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A Contemporary Pathomechanistic Nosology of Inherited Lysosomal Disorders

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Abstract

Lysosomal disorders (LDs) have traditionally been defined by intra-lysosomal substrate accumulation resulting from deficiencies of lysosomal enzymes or associated proteins. Advances in lysosomal biology have demonstrated that lysosomes function as central regulators of cellular signalling, membrane trafficking, autophagy, nutrient sensing, organelle communication, and cellular homeostasis, expanding the spectrum of inherited disorders associated with lysosomal dysfunction beyond classical storage phenotypes.

We developed a contemporary pathomechanistic nosology of inherited LDs through expert curation and targeted review of databases and published literature. Disorders were included when pathogenic variants resulted in lysosomal dysfunction as a major disease mechanism through defects affecting lysosomal degradation, membrane function, intracellular trafficking, biogenesis, autophagy–lysosome pathways, or lysosome-related organelles.

A total of 108 inherited lysosomal disorders caused by defects in 102 genes were identified and organised into 11 major disease categories. Neurologic and eye involvement were the most frequently affected organ-system categories, occurring in 80.6% and 68.5% of disorders, respectively. Digestive (including hepatosplenomegaly), dysmorphic, skeletal, and haematological involvement occurred in 48.1%, 45.4%, 40.7%, and 38.9% of disorders, respectively. Distinct phenotypic signatures were observed across disease categories despite substantial mechanistic overlap involving impaired autophagy, vesicular trafficking, lysosomal stress, and altered organelle homeostasis.

This proposed nosology extends disease classification beyond substrate accumulation alone and provides a biologically informed framework for disease classification, genomic interpretation, biomarker development, patient stratification, and the development of mechanism-based therapies.

Keywords: inherited lysosomal disorders; lysosomal storage disorders; lysosome; nosology; disease classification; autophagy; endolysosomal pathway; inherited metabolic disorders

1.0 Introduction

Lysosomes are heterogeneous membrane-bound organelles characterised by an acidic lumen and a complex proteome that facilitates the degradation and recycling of macromolecules through endocytic and autophagic pathways [1]. Beyond their classical hydrolytic role, lysosomes are now recognised as dynamic regulators of cellular signalling, nutrient sensing, membrane trafficking, autophagy, ion homeostasis, energy metabolism, and inter-organelle communication through membrane contact sites [2,3]. Consequently, lysosomal dysfunction results not only in substrate accumulation but also in widespread disturbances of cellular homeostasis, giving rise to complex multisystem inherited lysosomal disorders (LDs) associated with significant morbidity and mortality [2-4] (*Figure 1*).

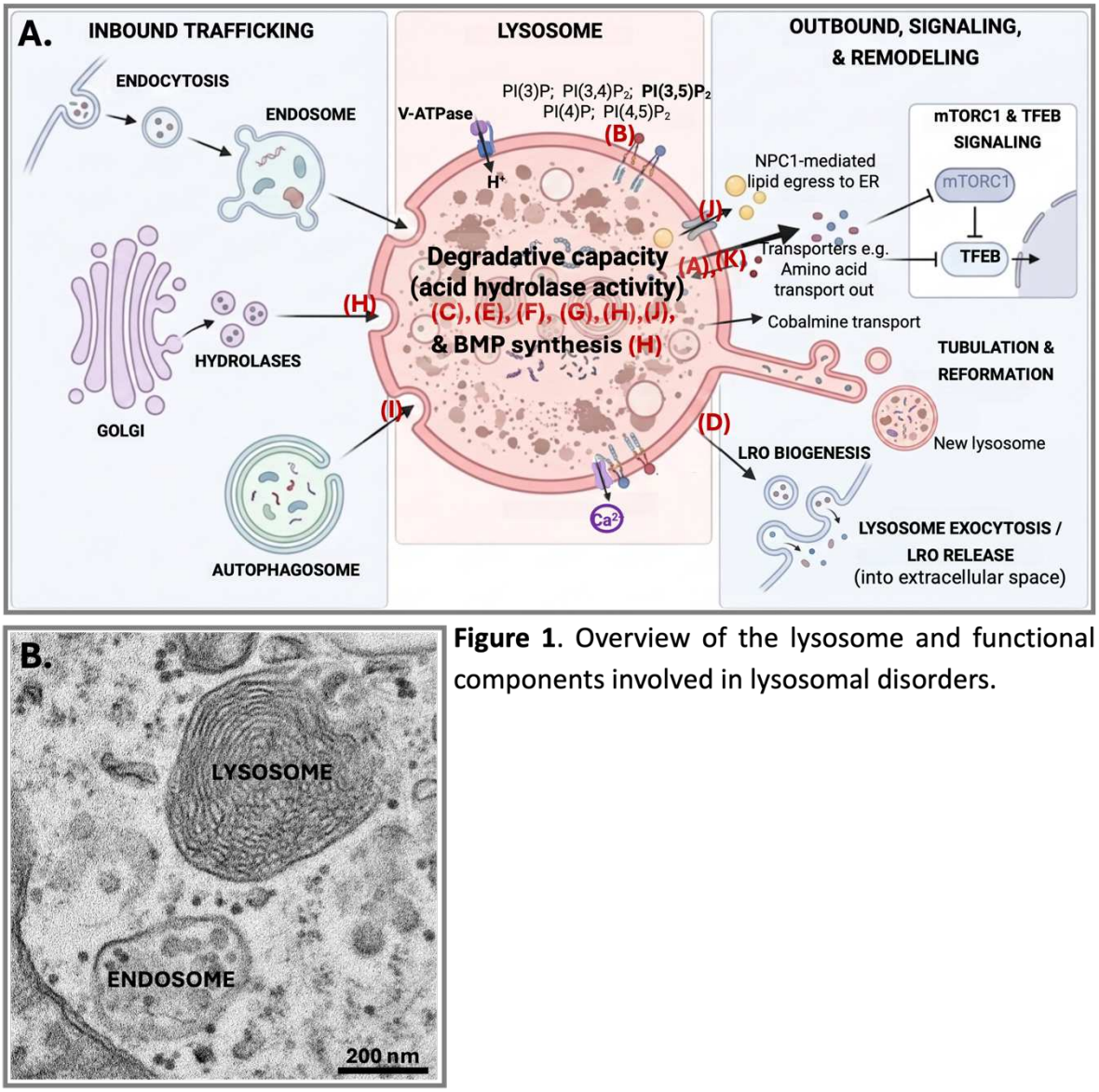


Figure 1. Overview of the lysosome and functional components involved in lysosomal disorders.

Although individually rare, inherited LDs collectively represent an important group of inherited metabolic disorders, with an estimated prevalence of 1 in 4,000–10,000 live births [5,6]. Despite their rarity, these disorders are associated with substantial lifelong morbidity, premature mortality, and significant healthcare burden due to their multisystem nature and the challenges of achieving timely diagnosis and effective treatment. Their recognised prevalence

is expected to increase further with the expanding implementation of next-generation sequencing (NGS) technologies and newborn screening (NBS) programmes [6,7].Clinically, these disorders frequently involve the central nervous system, skeleton, retina, liver, spleen, heart, kidneys, and immune system, reflecting the fundamental role of lysosomal biology in cellular and tissue homeostasis [2,6]. Despite marked genetic and biochemical heterogeneity, many converge on common downstream mechanisms, including impaired autophagy, oxidative stress, neuroinflammation, mitochondrial dysfunction, altered intracellular trafficking, and progressive neurodegeneration [2,8,9].

Historically, many LDs were classified as lysosomal storage disorders (LSDs), a framework primarily based on deficiencies of lysosomal hydrolases and the intra-lysosomal accumulation of undegraded substrates. Although this classification remains clinically valuable, advances in molecular genetics, cell biology, and systems medicine have substantially broadened our understanding of lysosomal dysfunction [3,8]. Previous conceptual frameworks have demonstrated that lysosomal disease extends beyond classical substrate storage and encompasses defects affecting lysosomal trafficking, membrane dynamics, organelle biogenesis, and autophagy-lysosome pathways [3,9]. Current concepts increasingly include disorders caused not only by deficiencies of lysosomal enzymes but also by defects in lysosomal membrane proteins, ion channels, trafficking machinery, phosphoinositide metabolism, autophagy-lysosome pathways, and lysosome-related organelles [2,8-10]. Moreover, pathogenic variants in proteins that do not localise directly to the lysosome may nevertheless result in substantial lysosomal dysfunction through disruption of pathways required for normal lysosomal homeostasis. Collectively, these advances demonstrate that inherited lysosomal disorders extend beyond classical LSDs and encompass a broader spectrum of disorders associated with lysosomal dysfunction.

The establishment of a biologically informed and clinically meaningful nosology is therefore increasingly important. A contemporary classification framework may improve diagnostic precision, refine genetic testing panels, facilitate integration into NBS programmes, and support biomarker development and therapeutic stratification [6,9]. Furthermore, emerging therapeutic approaches, including gene therapy, genome editing, pharmacological chaperones, substrate reduction therapies, and other pathway-directed small-molecule treatments, increasingly rely on mechanistic disease classification to guide therapeutic development and clinical trial design [11,12]. As genomic, metabolomic, and functional approaches continue to expand, biologically grounded classification systems will become increasingly important for integrating newly recognised disorders within the broader landscape of inherited metabolic disease.

The aim of this review was to develop a contemporary pathomechanistic nosology of inherited LDs by integrating molecular, cellular, and clinical evidence within a unified framework of lysosomal biology. Through expert curation and targeted review of databases and the published literature, we sought to establish a biologically grounded framework to support disease classification, diagnosis, genomic interpretation, biomarker development, and future therapeutic strategies across this expanding disease spectrum.

2.0 Methods

2.1 Inclusion and exclusion criteria

Inclusion criteria for LDs were agreed by all authors. Disorders were included when pathogenic variants resulted in lysosomal dysfunction as a major contributor to disease pathogenesis through one or more of the following mechanisms:

1. Impaired lysosomal degradation of substrates.
2. Defective lysosomal enzyme, membrane protein, transporter, or ion-channel function.
3. Abnormal lysosomal biogenesis, acidification, trafficking, positioning, maturation, or fusion.
4. Disruption of autophagy-lysosome pathways.
5. Dysfunction of lysosome-related organelles.
6. Disruption of cellular pathways required for normal lysosomal homeostasis resulting in demonstrable lysosomal dysfunction.

Disorders were eligible for inclusion irrespective of whether the causal protein localised directly to the lysosome, provided that genetic, biochemical, cellular, or functional evidence supported a central role for lysosomal dysfunction in disease pathogenesis. Only monogenic inherited disorders with an established disease-gene association were included. Final inclusion decisions were reached by consensus among the authors.

Exclusion criteria were agreed as follows:

1. Available evidence did not support lysosomal dysfunction as a significant contributor to disease pathogenesis.
2. Reported lysosomal abnormalities were considered epiphenomena or downstream consequences of disease without evidence that lysosomal dysfunction contributed substantially to disease pathogenesis.
3. The disease-gene association lacked sufficient evidence to support pathogenicity.
4. Evidence supporting lysosomal involvement was absent, limited, or conflicting.
5. Acquired, environmental, multifactorial, polygenic, or other non-monogenic disorders were excluded.

Reported lysosomal abnormalities alone were not considered sufficient for inclusion. Disorders were included only when available evidence supported lysosomal dysfunction as a substantial contributor to disease pathogenesis.

2.2 Curation of the gene list

The workflow used to generate the final LD gene list is summarised in *Figure 2*. Candidate genes were identified through cross-mapping of lysosomal disorder-associated genes from: (i) the International Classification of Inherited Metabolic Disorders (ICIMD) [13]; (ii) PanelApp UK (https://panelapp.genomicsengland.co.uk/) [14], an expert-curated gene panel resource used in the genomic evaluation of patients with suspected LDs; and (iii) published lysosomal disorder resources, including reference gene lists and review articles.

All candidate genes underwent evaluation against the predefined inclusion and exclusion criteria. Evidence relating to disease causality, lysosomal function, substrate accumulation, autophagy-lysosome pathway dysfunction, and broader disease pathogenesis was reviewed, with particular emphasis on experimental data demonstrating lysosomal dysfunction or

disruption of lysosomal pathways. Genes that did not satisfy the predefined criteria were excluded.

Where conflicting evidence existed regarding subcellular localisation, molecular function, or disease mechanisms, the primary literature and available functional studies were reviewed in detail. Borderline genes and disorders with uncertain lysosomal involvement underwent additional review, and final inclusion decisions were reached by consensus among the authors.

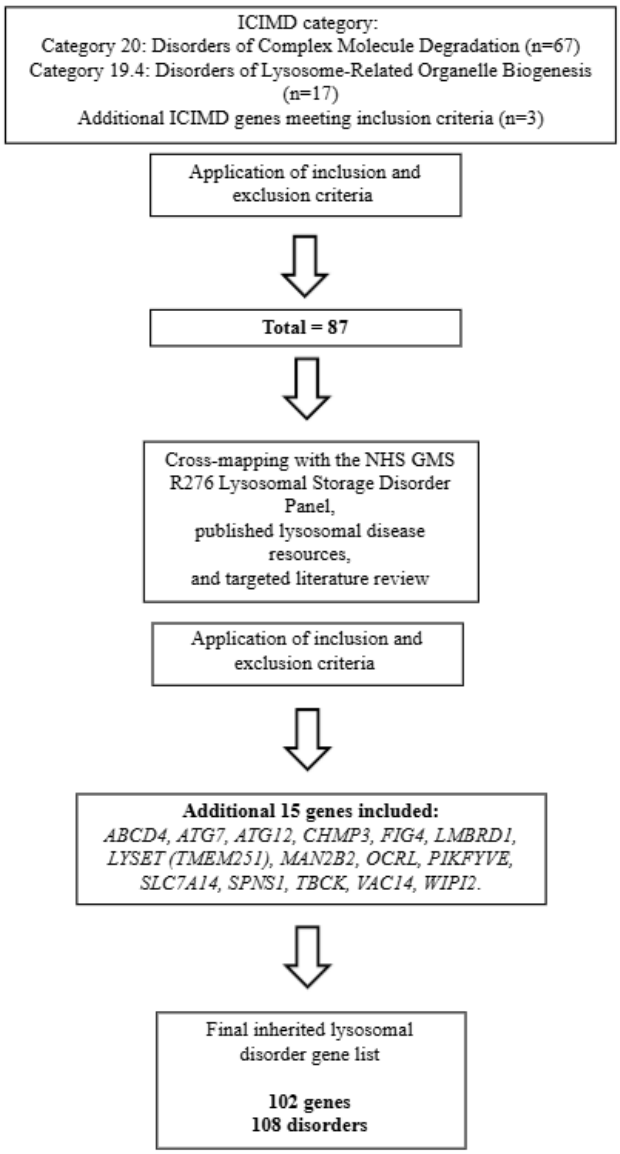


Figure 2. Workflow used to generate the final curated gene list for the proposed nosology. Genes were identified through cross-mapping of ICIMD lysosomal disorder categories, the Genomics England (NHS GMS) PanelApp R276 Lysosomal Storage Disorder Panel, and

targeted literature review. Candidate genes underwent evaluation using the predefined inclusion and exclusion criteria, resulting in a final curated list of 102 genes associated with inherited lysosomal disorders.

2.3 Disease classification

The proposed nosology was developed within the framework of the ICIMD, an expert-curated and regularly updated classification system for inherited metabolic diseases. Disease nomenclature followed the recently proposed dyadic nomenclature for monogenic diseases, whereby disorders are designated using the causal gene symbol followed by the associated disease name, with established historical or eponymous disease names retained as alternative names where appropriate [15]. Included LDs were then classified according to the biological mechanism considered most closely associated with lysosomal dysfunction and disease pathogenesis.

Classification categories were based on established lysosomal pathways and processes, including lysosomal substrate degradation, lysosomal membrane function, intracellular trafficking, autophagy-lysosome pathways, organelle biogenesis, and lysosome-related organelle biology.

When proteins were known to have multiple biological functions, classification was based on the pathway considered most relevant to disease pathogenesis. In cases where an LD could reasonably be assigned to more than one category, allocation was based on the mechanism considered most closely associated with lysosomal dysfunction. Given the substantial mechanistic overlap between lysosomal pathways, the proposed nosology was intended as a classification framework rather than a strict representation of mutually exclusive biological processes.

2.4 Sources of clinical and laboratory information

Sources of information included IEMbase (http://www.iembase.org) [16], Online Mendelian Inheritance in Man (OMIM; https://omim.org) [17], Human Phenotype Ontology (HPO; https://hpo.jax.org) [18], Orphanet (https://www.orpha.net) [19], GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/) [20], and the published literature. As of 17 May 2026, IEMbase catalogued 2,041 disorders and 4,522 corresponding clinical and biochemical signs and symptoms organised across multiple organ systems and disease categories.

Clinical, biochemical, molecular, and diagnostic information was extracted from these resources and harmonised to generate a comprehensive profile for each included disorder. Data were reviewed manually to minimise redundancy arising from differences in nomenclature across databases, ontologies, and publications.

2.5 Literature review and identification of newly recognised disorders

A targeted literature review was undertaken to identify recently described disease-causing genes not represented in the curated resources. PubMed searches and citation tracking were performed up to 17 May 2026. PubMed was searched using combinations of the terms "lysosomal disorder", "lysosomal disease", "lysosomal storage disorder", "lysosome", "lysosomal dysfunction", "lysosomal trafficking", "lysosomal membrane", "autophagy-lysosome pathway", "endolysosomal", "lysosome-related disorder", and "gene discovery", together with disease-, pathway-, and gene-specific search terms. Additional relevant publications were identified through citation tracking of key review articles and reference gene lists.

Candidate genes identified through the literature were evaluated using the same inclusion and exclusion criteria applied to established LDs. Where conflicting evidence existed regarding subcellular localisation, molecular function, or disease pathogenesis, the primary literature and available functional data were reviewed to determine the extent of lysosomal involvement. Newly identified genes were incorporated into the proposed nosology when sufficient genetic, functional, and clinical evidence supported lysosomal dysfunction as a major contributor to disease pathogenesis.

2.6 Clinical phenotype analysis

Clinical signs and symptoms were grouped into 20 organ-system categories: autonomic, cardiovascular, dental, dermatological, digestive, dysmorphic, ear, endocrine, eye, genitourinary, hair, haematological, immunological, muscular, neurologic, psychiatric, renal, respiratory, skeletal, and other. These categories were derived through harmonisation of Human Phenotype Ontology (HPO) and IEMbase organ-system classifications and refined by expert consensus.

Clinical manifestations associated with LDs were extracted and harmonised across these categories. Where possible, phenotypic terms were standardised according to HPO terminology to facilitate consistency across disorders and databases. Duplicate or synonymous terms arising from differences in nomenclature across data sources were consolidated prior to analysis.

Organ-system frequencies were calculated at the disorder level and represent the proportion of LDs exhibiting at least one clinical manifestation within the respective organ-system category.

2.7 Data analysis

Data curation, harmonisation, and descriptive analyses were performed using Python version 3.13.5 (Python Software Foundation, Wilmington, DE, USA), with pandas (The pandas development team, https://pandas.pydata.org/) and NumPy (NumPy Developers, https://numpy.org/) used for data processing and frequency calculations and matplotlib (Matplotlib Development Team, https://matplotlib.org/) used for figure generation. All data extraction, curation, and analyses were performed using the dataset current as of 17 May 2026.

Descriptive analyses were undertaken to characterise the distribution of genes, disease categories, clinical manifestations, organ-system involvement, and laboratory features across the final LD dataset. Organ-system frequencies were calculated as the proportion of disorders

exhibiting at least one manifestation within the respective organ-system category. No inferential statistical analyses were performed, as the objective was descriptive characterisation of the curated dataset.

3.0 Results

A total of 108 inherited LDs, caused by defects in 102 genes, were identified and classified according to the proposed nosology framework (*Table 1; Supplementary Table S1*). Disorders were organised into 11 major disease categories and evaluated across 20 organ-system categories.

Relative to the original ICIMD-derived lysosomal disease gene set (n=87), the largest expansion occurred within '*Disorders of Autophagy*', which accounted for five of the 15 additional genes (*ATG7, ATG12, TBCK, CHMP3,* and *WIPI2*). The remaining additions comprised '*Disorders of Phosphatidylinositol Metabolism*' (*FIG4, OCRL, PIKFYVE,* and *VAC14*), Other '*Disorders of Complex Molecule Degradation*' (*LYSET/TMEM251* and *SPNS1*), '*Disorders of Amino Acid Transport*' (*SLC7A14*), '*Disorders of N-linked Protein Glycosylation'* (*MAN2B2*), and '*Disorders of Cobalamin Metabolism'* (*LMBRD1* and *ABCD4*). Collectively, these additions reflect the expanding biological spectrum of inherited lysosomal disorders and highlight disease mechanisms extending beyond classical substrate storage disorders

To enable comparative analyses across disorders, harmonised phenotypic features were grouped into broad organ-system categories, while individual symptom annotations were retained in *Supplementary Table S1*

3.1 Overall distribution of system involvement

Neurologic involvement was the most frequently affected organ-system category, occurring in 87 of 108 disorders (80.6%), followed by eye involvement in 74 disorders (68.5%) (*Figure 3*). Digestive (including hepatosplenomegaly), dysmorphic, skeletal, and haematological involvement occurred in 52 (48.1%), 49 (45.4%), 44 (40.7%), and 42 (38.9%) disorders, respectively.

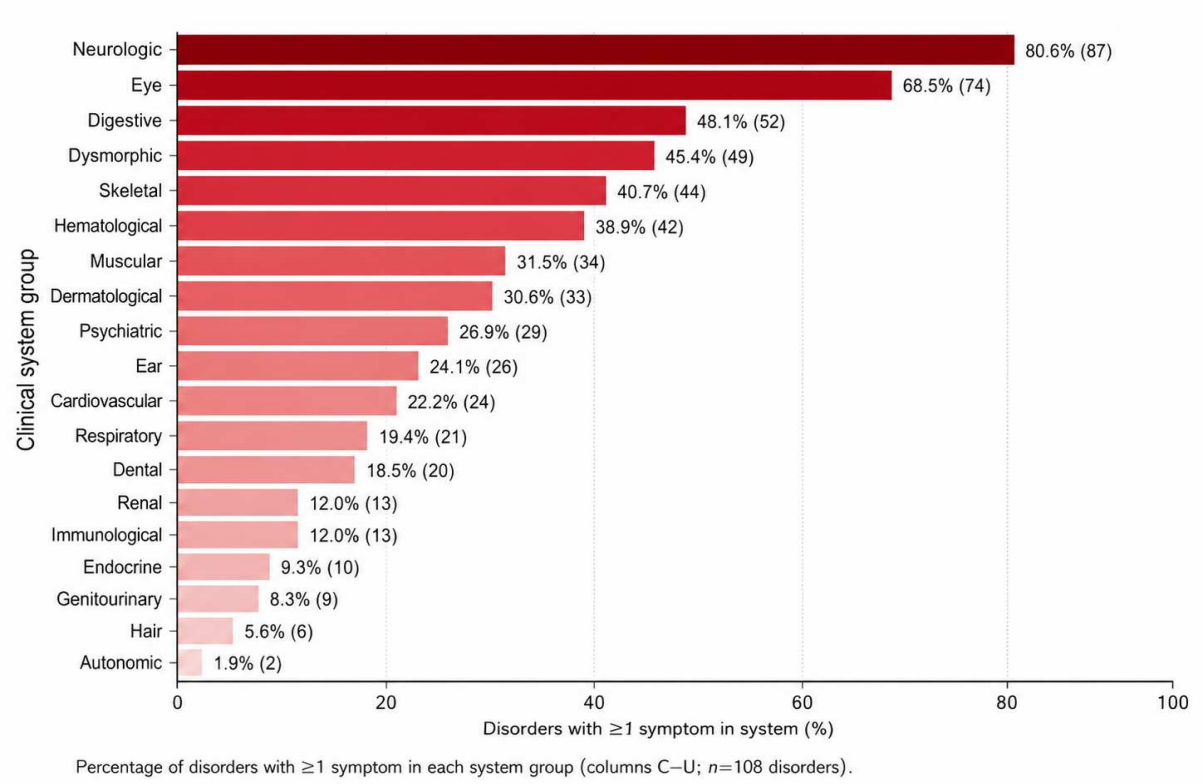


Figure 3. Organ-system involvement across 108 inherited lysosomal disorders. Bars represent the percentage of disorders with at least one recorded clinical manifestation within each organ-system category. Numbers in parentheses indicate the corresponding number of disorders.

Intermediate-frequency involvement was observed in muscular (34 disorders, 31.5%), dermatological (33, 30.6%), psychiatric (29, 26.9%), ear (26, 24.1%), cardiovascular (24, 22.2%), respiratory (21, 19.4%), and dental (20, 18.5%) categories. Less frequently affected categories included renal and immunological involvement, each present in 13 disorders (12.0%), endocrine involvement in 10 (9.3%), genitourinary involvement in 9 (8.3%), hair involvement in 6 (5.6%), and autonomic involvement in 2 (1.9%). Overall, LDs demonstrated marked multisystem involvement, with a predominance of neurologic and eye manifestations across disease categories.

Table 1 to be inserted here

Table 1. Summary of clinical phenotypes of inherited lysosomal disorders. For details see *Supplemental Table S1*.

Supplementary Table S1. List of lysosomal disorders, laboratory investigations, inheritance, OMIM references and IEMbase IDs.

3.2 Symptom-level clinical hot spots

At the individual symptom level, neurologic manifestations predominated. seizures represented the most frequent single symptom, occurring in 42 disorders (38.9%), followed by ataxia and intellectual disability, each present in 29 (26.9%), and spasticity in 27 (25.0%). Additional

recurrent neurologic manifestations included cerebral and cerebellar atrophy, developmental delay, dystonia, hypotonia, movement disorders, myoclonus, and microcephaly.

Among non-neurologic manifestations, coarse facial features represented the most frequent dysmorphic finding (25, 3.1%), while hepatosplenomegaly was the most common digestive manifestation (25, 23.1%). Dysostosis multiplex was the predominant skeletal abnormality (2, 18.5%). Haematological manifestations were characterised primarily by foam cells, thrombocytopenia, vacuolated lymphocytes, and Alder–Reilly anomaly. Foam cells were observed in 16 disorders (14.8%), thrombocytopenia in 9 (8.3%), and Alder–Reilly anomaly and vacuolated lymphocytes in 8 disorders each (7.4%).

Within the eye category, the most frequent manifestations were corneal clouding and optic atrophy, each occurring in 13 disorders (12.0%), followed by ocular albinism in 11 (10.2%), and nystagmus and retinal dystrophy in 10 disorders each (9.3%). Within the ear category, hearing impairment was the most common manifestation, occurring in 15 disorders (13.9%).

Although organ-system analyses grouped manifestations into broad clinical categories, symptom-level curation revealed substantial heterogeneity within individual systems. For example, ocular involvement encompassed optic atrophy, corneal clouding, retinal dystrophy, and ocular albinism, while dermatological manifestations included angiokeratomas, ichthyosis-like skin changes, pigmentary abnormalities, and albinism (*Supplementary Table S1*)

3.3 Disorder-group-specific clinical patterns

Heat-map analysis demonstrated distinct organ-system signatures across the major LD categories (*Figure 4*). '*Disorders of Sphingolipid Degradation'* showed universal neurologic involvement accompanied by frequent eye, digestive, skeletal, and muscular manifestations, consistent with a broad neurovisceral phenotype. '*Disorders of Glycoprotein Degradation'* demonstrated one of the broadest multisystem profiles, characterised by prominent neurologic, dysmorphic, eye, haematological, skeletal, dermatological, and digestive involvement.

'*Disorders of Glycosaminoglycan Degradation'* displayed a predominantly somatic phenotype characterised by extensive skeletal, dysmorphic, eye, ear, and digestive involvement, although neurologic manifestations were also common. In contrast, '*Disorders of Lysosome-related Organelle Biogenesis*' exhibited a distinctive dermatological–eye–haematological profile with comparatively lower neurologic involvement. '*Neuronal Ceroid Lipofuscinoses*' and '*Disorders of Autophagy'* were characterised by predominantly neurologic–eye phenotypes, with frequent muscular involvement in autophagy disorders and prominent psychiatric involvement among neuronal ceroid lipofuscinoses.

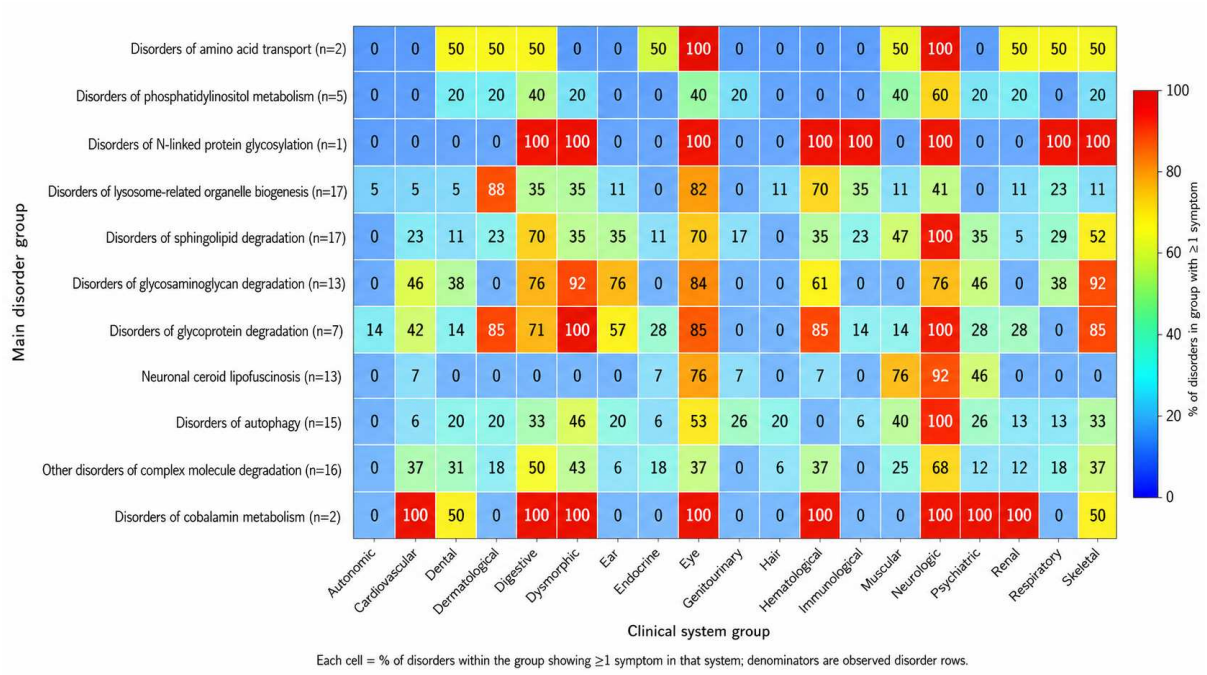


Figure 4. Heat map of organ-system involvement across major inherited lysosomal disorder categories. Each cell represents the percentage of disorders within a given disease category exhibiting at least one recorded clinical manifestation in the corresponding organ-system category. Percentages were calculated using the number of disorders within each disease category as the denominator. Colours indicate increasing frequencies of organ-system involvement, ranging from low (blue) to high (red).

3.4 Systemic disease burden

Beyond the dominant neurologic and eye manifestations, the dataset demonstrated substantial multisystem involvement across multiple LD categories. Renal manifestations were identified in 13 of 108 disorders (12.0%) and included Fanconi syndrome, nephrocalcinosis, nephrolithiasis, chronic renal failure, and renal osteodystrophy, particularly among disorders affecting amino acid transport and phosphoinositide metabolism.

Skeletal involvement was present in 44 disorders (40.7%) and represented a major component of systemic disease burden. Common manifestations included dysostosis multiplex, scoliosis, osteopenia, joint contractures, genu valgum, and rickets. Psychiatric manifestations were observed in 29 disorders (26.9%) and included behavioural abnormalities, psychosis, cognitive regression, and autism spectrum features, highlighting the broad neurological and behavioural consequences of lysosomal dysfunction.

Collectively, these findings demonstrate that LDs extend beyond isolated organ involvement and are characterised by substantial multisystem disease burden affecting multiple organ-system categories.

4.0 Discussion

We developed a contemporary nosology of inherited LDs that reflects the expanding biological and clinical spectrum of lysosomal dysfunction. neurologic and eye involvement predominated across the disease spectrum, although substantial differences in multisystem disease burden distinguished major disorder categories. '*Disorders of Sphingolipid Degradation*', '*Neuronal Ceroid Lipofuscinoses'*, and '*Disorders of Autophagy*' demonstrated predominantly neuronopathic phenotypes, whereas '*Disorders of Glycosaminoglycan Degradation*' and selected lysosome-related organelle biogenesis disorders showed greater skeletal, dysmorphic, digestive, haematological, dermatological, and ear involvement. These findings highlight the marked phenotypic heterogeneity and multisystem nature of LDs.

The proposed pathomechanistic framework builds upon these advances while highlighting the limitations of traditional substrate-centric classifications. Previous conceptual frameworks have recognised that lysosomal disease extends beyond classical lysosomal storage disorders to encompass defects in lysosomal trafficking, membrane dynamics, autophagy, and lysosome-related organelles [3,9]. Building upon these advances, the present nosology integrates systematic disease–gene curation within the ICIMD framework and incorporates 15 additional genes associated with lysosomal dysfunction. Notably, disorders of autophagy accounted for the largest proportion of newly incorporated genes, reflecting increasing recognition of the central role of autophagy–lysosome pathway dysfunction in inherited LDs.

Despite diverse genetic origins, impaired autophagy, defective vesicular trafficking, lysosomal stress, altered organelle homeostasis, and secondary mitochondrial dysfunction were recurrent features across included disorders [2,3,8,9], likely contributing to shared clinical manifestations [3,4,21,22]. These mechanisms are highly interconnected rather than representing discrete pathogenic processes. Lysosomal dysfunction may impair autophagic flux through defective cargo degradation and disruption of lysosome–autophagosome fusion, resulting in the accumulation of damaged proteins and organelles. Consequently, mitochondrial quality control and mitophagy are frequently impaired, while disruption of membrane contact sites and inter-organelle communication may further alter calcium signalling, lipid exchange, and cellular homeostasis.

Accordingly, the proposed framework is intended to complement, rather than replace, existing biochemical and clinical classifications. Rather than assigning disorders to rigid mechanistic categories, it provides an organisational framework based on the biological process considered most closely associated with lysosomal dysfunction while acknowledging the substantial mechanistic overlap that exists between disease pathways.

The broad continuum between neuronopathic and systemic phenotypes further illustrates the complexity of LD classification. Neurologic involvement across mechanistically distinct disease groups likely reflects shared vulnerabilities of post-mitotic neuronal systems to impaired autophagy, lysosomal stress, altered intracellular trafficking, and broader disturbances of cellular homeostasis [2,3,8]. Several disorders demonstrated phenotypic spectra ranging from severe neurodegenerative disease to attenuated multisystem presentations, likely influenced by residual protein activity, genetic modifiers, and broader cellular context [23,24]. Substantial overlap was observed across disorder categories, supporting a continuum model of LD involvement rather than strict separation into neuronopathic and systemic phenotypes [25,26]. Accordingly, the proposed classification should be viewed as an organisational framework rather than a representation of mutually exclusive disease mechanisms.

The absence of a unified and biologically grounded nosology has important clinical implications. Diagnostic pathways for LDs remain fragmented, particularly for disorders lacking classical storage phenotypes or clear biochemical signatures. Several recently recognised disorders demonstrate substantial lysosomal dysfunction despite historically being classified outside the lysosomal field, including disorders of phosphoinositide metabolism, lysosomal trafficking complexes, and autophagy pathways [27,28], as well as other newly recognised disorders associated with lysosomal dysfunction [29,30]. Eye involvement represented the second most common organ-system category in the present analysis, highlighting the vulnerability of retinal and visual pathways to lysosomal dysfunction across diverse disease groups. The retina and associated visual structures are highly dependent on lysosomal degradation pathways for photoreceptor maintenance, retinal pigment epithelium function, and cellular quality control, while chronic exposure to photo-oxidative stress may further increase susceptibility to lysosomal dysfunction. The recognition of LDs with predominant or isolated retinal phenotypes further illustrates the expanding clinical spectrum of lysosomal dysfunction beyond classical multisystem LSDs [31,32]. The proposed framework may facilitate diagnostic recognition, support incorporation into NGS panels and NBS strategies, and improve variant interpretation and disease discovery [33].

The expanding therapeutic landscape further reinforces the value of mechanistic disease classification. Current treatment paradigms remain centred largely on enzyme replacement therapy, substrate reduction therapy, and haematopoietic stem cell transplantation [34-36]. Although these approaches have improved survival and systemic outcomes in several disorders, important limitations remain, particularly for central nervous system disease because of poor blood–brain barrier penetration, limited tissue biodistribution, and incomplete correction of secondary cellular pathology [36-40]. Clinical responses also remain heterogeneous, even among patients sharing the same biochemical diagnosis or causal variant [41,42]. Pompe disease illustrates these limitations, as progressive skeletal muscle and respiratory decline may persist despite enzyme replacement therapy with alglucosidase alfa [43,44]. More broadly, substrate reduction therapies do not necessarily reverse established neurodegeneration or restore disrupted cellular homeostasis, supporting the need for therapies targeting shared downstream cellular mechanisms. This concept is further supported by emerging evidence from inflammatory pathway modulation in mucopolysaccharidosis type III, where treatment with anakinra demonstrated biological and clinical effects despite not directly correcting the underlying lysosomal defect [45].

Emerging therapies further support the importance of biologically informed classification systems. Genome editing approaches, including CRISPR/Cas systems, base editing, and targeted integration strategies, are increasingly being explored across several LDs, including mucopolysaccharidoses [46,47]. Similarly, pharmacological chaperones, substrate reduction therapies, antisense oligonucleotide- based approaches, and therapeutic modulation of autophagy are broadening treatment strategies beyond single-enzyme correction [48–50]. As therapies increasingly target shared cellular pathways, biologically informed classification may improve clinical trial design, therapeutic stratification, and identification of related disease groups. As therapies increasingly target shared cellular pathways, biologically informed classification may improve clinical trial design, therapeutic stratification, and identification of related disease groups. By grouping disorders according to shared pathogenic mechanisms rather than individual gene defects, this framework may facilitate the design of basket trials and accelerate evaluation of therapies targeting common downstream cellular pathways, particularly for ultra-rare disorders where conventional gene-specific trials are challenging. Current biomarkers frequently correlate imperfectly with disease severity, neurological

progression, or therapeutic response [51,52]. Biomarkers reflecting neurodegeneration, inflammation, autophagic dysfunction, lysosomal stress, or broader disturbances of intracellular homeostasis may ultimately prove more informative than measurements of accumulated substrate alone.

Several limitations of the proposed framework should be recognised. Mechanistic overlap between disease categories remains substantial, and classification boundaries will continue to evolve as understanding of lysosomal biology expands. Some disorders demonstrate complex disease mechanisms in which lysosomal dysfunction coexists with abnormalities affecting other cellular pathways, making assignment to discrete mechanistic categories challenging. In addition, several disorders with reported lysosomal abnormalities were excluded because available evidence does not support lysosomal dysfunction as a major driver of disease pathogenesis. The framework also relies heavily on published literature and curated databases and is focused on monogenic inherited disorders; consequently, milder, atypical, or oligogenic mechanisms of disease may be underrepresented. Ongoing refinement through functional studies, genomic discovery, and longitudinal clinical characterisation will therefore remain essential.

As knowledge of lysosomal biology continues to evolve, the proposed nosology should be regarded as a dynamic framework rather than a static classification. Future iterations could be integrated into established curated resources such as IEMbase, enabling periodic expert review and incorporation of newly recognised inherited LDs using the transparent inclusion and exclusion criteria described in this study. Such an approach would provide a sustainable mechanism for maintaining an up-to-date, evidence-based classification as advances in disease biology, genomics, and therapeutics continue to refine our understanding of these disorders. The methodology presented here provides a reproducible process for evaluating future candidate disorders, rather than requiring ad hoc additions.

Furthermore, the organ-system categories used for phenotypic analysis represent broad clinical domains and do not fully capture the biological and pathological heterogeneity of manifestations within individual systems. For example, dermatological involvement may arise through distinct mechanisms affecting epidermal barrier function, vascular structures, pigmentation, or connective tissue. Although detailed symptom-level annotations were retained in *Supplementary Table S1*, aggregation into broader organ-system categories was necessary to facilitate comparative analyses across the full dataset.

5.0 Conclusion

Advances in lysosomal biology have expanded the spectrum of disorders associated with lysosomal dysfunction beyond the classical storage disorders. We propose a contemporary pathomechanistic nosology that integrates molecular, cellular, and clinical features across 108 inherited disorders caused by defects in 102 genes. By incorporating both established and newly recognised disorders of lysosomal biology, this framework provides a biologically informed approach to disease classification, genomic interpretation, biomarker development, patient stratification, and the development of mechanism-based therapies. As understanding of lysosomal biology continues to evolve, biologically informed classification systems will play an increasingly important role in integrating newly recognised disorders, guiding therapeutic development, and advancing precision medicine across the expanding spectrum of lysosomal disease.

Abbreviations:
HPO-human phenotype ontology
ICIMD-international classification of inherited metabolic disorders
LD- lysosmal disorders
LSD- lysosomal storage disorders
NBS- newborn screening
NGS- next generation sequencing

DECLARATIONS:

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Legends

Figure 1 **Overview of the lysosome and functional components involved in lysosomal disorders.**
A. Schematic illustration. The degradative capacity of the lysosome is dependent on the activity of hydrolytic enzymes, trafficked from the Golgi, that require an acidic environment, maintained by the V-ATPase proton pump. A) Defects in amino acid transporters in the lysosome membrane are associated with lysosomal disorders (LDs) described in Table 1A. B) The diverse range of phosphoinositides in lysosomal membranes, maintained by localized kinases and phosphatases, play an important role in lysosome function, including in the regulation of mTORC1 activity, autophagy, Ca^{2+} channel activity (and therefore calcineurin and TFEB activity) and lysosome reformation. Defective lysosomal phosphoinositide

metabolism results in several LDs (Table 1B). C) Lysosomal degradation of glycoproteins and subsequent recycling is essential for the N-glycan synthesis pathway and is defective in the rare LD MAN2B2-CDG (Table 1C). D) Biogenesis/traffic of lysosome related organelles derived from endosomes/lysosomes is perturbed in LDs described in Table 1D. E) The accumulation of poorly degraded complex sphingolipids affects lysosomal degradative capacity and Ca^{2+} channel activity and can induce membrane damage, leading to LDs described in Table 1E. F) Impaired glycosaminoglycan (GAG) degradation in the lysosome results in Mucopolysaccharidoses (Table 1F). G) Defective glycoprotein degradation results in toxic accumulation of undigested oligosaccharides in several LDs (Table 1G). H) Loss of function or defective delivery of lysosomal enzymes or defects in synthesis of BMP (bis(monoacylglycero)phosphate) leads to toxic lipofuscin accumulation and Neuronal Ceroid Lipofuscinoses (Table 1H). I) The lysosome plays a key role in clearing/recycling material via autophagy, implicated in LDs described in Table 1D. J) Accumulation of lipids and carbohydrates due to impaired degradation, egress or autophagic flux cause LDs described in Table 1J. K) Impaired release of vitamin B12 (cobalmine) from the lysosome disrupts the methionine cycle in LDs described in table 1K. *Created using BioRender.com.*
B. Example transmission electron microscopy image of a lysosome showing characteristic luminal lamellae whorls and a multivesicular endosome prior to lysosomal fusion. Scale bar, 200 nm.

Figure 2 **Workflow used to generate the final curated gene list for the proposed nosology.** Genes were identified through cross-mapping of ICIMD lysosomal disorder categories, the Genomics England (NHS GMS) PanelApp R276 Lysosomal Storage Disorder Panel, and targeted literature review. Candidate genes underwent evaluation using the predefined inclusion and exclusion criteria, resulting in a final curated list of 102 genes associated with inherited lysosomal disorders.

Figure 3 **Organ-system involvement across 108 inherited lysosomal disorders.** Bars represent the percentage of disorders with at least one recorded clinical manifestation within each organ-system category. Numbers in parentheses indicate the corresponding number of disorders.

Figure 4 **Heat map of organ-system involvement across major inherited lysosomal disorder categories.** Each cell represents the percentage of disorders within a given disease category exhibiting at least one recorded clinical manifestation in the corresponding organ-system category. Percentages were calculated using the number of disorders within each disease category as the denominator. Colours indicate increasing frequencies of organ-system involvement, ranging from low (blue) to high (red).

Table 1 **Summary of clinical phenotypes of inherited lysosomal disorders.** For details see *Supplemental Table S1*.

Supplemental Table S1**. List of lysosomal disorders, laboratory investigations, inheritance, OMIM references and IEMbase IDs.**

Table 1. Summary of clinical phenotypes of inherited lysosomal disorders. For details see Supplemental Table S1.

Dyadic names (n=108)	Alternative names	Autonomic	Cardiovascular	Dental	Dermatological	Digestive	Dysmorphic	Ear	Endocrine	Eye	Genitourinary	Hair	Hematological	Immunological	Muscular	Neurologic	Psychiatric	Renal	Respiratory	Skeletal
A) Disorders of amino acid transport (n=2)																				
CTNS-related Nephropathic cystinosis	Infantile nephropathic cystinosis; Cystinosis			X	X	X			X	X					X	X		X	X	X
SLC7A14-related Lysosomal cationic amino acid transporter deficiency	SLC7A14 deficiency									X						X				
B) Disorders of phosphatidylinositol metabolism (n=5)																				
FIG4-related Phosphatidylinositol 3,5-bisphosphate-5-phosphatase deficiency, neurologic phenotype (ALS11)	Amyotrophic lateral sclerosis type 11 (ALS11)																			
FIG4-related Phosphatidylinositol 3,5-bisphosphate-5-phosphatase deficiency, neuroskeletal phenotype (CMT4J)	Charcot–Marie–Tooth disease type 4J (CMT4J)														X	X				
OCRL-related Phosphatidylinositol 4,5-bisphosphate-5-phosphatase deficiency	Lowe syndrome; Oculocerebrorenal syndrome of Lowe			X	X	X	X			X	X					X	X	X		X
PIKFYVE-related Phosphatidylinositol-3-phosphate 5-kinase deficiency	Fleck corneal dystrophy									X										
VAC14-related Lenk-Ploski syndrome	VAC14 deficiency					X									X	X				
C) Disorders of N-linked protein glycosylation (n=1)																				
MAN2B2-related Congenital disorder of glycosylation (CDG)	MAN2B2-CDG					X	X			X			X	X		X			X	X

D) Disorders of lysosome-related organelle biogenesis (n=17)																			
VPS33A-related Mucopolysaccharidosis-plus syndrome	MPS-plus syndrome		X			X	X			X		X	X	X		X		X		X
VPS33B-related Arthrogryposis-renal dysfunction-cholestasis syndrome type 1	ARC syndrome; ARCS1				X	X	X	X							X			X		X
VPS11-related Hypomyelinating leukodystrophy type 12		X						X		X						X				
HPS1-related Hermansky-Pudlak syndrome type 1					X					X			X						X	
AP3B1-related Hermansky-Pudlak syndrome type 2					X	X	X			X			X	X		X			X	
HPS3-related Hermansky-Pudlak syndrome type 3					X					X			X							
HPS4-related Hermansky-Pudlak syndrome type 4					X					X									X	
HPS5-related Hermansky-Pudlak syndrome type 5					X	X				X			X							
HPS6-related Hermansky-Pudlak syndrome type 6					X					X			X							
DTNBP1-related Hermansky-Pudlak syndrome type 7					X		X			X			X							
BLOC1S3-related Hermansky-Pudlak syndrome type 8					X					X			X							
BLOC1S6-related Hermansky-Pudlak syndrome type 9					X					X			X			X				
AP3D1-related Hermansky-Pudlak syndrome type 10					X	X	X			X			X	X		X			X	

LYST-related Chediak-Higashi syndrome				X	X	X				X			X	X						
MYO5A-related Griscelli syndrome type 1					X		X			X				X		X				
RAB27A-related Griscelli syndrome type 2					X								X	X	X	X				
MLPH-related Griscelli syndrome type 3					X							X								
E) Disorders of sphingolipid degradation (n=17)																				
GBA-related Glucocerebrosidase deficiency	Gaucher disease			X	X	X	X			X			X			X			X	X
PSAP-related Gaucher disease-like disorder due to saposin C deficiency	Saposin C deficiency					X				X			X			X				X
SMPD1-related Acid sphingomyelinase deficiency	Niemann–Pick disease types A and B (ASMD)					X		X		X			X	X		X			X	
SMPD4-related Neutral sphingomyelinase 3 deficiency			X				X								X	X				X
GLB1-related Beta-galactosidase 1 deficiency (GM1 gangliosidosis)			X			X	X	X		X			X		X	X	X		X	X
HEXA-related Beta-hexosaminidase subunit alpha deficiency	Tay–Sachs disease					X				X	X				X	X	X			X
HEXB-related Beta-hexosaminidase subunit beta deficiency	Sandhoff disease					X	X			X	X		X		X	X				X
GM2A-related GM2 activator protein deficiency	AB variant GM2 gangliosidosis									X	X				X	X	X			
GALC-related Beta-galactosylceramidase deficiency	Krabbe disease; Globoid cell leukodystrophy					X		X		X				X		X	X			

PSAP-related Krabbe disease-like disorder due to saposin A deficiency							X		X		X				X		X	X			
ARSA-related Arylsulfatase A deficiency	*Metachromatic leukodystrophy (MLD)*															X	X	X			
PSAP-related Metachromatic leukodystrophy-like disorder due to saposin B deficiency																X	X	X			
SUMF1-related Formyl-glycine generating enzyme deficiency	Multiple sulfatase deficiency (MSD)		X	X	X	X	X		X	X						X	X				X
GLA-related Alpha-galactosidase A deficiency	Fabry disease		X		X	X	X	X	X	X							X		X	X	
ASAH1-related Acid ceramidase deficiency, inflammatory phenotype	Farber disease; Farber lipogranulomatosis				X	X				X			X	X			X			X	X
ASAH1-related Acid ceramidase deficiency, primary neurologic phenotype	Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME)							X								X	X				X
PSAP-related Combined saposin deficiency	Combined saposin deficiency					X							X				X				
F) Disorders of glycosaminoglycan degradation (n=13)																					
IDUA-related Alpha-iduronidase deficiency	Mucopolysaccharidosis type I (MPS I); Hurler syndrome; Hurler–Scheie syndrome; Scheie syndrome		X	X		X	X	X		X			X			X	X		X	X
IDS-related Iduronate 2-sulfatase deficiency	Mucopolysaccharidosis type II (MPS II); Hunter syndrome		X	X		X	X	X		X			X			X	X		X	X
SGSH-related Heparan N-sulfatase deficiency	Mucopolysaccharidosis type IIIA (MPS IIIA); Sanfilippo syndrome type A					X	X	X		X			X			X	X			X
NAGLU-related N-acetylglucosaminidase deficiency	Mucopolysaccharidosis type IIIB (MPS IIIB); Sanfilippo syndrome type B					X	X	X		X						X	X			X
HGSNAT-related Heparan-alpha-glucosaminide N-acetyltransferase deficiency	Mucopolysaccharidosis type IIIC (MPS IIIC); Sanfilippo syndrome type C					X	X	X		X			X			X	X			X

GNS-related N-Acetylglucosamine 6-sulfatase deficiency	Mucopolysaccharidosis type IIID (MPS IIID); Sanfilippo syndrome type D					X	X	X		X			X			X	X			X
GALNS-related N-Acetylgalactosamine 6-sulfatase deficiency	Mucopolysaccharidosis type IVA (MPS IVA); Morquio A syndrome		X	X		X	X	X		X			X			X			X	X
GLB1-related Beta-galactosidase 1 deficiency, Morquio B	Mucopolysaccharidosis type IVB (MPS IVB); Morquio B syndrome		X			X	X	X		X						X			X	X
ARSB-related N-Acetylgalactosamine 4-sulfatase deficiency	Mucopolysaccharidosis type VI (MPS VI); Maroteaux–Lamy syndrome		X	X		X	X	X		X			X			X			X	X
GUSB-related Beta-glucuronidase deficiency	Mucopolysaccharidosis type VII (MPS VII); Sly syndrome		X	X		X	X			X			X			X				X
HYAL1-related Hyaluronidase deficiency	Mucopolysaccharidosis type IX (MPS IX); Natowicz syndrome						X													X
ARSK-related Arylsulfatase K deficiency	Mucopolysaccharidosis type X (MPS X)						X													X
ARSG-related Arylsulfatase G deficiency	Usher syndrome type 4 (USH4)							X		X										
G) Disorders of glycoprotein degradation (n=7)																				
NEU1-related Alpha-neuraminidase deficiency (CDG)	Sialidosis				X	X	X	X		X			X			X		X		X
CTSA-related Cathepsin A deficiency	Galactosialidosis		X		X	X	X		X	X			X			X		X		X
MAN2B1-related Alpha-mannosidase B deficiency	Alpha-mannosidosis			X		X	X	X		X			X	X		X	X			X
MANBA-related Beta-mannosidase deficiency	Beta-mannosidosis				X		X	X		X			X			X	X			X
NAGA-related Alpha-N-acetylgalactosaminidase deficiency	Schindler disease; Kanzaki disease		X		X		X			X						X				

FUCA1-related Alpha-L-fucosidase deficiency	Fucosidosis	X			X	X	X	X		X			X			X				X
AGA-related Aspartylglucosaminidase deficiency	Aspartylglucosaminuria (AGU)		X		X	X	X		X				X		X	X				X
H) Neuronal ceroid lipofuscinosis (n=13)																				
PPT1-related Palmitoyl-protein thioesterase 1 deficiency	CLN1 disease; Infantile neuronal ceroid lipofuscinosis									X					X	X				
TPP1-related Tripeptidyl-peptidase 1 deficiency	CLN2 disease; Late-infantile neuronal ceroid lipofuscinosis									X					X	X				
CLN3-related Lysosomal transmembrane protein deficiency	CLN3 disease; Juvenile neuronal ceroid lipofuscinosis; Batten disease		X							X			X		X	X	X			
DNAJC5-related Kufs disease	CLN4 disease; Kufs disease															X	X			
CLN5-related Lysosomal protein deficiency	CLN5 disease									X					X	X				
CLN6-related Kufs disease	CLN6 disease															X	X			
MFSD8-related CLN7 Turkish variant	CLN7 disease									X					X	X	X			
CLN8-related Lysosomal protein deficiency	CLN8 disease									X					X	X	X			
CTSD-related Cathepsin D deficiency	CLN10 disease									X					X	X				
GRN-related Progranulin deficiency	CLN11 disease									X					X	X				
ATP13A2-related Lysosomal type 5 P-type ATPase deficiency	CLN12 disease								X	X	X									

CTSF-related Cathepsin F deficiency	CLN13 disease													X	X	X				
KCTD7-related CLN14 disease	CLN14 disease									X				X	X					
I) Disorders of autophagy (n=15)																				
EPG5-related Vici syndrome			X		X		X	X	X	X				X		X		X		
WDR45-related Neurodegeneration with brain iron accumulation 5	BPAN; Beta-propeller protein-associated neurodegeneration														X					
SNX14-related Spinocerebellar ataxia 20	SCAR20						X								X					X
SPG11-related Axonal Charcot-Marie-Tooth disease type 2X	CMT2X; SPG11-related disorder					X				X	X				X	X	X			X
ZFYVE26-related Spastizin deficiency	SPG15; Hereditary spastic paraplegia type 15										X				X	X	X			X
AP5Z1-related Spastic paraplegia 48	SPG48; Hereditary spastic paraplegia type 48									X	X				X					
TECPR2-related Spastic paraplegia 49	SPG49; TECPR2-associated hereditary spastic paraplegia			X		X	X					X			X				X	
TBK1-related Frontotemporal dementia and/or amyotrophic lateral sclerosis type 4	FTDALS4; TBK1-associated ALS/FTD					X								X	X	X				
RAB7A-related Charcot-Marie-Tooth disease type 2B	CMT2B				X									X	X					X
ATG5-related Spinocerebellar ataxia	ATG5 deficiency; Childhood-onset ataxia due to ATG5 deficiency									X					X					
ATG7-related Spinocerebellar ataxia, autosomal recessive 31	SCAR31			X			X	X		X				X	X					

ATG12-related Neurodevelopmental disorder	ATG12 deficiency				X	X	X	X		X	X	X				X		X		
TBCK-related Hypotonia, infantile, with psychomotor retardation and characteristic facies	TBCK syndrome; IHPRF3			X		X	X			X		X				X			X	
CHMP3-related Hereditary spastic paraplegia CHMP3	CHMP3-associated hereditary spastic paraplegia									X					X	X				
WIPI2-related Intellectual developmental disorder with short stature and variable skeletal anomalies	WIPI2 deficiency						X									X	X			X
J) Other disorders of complex molecule degradation (n=16)																				
GAA-related Alpha-glucosidase deficiency	Pompe disease; Glycogen storage disease type II (GSD II)		X	X		X	X								X	X			X	
LAMP2-related Lysosome-associated membrane protein 2 deficiency	Danon disease		X							X			X		X	X				
SCARB2-related Glucocerebrosidase receptor deficiency	Action-myoclonus renal failure syndrome (AMRFS)		X													X		X		
NPC1-related Niemann-Pick disease type C1						X				X			X			X	X			
NPC2-related Niemann-Pick disease type C2						X				X			X			X	X			
LIPA-related Lysosomal acid lipase deficiency	Lysosomal acid lipase deficiency (LAL-D); Wolman disease; Cholesteryl ester storage disease (CESD)		X			X			X				X			X			X	
GNPTAB-related UDP-N-acetylglucosamine-1-phosphotransferase subunit alpha/beta deficiency (CDG)	Mucolipidosis II; I-cell disease; Mucolipidosis III alpha/beta		X	X	X	X	X			X			X			X				X
GNPTG-related UDP-N-acetylglucosamine-1-phosphotransferase subunit gamma deficiency (CDG)	Mucolipidosis III gamma						X	X								X				X

LYSET-related TMEM251 deficiency (CDG)				X			X									X				X
MCOLN1-related Mucolipin 1 deficiency	Mucolipidosis IV (ML IV)					X				X			X		X	X				
MBTPS1-related Site-1 protease deficiency	CAOP syndrome; S1P deficiency						X		X	X										X
CTSB-related Cathepsin B superactivity					X															
CTSC-related Cathepsin C deficiency	Papillon–Lefèvre syndrome			X	X		X													X
CTSK-related Cathepsin K deficiency	Pycnodysostosis			X			X		X										X	X
CLCN7-related Chloride channel 7 superactivity						X						X				X		X		
SPNS1-related Sphingolipid transporter 1 deficiency			X			X									X					
K) Disorders of cobalamin metabolism (n=2)																				
LMBRD1-related Methylmalonic aciduria and homocystinuria, cblF type			X	X		X	X			X			X			X	X	X		X
ABCD4-related Methylmalonic aciduria and homocystinuria, cblJ type			X			X	X			X			X			X	X	X		

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