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Neuropathic Lysosomal Storage Disorders

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Abstract

The lysosomal storage disorders (LSDs) are a clinically heterogeneous group of inborn errors of metabolism, associated with the accumulation of incompletely degraded macromolecules within several cellular sites. Affected individuals present with a broad range of clinical problems, including hepatosplenomegaly and skeletal dysplasia. Onset of symptoms may range from birth to adulthood. The majority are associated with neurological features, including developmental delay, behavioral/psychiatric disturbances, seizures, acroparesthesia, motor weakness, cerebrovascular ischemic events and extra-pyramidal signs. It should be noted that later-onset forms are often misdiagnosed as symptoms, which might include psychiatric manifestations, are slowly progressive and may precede other neurologic or systemic features. Inheritance is primarily autosomal recessive. For all subtypes, diagnosis can be confirmed using a combination of biochemical and/or molecular assays. In a few LSDs, treatment with either hematopoietic stem cell transplantation, enzyme replacement or substrate reduction therapy is available. Genetic counseling is important, so patients and their families can be informed of reproductive risks, disease prognosis and therapeutic options. Investigations of disease mechanisms are providing insights into potential therapeutic approaches. Symptomatic care, which remains the mainstay for most subtypes, can lead to significant improvement in quality of life.

Keywords

lysosomal storage disorders; stroke; myopathy

Introduction

Definition

The lysosome is a subcellular organelle with an acidified milieu, wherein metabolites that are generated as a byproduct of cellular turnover are directed for degradation (1). Deficiency

of a particular enzyme or its co-factor results in the accumulation of various substrates within the lysosome, which initiate a cascade of cellular events including aberrant inflammatory and apoptotic responses. Affected individuals may present with clinical signs of tissue storage, such as hepatosplenomegaly or cardiomyopathy, although these may not be evident in those with predominant neuropathic involvement, in whom developmental delay and subsequent regression develop (2, 3). Neuronopathic subtypes, particularly those without overt visceral signs, are often associated with delayed or missed diagnoses, particularly in adult-onset cases and in the absence of a family history. Table 1A and B lists the various LSDs, the underlying gene affected and its respective *locus*.

Symptoms and Clinical Course

The LSDs are mainly chronic conditions, and clinical problems may evolve over years to decades. In contrast to other inborn errors of metabolism due to defects in intermediate metabolism (such as amino acidopathies, organic acidurias and fatty acid oxidation defects), the onset of symptoms in LSDs has no temporal relationship to diet or the fasting state.

Age of onset can be broad, with non-immune hydrops evident at birth, ataxia or spasticity in childhood, and stroke in a young adult without any antecedent risk factors (*e.g.*, hypertension, atherosclerosis). Clinical signs, such as the cherry red spot (Table 2) or leukodystrophy evident on brain MRI, serve as clues to particular clinical forms. Deafness can be a feature of LSDs, and can be conductive, sensorineural, or a combination, with involvement of cochlea and CNS dysfunction.

Extra-neurologic findings can also be instructive, *e.g.*, cardiomyopathy in an infant with hypotonia (Pompe disease) or young adult with Fabry disease. Table 3 lists several clinical features associated with particular LSDs. As noted, there often is multisystemic disease, following a pattern often reflecting the tissue sites of substrate storage.

Late-onset forms of G_{M2} -gangliosidosis and MLD may present with impaired intellectual function, emotional lability, hallucinations and delusions that may initially be attributed to a psychiatric diagnosis (4, 5).

Nature of Disease

Although individually infrequent to rare, collectively the LSDs have a combined prevalence of approximately 1 in 2,000 (6, 7). Certain entities are overrepresented in particular populations, such as the Ashkenazi Jews (of Central and Eastern European descent) and Finnish ancestry, as a consequence of founder effect (see Table 4) (8).

Clinical Findings

Physical Examination

Non-immune hydrops fetalis (NIHF) may be evident at birth in several conditions (Table 5) (9). Dysmorphic features may develop in childhood, primarily in the mucopolysaccharidoses (MPS) and oligosaccharidoses, although these can be subtle in attenuated cases (10). However, the majority of conditions, particularly those with predominant neurologic involvement, are not associated with distinctive facies. In these cases, affected children may

display developmental delay, speech problems and/or ataxia. Peripheral neuropathy can also be a problem, and tissue infiltration in the MPS and oligosaccharidoses can lead to carpal tunnel syndrome or a radiculopathy (11, 12). In patients with certain later onset LSDs, psychiatric features may be a presenting complaint (13).

Imaging

Leukodystrophy predominantly is seen in arylsulfatase A deficiency (metachromatic leukodystrophy, MLD) and Krabbe disease (globoid cell leukodystrophy, GLD), Figure 1. Interest in understanding the natural history of disease and investigations of potential therapies has prompted development of brain disease MRI severity scoring systems for both MLD (Eichler *et al.* (14)) and for GLD (Loes *et al.* (15)). These scoring systems were based on the evolution and severity of brain MRI findings observed in X-linked adrenoleukodystrophy (peroxisomal disorder) (16). In nine infants with GLD, correlations have been shown between neurodevelopmental features (i.e., mental development, gross and fine motor dysfunction) and total Loes score (15).

Other Diagnostic Modalities

Skeletal X-rays of the thoracolumbar spine and long bones reveal a constellation of findings (*dysostosis multiplex*) in patients with MPS and oligosaccharidosis, Figure 2. Odontoid hypoplasia can also be a feature in these disorders (3). Hepatosplenomegaly, detectable by ultrasound or palpation is seen in Gaucher and Niemann-Pick A, B and C diseases (10). Cardiomyopathy, detectable by echocardiography, is encountered in infantile Pompe, Fabry and Danon diseases (17–19).

Disease Pathology

Until recently, the LSDs were classified according to the nature of the substrate accumulation (i.e., glycosphingolipid, glycosaminoglycans, etc.), which could be measured in samples obtained during the diagnostic work-up, *e.g.* liver or bone marrow tissue, serum, urine. Characterization of the underlying gene defects and molecular basis has enabled the introduction of a molecular classification (*e.g.*, enzyme deficiency, transport defect, etc.).

Genetics

Genetic Basis of Disease

The primary defect can arise in a gene that encodes a hydrolytic enzyme or its co-factor/activator (Figure 3). Alternatively, the mutated gene may encode a transmembrane protein involved with substrate transport or vesicle fusion (1). Occasionally, the defect may involve a protein required for post-translational modification of a lysosomal enzyme/protein; consequently, the target protein may be non-functional (*e.g.* SUMF-1, formylglycine-generating enzyme, critical for the introduction of formylglycine residue in sulfatases), prematurely degraded (neuraminidase, which is part of a multiunit complex including protective protein or cathepsin A) or mistargeted (*e.g.*, GNPTAB in I-cell disease, resulting in a defect of post-translation modification/glycosylation, required as most lysosomal enzymes rely on mannose-6-phosphate residues for lysosomal targeting or delivery).

The LSDs are transmitted as autosomal recessive traits, except for three X-linked disorders: Fabry, Danon and Hunter syndrome (MPS-II). Hunter syndrome only affects males, except for unusual female carriers who either also have Turner syndrome (45,X) or an X-autosome translocation wherein the functional X-chromosome happens to bear a mutation of the *IDS* gene encoding iduronate-2-sulfatase (20). Males and females with a mutation of either the *GLA* gene which encodes α -galactosidase (deficient in Fabry disease) or the *LAMP2* gene, which encodes the lysosomal-associated membrane protein-2 (defective in Danon disease), show characteristic clinical features encountered in affected males. However, age of symptom onset and disease severity can be highly variable among female patients.

Molecular Pathogenesis

Deleterious alleles cause the complete obliteration of enzyme or protein function, which leads to early onset cases associated with rapid progression and death in infancy or early childhood. Alleles generating a protein with residual function enable a sub-acute or chronic disease course. In these latter cases, lifespans can extend into decades (10). However, genotype-phenotype correlations are often imperfect, particularly in insidious cases, and there remains incomplete understanding of factors that modify clinical course. In terms of lysosomal hydrolases, in general, a specific critical threshold, below which symptoms have been observed, has been determined (varying between 10–25%) (21, 22).

Previously, loss of enzyme function was largely attributed to mutations which inactivated the catalytic site or resulted in a gene product subjected to nonsense mediated decay or a highly unstable or truncated non-functional protein. However, several studies have shown that certain mutations can result in misfolding of the nascent protein that is subsequently diverted away from the lysosome by its premature elimination via endoplasmic reticulum (ER) associated degradation (ERAD). This pathway diverts misfolded and unstable proteins in the course of their ER synthesis towards the ubiquitin-proteasome system (UPS) in the cytoplasm (23). These observations are of particular interest, in relation to potential therapeutic approaches such as the use of pharmacologic chaperones and agents that influence proteostasis regulation (*see below*).

Although substrate accumulation and the resultant altered trafficking and recycling of various metabolites may represent the initial insult to cells, several studies have shown a cascade of pathologic events (See Table 6) (24–27). It is likely an interplay of factors contribute to disease expression, but the mechanistic links between underlying gene defect and clinical manifestations have not been fully elucidated. For a subset of the sphingolipidosis, the deacylated (psychosine) forms of the primary accumulating substrate might mediate cellular toxicity. For instance, in Fabry disease studies have shown the presence of globotriaosylsphingosine (LysoGb3), which may have a role in the development of increased carotid intima-media thickness and altered brachial flow-mediated dilation. Additionally, altered vascular reactivity and a prothrombotic state may contribute to the increased risk for stroke in these patients.

Of various mechanisms, recent interest has focused on the inhibition of autophagy; in particular its role in Pompe disease, which is a LSD caused by α -glucosidase (GAA) deficiency and characterized by an accumulation of autophagosomes in muscles and tissue

wasting. Interestingly, in late onset cases (acid maltase myopathy) a correlation has been demonstrated among autophagy impairment (assessed by monitoring expression of p62-containing protein aggregates), the degree of muscle fiber atrophy and disease progression (28). Also, defects of autophagy appear to also compromise the uptake and delivery to the lysosome of recombinant GAA, which might adversely influence therapeutic outcome (29). Reactivation of autophagy *in vitro* contributes to GAA maturation in both healthy and diseased myotubes.

A gene-expression array analysis of brain tissue obtained from the MPS VII knockout mouse ($\text{gus}^{\text{mps}}/\text{gus}^{\text{mps}}$) revealed several alterations including up-regulation of key components of the immune system along with those related to inflammatory response (30). In the MPS-IIIB mouse model, there was down-regulation of major oligodendrocyte-related genes, indicating defects in myelination, and perturbations in multiple developmental genes (31–33). The variation in gene dysregulation observed between brain regions in these mouse models indicates that different neuropathologic mechanisms may predominate within specific regions of a diseased brain, which may translate in differentiating neurological symptoms and signs (30).

Relevant Disease Models

Several animal models, including spontaneously occurring and those generated by recombinant genetic techniques have been described. These models have been invaluable in understanding underlying disease mechanisms, particularly pre-symptomatic changes. For instance: During myelination, galactosylation of sphingosine produces psychosine which is catalyzed by UDP-galactose:ceramide galactosyltransferase (i.e., the Cleland-Kennedy pathway) (34). Physiologically, the low level of psychosine produced is rapidly degraded by GALC (35). In the setting of GALC deficiency (Krabbe disease), psychosine levels are elevated in the brain (36). At high levels, psychosine becomes cytotoxic, particularly to oligodendrocytes (myelin-forming neural cells), resulting in apoptosis and extensive demyelination observed in brain imaging studies of Krabbe disease patients (35). In the *Twitchee*, naturally occurring Krabbe disease mouse model, psychosine has been shown to induce the dephosphorylation of neurofilaments by deregulation of two serine/threonine phosphatases (PP1 and PP2A) (37). Studies involving several mouse models of distinct LSDs affecting the sphingolipid metabolism (i.e., sphingolipidoses, such as G_{M1} - and G_{M2} -gangliosidosis) have revealed elevated levels of pro-inflammatory cytokines (tumor necrosis- α , interleukin-1 β) (38).

Moreover, proof of therapeutic potential has been shown in preclinical studies involving several animal models prior to drug introduction in human clinical trials. However, results of studies in animal models should be interpreted with caution, as occasionally, a particular mouse model may not mimic disease in humans even when biochemical or histological changes may be present, because of an alternative metabolic pathway or incompletely understood reasons (39).

Evaluation and Management

Strategies for Diagnosis

In suspected cases, diagnosis of a specific LSD can be readily confirmed by a biochemical and/or molecular assay, using cells derived from peripheral blood. Testing is available through specialized laboratories (listed in *Genetests*; <http://www.ncbi.nlm.nih.gov/sites/GeneTests/>). Special considerations: ARSA pseudo-deficiency is found in 10–15% of individuals in the general population, which can lead to diagnostic errors; rare cases of Saposin deficiency may be missed and usually requires screening for elevated levels of the substrate in body fluids and molecular analysis. Characterization of the putative gene defect, as the cause of a particular LSD, is increasingly available and molecular confirmation of the diagnosis is ideally undertaken, prior to any therapeutic intervention.

Newborn screening aimed at the identification of inborn errors of metabolism has largely focused on the amino acidopathies and organic acidurias, including fatty acid oxidation defects. The availability of treatment has led to development of guidelines for managing patients with selected LSDs, potentially including screening of newborns and high-risk populations.

Current Management and Therapeutic Options

Genetic counseling is central to management of affected individuals and their relatives. Geneticists\counselors often facilitate the multi-disciplinary care required by patients, and can arrange carrier\prenatal testing for individuals\couples at risk.

Symptomatic treatment remains the only option for most LSDs. For certain disorders, such as the MPS physical and occupational therapy are components of a comprehensive program to facilitate performance of activities of daily living. Special precautions are necessary in children with MPS who need anesthesia, because of risks associated with cardiopulmonary disease and cervical manipulation in cases with odontoid hypoplasia (40, 41). Pulmonary assistance (BiPAP or CPAP) provides significant relief for patients with MPS and sleep apnea, and for those with both infantile and late onset Pompe disease who suffer from intercostal and diaphragmatic muscle weakness (42, 43). Adjunctive therapies to control seizures, behavioral and sleep problems, which can be challenging concerns, help improve patient quality of life. Anti-platelet agents and lipid lowering drugs, in conjunction with ERT in Fabry disease may reduce the risk for cerebrovascular events (44).

Disorders caused by a deficiency of an enzyme or soluble protein may be modifiable by cellular; i.e., hematopoietic stem cells transplantation (HSCT) or protein\recombinant enzyme replacement therapy. Microglia derived from donor stem cells can penetrate the blood brain barrier (BBB) and secrete functional enzyme. In MPS-I (Hurler syndrome), HSCT results in stabilization or improvement of cognitive function (45, 46); in patients with infantile Krabbe disease (KD), HSCT prolongs survival when undertaken in the first weeks of life (47). However, follow up studies indicate >80% of transplanted KD infants who survive beyond age 2 years experience some degree of motor difficulty (48). Skeletal dysplasia in the MPS is not fully corrected by HSCT, although there are indications of a

positive effect on odontoid hypoplasia (45). To obtain maximal enzyme activity following HSCT, donor cells should be derived from non-carriers (46).

Enzyme replacement therapy (ERT) has been shown to modify disease course in various LSDs, but not alter ultimate neurologic prognosis in severe subtypes (e.g., Hunter syndrome, neuropathic Gaucher disease) (49). In patients with infantile Pompe disease, ERT enables the resolution of cardiomyopathy and increased survival, except for those with high antibody titers in whom prognosis remained guarded to poor (50). Among survivors, cognitive development at school age ranged between normal and mildly delayed (50). In a study including 38 adult patients with late onset Pompe disease receiving alglucosidase alfa for 36-months, ERT led to improvement in physical endurance (as measured by the 6-minute walk test) and stabilization of forced vital capacity (51).

In a proportion of ERT-treated patients, antibodies can develop against recombinant enzymes that might neutralize the activity of the infused protein or interfere with its cellular uptake. Long term studies are required to establish the full efficacy of ERT and its impact on health-related quality of life (52, 53).

Substrate reduction therapy (SRT) is available for certain glycosphingolipidoses, wherein the use of a small molecular agent (miglustat in Gaucher disease and Niemann-Pick disease type C (NPC)) has been shown to inhibit precursor synthesis, reduce tissue substrate burden and alter the rate of disease progression (54). Other approaches, such as the use of pharmacologic chaperones (migalastat in Fabry disease) or agents that influence proteostasis regulation and gene therapy are under investigation (55).

Investigations of misfolding mutant protein suggest potential rescue by pharmacologic chaperones which mimic the natural substrate and act as templates to facilitate proper enzyme folding and its subsequent transit to the lysosome; wherein the higher affinity of the substrate displaces the drug, partially restoring intralysosomal enzyme activity (56–58). In addition, a potentially complementary approach involves the use of drugs which influence proteostasis regulation (59). Significant increases of glucocerebrosidase activity were obtained with the use small molecule inhibitors of histone deacetylase that cross the BBB. Gene therapy is the subject of investigations (60).

Future Directions in Therapy and Diagnosis

Newborn screening aimed at the identification of inborn errors of metabolism have largely focused on conditions that are largely modifiable by dietary modification and/or vitamin/co-factor supplementation. These therapeutic options are not applicable to LSDs, but the increasing availability of approaches such as ERT have led to advocacy for incorporating some these disorders in an expanded NBS program. In the State of NY, screening for Krabbe disease was introduced in 2006, which has enabled consideration of HSCT for affected infants and prenatal diagnosis for future pregnancies in couples at risk. (61).

A major challenge in the development of treatment for neuropathic LSD is drug delivery across the blood brain barrier (BBB), and additionally the likelihood there are disease mechanisms not modifiable by administration of exogenous enzyme or protein. In this

setting, small molecule pharmacological agents are more likely to penetrate the BBB and allow the manipulation of specific upstream (*e.g.* reduction of substrate synthesis) and downstream pathways (*e.g.* autophagy disturbances) potentially influence disease outcome. Deleterious cellular events precede the onset of clinical symptomatology, and thus early diagnosis and intervention will be a key to achieving an optimal outcome.

Therapeutic approaches under consideration include HSCT with autologous cells that have been genetically modified to constitutively express supra-physiological enzyme levels. Additionally, trials with recombinant enzyme administered intravenously and intrathecally have been undertaken or are on-going (62). Gene therapy with oligodendroglial, neural progenitor, embryonic and microencapsulated recombinant cells is also under investigation.

Summary

The LSDs are chronic disorders that can have a significant impact on quality of life and lead to shortened lifespans, particularly in the subtypes associated with neuropathic involvement. A high index of suspicion should be maintained, even when signs (*e.g.*, hepatosplenomegaly) suggestive of a storage disorder are not evident. Developmental delay, behavioral and/or psychiatric problems may be presenting symptoms. Diagnosis can be confirmed in all LSDs, by biochemical and/or molecular testing; which is essential for appropriate genetic counseling and management. Treatment is available for several, and studies are on-going to expand the therapeutic options for disease control.

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Box 1**LSDs associated with Non-immune *hydrops fetalis***

- Farber disease
- Galactosialidosis
- Gaucher disease type 2
- GM1-gangliosidosis
- I-cell disease
- MPS types IV and VII
- Niemann-Pick types A and C
- Sialidosis type II
- Salla disease and ISSD
- Wolman disease

Box 2**Pathologic events in LSDs[#]**

- Accumulation of primary substrates and secondary metabolites
- Increased lysosomal membrane permeability
- Altered lysosomal pH
- ER stress and unfolded protein response activation
- Oxidative stress
- Altered calcium homeostasis
- Autophagy impairment^{*}
- Inflammation, microglial activation
- Apoptosis

[#]Reviewed in ref #24.

^{*}Autophagy is a highly conserved homeostatic process for lysosome-mediated degradation of cytoplasmic components, including damaged organelles and toxic protein aggregates (27).

Key Points

- Patients with a LSD may present with neurologic problems, such as developmental delay, myoclonic seizures, ataxia or stroke, and the absence of features (e.g., hepatosplenomegaly) suggestive of an underlying storage disorder may lead to misdiagnosis.
- Diagnosis can be readily confirmed by blood tests, although testing may be limited to specialized laboratories.
- Carrier testing and pre-implantation or prenatal diagnosis are available option for carrier couples at risk of having an affected child.
- Treatment is available for certain subtypes and early diagnosis and intervention is critical in enabling optimal outcomes. Although ultimate neurologic prognosis may not be fully modified, available therapies can improve quality of life.
- Elucidation of pathophysiology is shedding light on disease mechanisms that may be broadly applicable to the understanding of more common disorders, such as Parkinson disease and other neurodegenerative disorders.
- Several novel therapeutic strategies, such as substrate reduction therapy, use of pharmacologic chaperones and gene therapy, are being pursued to expand the number of potentially treatable conditions.

Figure 1. Leukodystrophic LSDs, Brain MRI

In metachromatic leukodystrophy (MLD) and globoid-cell leukodystrophy (GLD), there is progressive CNS demyelination. (A and B) A 22-month old girl diagnosed with MLD who presented with global psychomotor delay and fronto-occipital periventricular demyelination on imaging. (C) A 26-year old man with late-onset MLD who presented with behavioral disturbances, initially diagnosed with schizophrenia. Diffuse periventricular T2 hyperintensity extending into U-fibers was noted, associated with cerebral atrophy. (D–F) A 61-year old man diagnosed with GLD who presented with late-onset gait problems evolving to spastic paraparesis. Brain MRI showed typical parietal occipital T2 hyperintensity bilaterally with extension to temporal white matter and basal ganglia.

Figure 2. Multiplex dysostosis associated with mucopolysaccharidosis (MPS)

(A) Broadened clavicles and ribs. (B) Short and thin metacarpals with proximal tapering and distal erosions of middle and distal phalanges. (C) Shallow and wider acetabuli, which may result in subluxation or dislocation of the femoral heads. (D) Gibbus deformity, with anterior wedging, retrolisthesis of the apex vertebrae at the thoracolumbar transition.

Figure 3. Sphingolipid molecular structures and their degradation pathway

The sphingolipids consist in a ceramide molecule attached to a long-chain sphingoid base (sphingosine), which is bound to a long-chain fatty acid. The degradation of specific sphingolipids requires specific enzymes, which are depicted here in each step of the pathway. The correspondent lysosomal storage disease (underlined) associated with each enzyme (italic) is also shown. Some the lysosomal enzymes need co-factors called sphingolipid activator proteins for the catalysis of their specific substrates. Examples of these co-factors are a group of proteins called saponins (Sap), here described as Sap A, B, C and D.

Table 1

Enzyme-deficiency LSDs, classified according to primary substrate storage

Disease	Defective protein	Main storage materials	Gene and locus	OMIM
Sphingolipidoses				
Fabry	α -Galactosidase A	Globotriasylceramide	<i>GLA</i> Xq22	301500
Farber	Acid ceramidase	Ceramide	<i>ASAHI</i> 8p22	228000
Gangliosidosis G _{M1} (Types I, II, III)	G _{M1} - β -galactosidase	G _{M1} ganglioside, Keratan sulphate, oligos, glycolipids	<i>PSAP</i> 10q22.1	230500 230600 230650
Gangliosidosis G _{M2} , Tay-Sachs Variant	β -Hexosaminidase A	G _{M2} ganglioside, oligos, glycolipids	<i>HEXA</i> 15q23	272800
Gangliosidosis G _{M2} , Sandhoff Variant	β -Hexosaminidase A + B	G _{M2} ganglioside, Oligos, glycolipids	<i>HEXB</i> 5q13	268800
Gaucher (Types I, II, III)	Glucosylceramidase	Glucosylceramide	<i>GBA</i> 1q21	230800 230900 231000
Krabbe	β -Galactosylceramidase	Galactosylceramide	<i>GALC</i> 14q31.3	245200
Metachromatic Leukodystrophy	Arylsulphatase A	Sulphatides	<i>ARSA</i> 22q13.33	250100
Niemann-Pick (type A, type B)	Sphingomyelinase	Sphingomyelin	<i>SMPD1</i> 11p15.4	257200 607616
Mucopolysaccharidoses (MPSs)				
MPS I (Hurler, Scheie, Hurler/Scheie)	α -Iduronidase	Dermatan sulphate, heparan sulphate	<i>IDUA</i> 4p16.3	607014 607015 607016
MPS II (Hunter)	Iduronate sulphatase	Dermatan sulphate, heparan sulphate	<i>IDS</i> Xq28	309900
MPS III A (Sanfilippo A)	Heparan sulphamidase	Heparan sulphate	<i>SGSH</i> 17q25.3	252900
MPS III B (Sanfilippo B)	Acetyl α -glucosaminidase	Heparan sulphate	<i>NAGLU</i> 17q21.2	252920
MPS III C (Sanfilippo C)	Acetyl CoA: α -glucosaminide N-acetyltransferase	Heparan sulphate	<i>HGSNAT</i> 8p11.21	252930
MPS III D (Sanfilippo D)	N-acetyl glucosamine-6-sulphatase	Heparan sulphate	<i>GNS</i> 12q14.3	252940
MPS IV A (Morquio A)	Acetyl galactosamine-6-sulphatase	Keratan sulphate, chondroitin 6-sulphate	<i>GALNS</i> 16q24.3	253000
MPS IV B (Morquio B)	β -Galactosidase	Keratan sulphate	<i>GLB1</i> 3p22.3	253010
MPS VI (Maroteaux-Lamy)	Acetyl galactosamine 4-sulphatase (arylsulphatase B)	Dermatan sulphate	<i>ARSB</i> 5q14.1	253200
MPS VII (Sly)	β -Glucuronidase	Dermatan sulphate, heparan sulphate, chondroitin 6-sulphate	<i>GUSB</i> 7q11.21	253220
MPS IX (Natowicz)	Hyaluronidase	Hyluronan	<i>HYAL1</i> 3p21.31	601492
Olygosaccharidoses (glycoproteinoses)				
Aspartylglucosaminuria	Glycosylasparaginase	Aspartylglucosamine	<i>AGA</i> 4q34.3	208400

Disease	Defective protein	Main storage materials	Gene and locus	OMIM
Fucosidosis	α -Fucosidase	Glycoproteins, glycolipids, Fucoside-rich oligos	<i>FUCA1</i> 1p36.11	230000
α -Mannosidosis	α -Mannosidase	Mannose-rich oligos	<i>MANSA</i> 19p13.2	248500
β -Mannosidosis	β -Mannosidase	Man (β 1 $\rightarrow$ 4)GlnNAc	<i>MANBA</i> 4q24	248510
Schindler	<i>N</i> -acetylgalactosaminidase	Sialylated/asialoglycopeptides, glycolipids	<i>NAGA</i> 22q13.2	609241
Sialidosis	Neuraminidase	Oligos, glycopeptides	<i>NEU1</i> 6p21.33	256550
Glycogenoses				
Glycogenosis II/Pompe	α 1,4-glucosidase (acid maltase)	Glycogen	<i>GAA</i> 17q25.3	232300
Lipidoses				
Wolman/CESD	Acid lipase	Cholesterol esters	<i>LIPA</i> 10q23.31	278000

Table 2

Other LSDs, classified according to underlying molecular defect disease

Disease	Defective protein	Main storage materials	Gene and locus	OMIM
Non-enzymatic lysosomal protein defects				
Gangliosidosis G _{M2} , activator defect	G _{M2} activator protein	G _{M2} ganglioside, oligos	GMA2A 5q13.3	272750
Metachromatic leukodystrophy	Saposin B	Sulphatides	PSAP 10q22.1	249900
Krabbe	Saposin A	Galactosylceramide	PSAP 10q22.1	611722
Gaucher	Saposin C	Glucosylceramide	PSAP 10q22.1	610539
Transmembrane protein defects				
Sialic acid storage disease; infantile form (ISSD) and adult form (Salla)	Sialin	Sialic acid	SLC17A5 6q13	269920 604369
Cystinosis	Cystinosin	Cystine	CTNS 17p13.2	219800
Niemann-Pick Type C1	Niemann-Pick type 1 (NPC1)	Cholesterol and sphingolipids	NPC1 18q11.2	257220
Niemann-Pick, Type C2	Niemann-Pick type 2 (NPC2)	Cholesterol and sphingolipids	NPC2 14q24.3	607625
Structural Proteins				
Danon	Lysosome-associated membrane protein 2	Cytoplasmatic debris and glycogen	LAMP2A Xq24	300257
Mucopolidosis IV	Mucolipin	Sulphatides, glycolipids, GAGs	TRMPL1 19p13.2	252650
Lysosomal enzyme protection defect				
Galactosialidosis	Protective protein cathepsin A (PPCA)	Sialyloligosaccharides	CTSA 20q13.12	256540
Post-translational processing defect				
Multiple sulphatase deficiency	Multiple sulphatase	Sulphatides, glycolipids, GAGs	SUFMI 3p26.1	272200
Trafficking defect in lysosomal enzymes				
Mucopolidosis IIα/β, IIIα/β	GlcNAc-1-P transferase	Oligos, GAGs, lipids	GNPTAB 12q23.2	252500 252600 232605
Mucopolidosis III γ	GlcNAc-1-P transferase	Oligos, GAGs, lipids		
Polypeptide degradation defect				
Pycnodysostosis	Cathepsin K	Type I collagen (major component of long bone), and type II collagen (major component of cartilage)	CTSK 1q21.3	265800
Neuronal ceroid lipofuscinoses (NCLs)				
NCL 1	Palmitoyl protein thioesterase (PPT1)	Saponins A and D (++), oligosaccharyl diphosphodolichol (oligo-PP-dol) (+), subunit c of mitochondrial ATP synthase	PPT1 1p34.2	256730

Disease	Defective protein	Main storage materials	Gene and locus	OMIM
NCL 2	Tripeptidyl peptidase 1 (TPP1)	Oligosaccharyl diphosphodolichol (oligo-PP-dol) (++), subunit c of mitochondrial ATP synthase	<i>CLN2</i> 11p15.4	204500
NCL 3	Battenin	Oligo-PP-dol (++), subunit c of mitochondrial ATP synthase	<i>CLN3</i> 16p11.2	204200
NCL4B, Parry type	DnaJ homolog subfamily C member 5	Oligo-PP-dol, subunit c of ATP Synthase	<i>DNAJC5</i> 20q13.33	162350
NCL 5	Ceroid-lipofuscinosis neuronal protein 6	Oligo-PP-dol, subunit c of ATP Synthase	<i>CLN5</i> 13q22.3	256731
NCL 6	Ceroid-lipofuscinosis neuronal protein 6	Oligo-PP-dol, subunit c of ATP Synthase	<i>CLN6</i> 15q23	601780
NCL 7	Major facilitator superfamily domain-containing protein 8	Oligo-PP-dol, subunit c of ATP Synthase	<i>MFSD8</i> 4q28.2	610951
NCL 8	CLN8, transmembrane protein of endoplasmic reticulum	Oligo-PP-dol, subunit c of ATP Synthase	<i>CLN8</i> 8p23.3	600143
NCL 10	Cathepsin D	Oligo-PP-dol, subunit c of ATP Synthase	<i>CTSD</i> 11p15.5	610127

Table 3

LSDs associated with cherry red spot and their typical features

<ul style="list-style-type: none"> • Galactosialidosis • G_{M1}-gangliosidosis • Infantile free sialic acid storage disease (ISSD) • Mucopolidosis II (I-cell disease) • Mucopolysaccharidosis types IV (MPS IV) and VII (MPS VII) • Neuronal ceroid lipofuscinosis (NCL) • Niemann-Pick disease type A • Sialidosis type 1 • Sandhoff disease • Tay-Sachs disease 	<ul style="list-style-type: none"> • Cerebellar ataxia, myoclonus, visual failure; onset in late childhood or adolescence • Coarse facial features, corneal clouding, hepatomegaly, skeletal dysplasia, learning disability, myoclonus • Coarse facies, fair complexion, hepatosplenomegaly, and severe psychomotor retardation, nephrotic syndrome • Coarse facies, short stature, kyphoscoliosis, umbilical and inguinal hernias • Short stature, skeletal dysplasia • Cerebellar ataxia; myoclonus; visual failure; onset by late childhood or adolescence • Hepatosplenomegaly, spasticity • Juvenile or adult onset; intention and action myoclonus • Exaggerated acousticomotor reflex, splenomegaly • Exaggerated acousticomotor reflex, megalencephaly
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Table 4

Neurologic clinical manifestations reported in patients with a LSD.

<u>Optic atrophy, Visual loss</u> <ul style="list-style-type: none"> Galactosialidosis G_{M1}-gangliosidosis Infantile free sialic acid storage disease (ISSD) Mucopolipidosis II (I-cell disease) Mucopolysaccharidosis types IV (MPS IV) and VII (MPS VII) Neuronal ceroid lipofuscinosis Niemann-Pick disease type A Sialidosis type 1 Sandhoff disease Tay-Sachs disease <u>Retinitis pigmentosa</u> <ul style="list-style-type: none"> Neuronal ceroid lipofuscinosis <u>Corneal opacities (clouding)</u> <ul style="list-style-type: none"> I-cell disease (ML II) Mucopolipidosis IV (MLIV) MPS I, IV, VI Oligosaccharidosis (late-onset α-mannosidosis) Fabry disease <u>Lenticular opacities (cataracts)</u> <ul style="list-style-type: none"> Oligosaccharidosis (sialidosis, α-mannosidosis) Fabry disease <u>Ophthalmoplegia (Abnormal eye movements), Nystagmus</u> <ul style="list-style-type: none"> Gaucher disease 3 Niemann-Pick C 	<u>Leukodystrophy</u> <ul style="list-style-type: none"> Krabbe disease MLD Fabry disease * <u>Myoclonic seizures</u> <ul style="list-style-type: none"> Galactosialidosis Gaucher disease III G_{M2}-gangliosidosis Neuronal ceroid lipofuscinosis Niemann-Pick C Oligosaccharidosis (α-N-acetylglucosaminidase deficiency, fucosidosis, Sialidosis type 1) <u>Deafness</u> <ul style="list-style-type: none"> Fabry disease Galactosialidosis Gaucher disease type 2 I-cell disease MPS I, II, IV Oligosaccharidosis (α- and β-mannosidosis) Metachromatic leukodystrophy Infantile Pompe disease 	<u>Macrocephaly</u> <ul style="list-style-type: none"> Tay-Sachs disease Sandhoff disease Krabbe disease <u>Peripheral neuropathy</u> <ul style="list-style-type: none"> Krabbe disease MLD (spastic paraplegia) Multiple sulfatase deficiency <u>Cortical atrophy</u> <ul style="list-style-type: none"> Late stage of G_{M1}- and G_{M2}-gangliosidosis (cerebellar atrophy) MLD I-cell disease Neuronal ceroid lipofuscinosis <u>Cerebrovascular or stroke-like episodes and other vascular events (e.g., Raynaud's phenomenon)</u> <ul style="list-style-type: none"> Fabry disease 	<u>Ataxia</u> <ul style="list-style-type: none"> Galactosialidosis Gaucher disease III G_{M1}-gangliosidosis Late-onset G_{M2}-gangliosidosis (cerebellar hypoplasia) Krabbe disease MLIV MLD Neuronal ceroid lipofuscinosis Niemann-Pick C Salla disease Sialidosis I <u>Extrapyramidal signs</u> <ul style="list-style-type: none"> Gaucher disease 3 G_{M1}-gangliosidosis (adult form) Late-onset G_{M2}-gangliosidosis Krabbe disease Niemann-Pick C Oligosaccharidosis <u>Dementia, Psychosis</u> <ul style="list-style-type: none"> Fabry disease Gaucher disease 3 G_{M1}-gangliosidosis Late-onset G_{M2}-gangliosidosis Krabbe disease MLD MPS III (Sanfilippo disease) Neuronal ceroid lipofuscinosis Niemann-Pick C
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* Signal abnormalities consistent with leukoariosis.

Table 5

LSDs prevalent in two communities and common mutations

Ashkenazi Jews	Finns
<ul style="list-style-type: none">• GM2 gangliosidosis (Tay-Sachs disease)• Gaucher disease type 1• Niemann-Pick A and B disease• Mucopolipidosis IV	<ul style="list-style-type: none">• Aspartylglucosaminuria• Infantile Neuronal Ceroid Lipofuscinosis