Glycinated *lyso*-sulfatide
2207	N-Hexanoyl-biotin-sulfatide
1536	N-*omega*-CD_3-Octadecanoyl-sulfatide



DISEASE CHARACTERISTICS

Farber's Disease

- Excess lipid: ceramides
- Enzyme deficiency: ceramidase
- Systems affected: various organs and CNS
- Potential therapy: hematopoietic stem cell transplant

Fabry Disease

- Excess lipid: globotriaosylceramide (CTH)
- Enzyme deficiency: α-galactosidase A
- Systems affected: CNS and heart

Niemann-Pick Disease Types A and B

- Excess lipid: sphingomyelin
- Enzyme deficiency: sphingomyelinase
- Systems affected: neurons and organs

GM_1 Gangliosidosis

- Excess lipids: ganglioside GM_1 and asialoganglisoide GM_1
- Enzyme deficiency: β-galactosidase
- System affected: CNS
- Potential therapy: ERT and substrate reduction

Krabbe Disease

- Excess lipids: galactosylcerebroside and psychosine
- Enzyme deficiency: β-galactosidase
- Systems affected: myelin sheath and axons
- Potential therapy: bone marrow transplant

Sandhoff Disease

- Excess lipids: globoside and monosialoganglioside GM_2
- Enzyme deficiency: β-hexosaminidase A and B activity
- System affected: CNS
- Potential therapy: glycolipid inhibitors or viral vectors

Sialidosis

- Excess lipid: gangliosides; sialic acid-rich glycoproteins and oligosaccharides
- Enzyme deficiency: α-N-acetyl neuraminidase
- System affected: nervous system

Tay-Sachs Disease

- Excess lipid: ganglioside GM_2
- Enzyme deficiency: β-hexosaminidase A
- System affected: CNS
- Potential therapy: ERT

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