



The prevalence of diseases caused by lysosome-related genes in a cohort of undiagnosed patients



Filippo Pinto Vairo^a, Nicole J. Boczek^a, Margot A. Cousin^a, Charu Kaiwar^f, Patrick R. Blackburn^a, Erin Conboy^b, Brendan C. Lanpher^{a,b}, Ralitzia H. Gavrilo^{a,b,e}, Pavel N. Pichurin^{a,b}, Konstantinos N. Lazaridis^{a,d}, Dusica Babovic-Vuksanovic^{a,b}, Eric W. Klee^{a,b,c,*}

^a Center for Individualized Medicine, Health Sciences Research, Mayo Clinic, Rochester, MN, USA

^b Department of Clinical Genomics, Mayo Clinic, Rochester, MN, USA

^c Department of Biomedical Informatics, Mayo Clinic, Rochester, MN, USA

^d Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

^e Department of Neurology, Mayo Clinic, Rochester, MN, USA

^f Center for Individualized Medicine, Mayo Clinic, Scottsdale, AZ, USA

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ABSTRACT

Lysosomal diseases (LD) comprise a group of approximately 60 hereditary conditions caused by progressive accumulation of metabolites due to defects in lysosomal enzymes and degradation pathways, which lead to a wide range of clinical manifestations. The estimated combined incidence of LD is between 1 in 4000 to 1 in 13,000 live births, with recent data from pilot newborn screening studies showing even higher incidence. We aimed to determine the prevalence of the classical LD and other diseases caused by lysosome-related genes in our cohort of diagnostic odyssey patients. The Individualized Medicine Clinic at Mayo Clinic is increasingly utilizing whole exome sequencing (WES) to determine the genetic etiology of undiagnosed Mendelian disease. From September 2012 to April 2017, WES results from 350 patients with unexplained symptoms were reviewed. Disease-causing variants were identified in *MYO6*, *CLN6*, *LRBA*, *KCTD7*, and *ARSB* revealing a genetic diagnosis of a LD in 8 individuals from 5 families. Based on our findings, lysosome-related disorders may be collectively common, reaching up to 1.5% prevalence in a cohort of patients with undiagnosed diseases presenting to a genetics clinic.

1. Introduction

The lysosomal diseases (LD), classically named lysosomal storage diseases, are a group of inherited disorders caused by defects in enzymes, enzyme activator proteins, membrane proteins, or transporters targeted to the lysosome with resulting abnormal accumulation of complex macromolecules. When a lysosomal metabolic pathway is impaired, there is progressive storage of a variety of non-degraded or partially degraded products such as lipids, glycolipids, sphingolipids, glycoproteins, sulfatides, sphingomyelin, and gangliosides [1]. Additionally, defective targeting of lysosomal enzymes to lysosomes, abnormal lysosomal membrane proteins, and defective egress of substrate may also cause abnormal storage. Clinical variability and overlapping symptoms among LDs make determining the precise diagnosis difficult or impossible in many cases. Although individually rare, the prevalence of LDs (approximately 60 diseases and growing) is significant when the

group is considered as a whole [2], varying from one case in every 4000 to 13,000 births across different studies [3–6], a frequency that is projected to increase as data emerging from newborn screening programs become available [7]. Notably, certain ethnic groups may have an increased prevalence of a given condition. Examples include an increased occurrence of Tay-Sachs disease, Gaucher disease type 1, Niemann-Pick disease type A, and mucopolidosis IV in the Ashkenazi Jewish population [8], and an increased frequency of infantile neuronal ceroid lipofuscinosis, Salla disease, and aspartylglucosaminuria in patients of Finnish descent [9].

Lysosomes play a key role in phagocytosis and antigen presentation. The lysosome-endosomal system is intimately involved in regulation of apoptosis, autophagy, and cell death [10]. Mutations in genes in the autophagy-lysosomal pathway (ALP) can be associated with neurodegenerative disorders, such as Parkinson [11] and Alzheimer diseases [12]. Hence, it is possible that an increasing number of variants in the

* Corresponding author at: 200 First Street SW, Rochester, MN, 55905, USA.
E-mail address: klee.eric@mayo.edu (E.W. Klee).

ALP pathway will be identified within an expanding spectrum of diseases that can be characterized as lysosomal dysfunction disorders, including immune dysfunction and other phenotypic presentations. In this paper, we aim to determine the prevalence of the classical LD and other diseases caused by lysosome-related genes in a cohort of patients with undiagnosed suspected Mendelian diseases referred to the Individualized Medicine Clinic of the Mayo Clinic's Center for Individualized Medicine (CIM) [13].

2. Methods

The Individualized Medicine Clinic of CIM at Mayo Clinic is increasingly utilizing whole exome sequencing (WES) to determine the genetic etiology of undiagnosed Mendelian disease. An integral part of our Individualized Medicine Clinic is the Genomic Odyssey Board (GOB), comprised of clinicians and scientists. This group recommends clinical follow-up or research testing that may clarify variants of uncertain significance that are suspected to be causative [13]. From September 2012 to April 2017, the GOB reviewed WES results from patients with unexplained symptoms despite extensive clinical, biochemical testing, imaging, and genetic investigation. Clinical data were extracted from electronic medical records. All families received formal pre- and post-test genetic counseling, and written informed consent was obtained from the patient or the legal guardians. Most of the WES was performed in CLIA certified laboratories. When research WES was done, the putative variants found were confirmed by Sanger sequencing in a CLIA certified laboratory. The research protocol for this study was approved by Mayo Clinic's Institutional Review Board. The list of 144 lysosome-related genes (Supplementary Table 1) associated with Mendelian diseases was generated based on a list published by Di Fruscio et al. [14], which contains genes encoding proteins with an established or predicted role in autophagy or in the endocytic pathways, proteins with lysosomal localization, and genes associated with classical lysosomal diseases.

3. Results

Of the three hundred and fifty probands evaluated by the GOB from September 2012 to May 2017, eighty-five patients were given a definitive diagnosis with an overall diagnosis rate of 24.2%. Of these 85, five individuals received a genetic diagnosis associated with a lysosome-related gene (Table 1). Two of those were diagnosed with a disease associated to the ALP pathway (Patients A and D), two with a neuronal ceroid lipofuscinosis (NCL) (Patients B and C), and one with a mucopolysaccharidosis (Patient E). The potential differential diagnoses, genetic and biochemical investigations prior to the WES for the patients diagnosed with a LD are listed in Table 2.

The summary of the patients' histories are as follows:

Table 1
Patients with disease-causing variants in lysosome-related genes.

Patient	Gene	Transcript ID	Nucleotide	Amino acid	Zygosity	Inheritance	Classification ^a	Disease
A	<i>MYO6</i>	NM_004999.3	c.1983+1G > A	p.?	hom	AR	Pathogenic	Deafness type 37
B	<i>CLN6</i>	NM_017882.2	c.[697_705del]; [c.13C > T]	p.[Leu233_Ile235del]; [Arg5Trp]	comp.het	AR	Pathogenic	Ceroid lipofuscinosis neuronal type 6
C	<i>KCTD7</i>	NM_001167961.2	c.422T > C	p.Leu141Pro	hom	AR	Likely Pathogenic	Ceroid lipofuscinosis neuronal type 14
D	<i>LRBA</i>	NM_006726.4	c.3985_3986del	p.Asp1329Tyrfs*18	hom	AR	Pathogenic	Immunodeficiency common variable 8
E	<i>ARSB</i>	NM_000046.3	c.[310C > A]; [928A > G]	p.[Gln104Lys];[Asn310Asp]	comp.het	AR	Likely Pathogenic	Mucopolysaccharidosis type VI

hom = homozygous; comp.het = compound heterozygous; het = heterozygous; AR = autosomal recessive; AD = autosomal dominant; VUS = variant of uncertain significance.

^a following the ACMG 2015 guidelines.

3.1. Patient A

The patient is a 25-year-old woman from Kuwait, who was referred to Clinical Genomics clinic for evaluation of possible underlying genetic condition due to the personal and family history of prelingual deafness and seizures. She was born full term via vaginal delivery after uncomplicated pregnancy to a consanguineous couple. No known congenital anomalies were noted. In the absence of a newborn hearing screen, the family noticed she had hearing impairment at the age of 6 to 8 months. Of note, hearing impairment was present in her six other affected sisters. She and two of her sisters also have a seizure disorder, which started in their late 20's, and a third sister developed seizures at the age of 2 years, which then resolved from the age of 7 years until recurring in the late 20's. Subsequent magnetic resonance imaging (MRI) of the brain demonstrated bilateral subependymal gray matter heterotopia. After extensive genetic and metabolic screening failed to reveal a cause, WES was performed and detected a homozygous NM_004999.3(*MYO6*):c.1983+1G > A pathogenic variant (the mother is heterozygous for the mutation and father was not available for confirmatory testing) in the *MYO6* gene. The variant is classified as pathogenic based on the ACMG 2015 guidelines [15]. Homozygous pathogenic variants in the *MYO6* gene are the cause of autosomal recessive deafness type 37 (DFNB37; OMIM: 607821). Additionally, three variants of uncertain significance (VUS) in genes associated with epilepsy (*CACNA1H*, *CHRNA4*, and *SZT2*) were also detected, which at this time could not be ruled in or out as causative for her personal and family history of seizures. This case was included in the paper describing the first 18 months of experience of performing WES for diagnostic odyssey patients in Mayo Clinic Center for Individualized Medicine [16].

3.2. Patient B

The patient is a 21-year-old man with European ancestry, one of three affected brothers, who was referred to the Clinical Genomics clinic for evaluation of progressive neurological disease. He was a product of a normal pregnancy, and had normal early childhood development. Starting in grade school, he began to have cognitive difficulties eventually qualifying him for special services. At 14 years, he developed seizures and his cognitive abilities began to deteriorate. He developed an unsteady gait, tremor of the whole body, dysarthria and swallowing difficulties. His eye exam was normal and he had no hearing loss. Brain MRI showed generalized cerebral atrophy, and slightly more pronounced cerebellar atrophy. No other significant abnormalities were noted. Metabolic screening was unremarkable, and a skin biopsy with electron microscopy did not show evidence of a storage disease. A next-generation DNA sequencing based epilepsy panel of 126 genes plus mitochondrial DNA in 2014 found a heterozygous in-frame deletion in exon 7 of the *CLN6* gene, NM_017882.2(*CLN6*):c.697_705del, p.Leu233_Ile235del. Although

Table 2
Differential diagnoses and investigation prior to the WES.

Patient	Signs and symptoms	Differential diagnoses	Genetic investigation	Biochemical investigation	Laboratory clue of a possible LD
A	Congenital prelingual hearing loss, intractable seizures, subependymal gray matter heterotopia	FLNA-related disorders	FLNA full gene sequencing and deletion/duplication; CMA	Biotinidase, coenzyme Q10, peroxisomal panel, Smith-Lemli-Opitz screening, quantitative plasma and urine amino acids, CDG screening, oligosaccharide and mucopolysaccharide screening, urinary organic acids	None
B	Progressive encephalopathy, cerebellar ataxia, dysphagia, hyperreflexia, cognitive decline	NCL, GM1 and GM2 gangliosidosis, Farber disease, Creatine deficiency, CDG, Giant axonal dystrophy, Lafora disease, Mitochondrial disease	Comprehensive epilepsy NGS panel; mitochondrial DNA sequencing	Lactate, pyruvate, quantitative plasma and urine amino acids, urinary organic acids, CSF analysis, skin biopsy for storage material. In the affected brother: beta-glucosidase, hexosaminidases, oligosaccharidoses screening, CDG screening, vitamin E, ceruloplasmin, copper, frataxin	One VUS in <i>CLN6</i> found in a multi-gene NGS panel
C	Developmental delay, neurodegeneration, ataxia, myoclonic epilepsy	Several	CMA; mitochondrial DNA sequencing and deletion testing	Lactate, ammonia, quantitative plasma and urine amino acids, acylcarnitine profile, urinary organic acids, urinary acylglycines, oligosaccharidoses and mucopolysaccharidoses screening, vitamin E, biotinidase, ceruloplasmin, copper, coenzyme Q10, CDG screening, alpha fetoprotein, CSF amino acids analysis, neurotransmitters, purine and pyrimidine panel	None
D	Chronic diarrhea, failure to thrive, systemic autoimmune disorder	<i>MYO5B</i> -related disorder, EPCAM-related disorder, IPEX	CMA; <i>RSF13B</i> , <i>STAT5B</i> , <i>STAT1</i> , <i>NOD2</i> , <i>MYO5B</i> , <i>CD25</i> , and <i>FOXP3</i> genes sequencing	FOXP3 protein expression, cytokines analyses, CDG screening, T and B cell tests, lactate, alpha-1-antitrypsin, auto-antibodies, CSF analysis	None
E	Corneal clouding, thickened mitral valve, joint pain, contractures	Skeletal dysplasia, Genetic peripheral neuropathies, Lysosomal storage disorder	None	Lysosomal screening panel in blood (alpha-galactosidase, hexosaminidase, alpha-L-iduronidase), Lysosomal screening panel in urine (ceramide trihexoside, sulfatides, oligosaccharides, glycosaminoglycans), mucopolysaccharides screening	Mild elevation of urinary GAG; mild excretion of dermatan sulfate

CDG: congenital disorders of glycosylation; CMA: chromosomal microarray; NCL: neuronal ceroid lipofuscinosis; NGS: next generation sequencing; CSF: cerebral spinal fluid; IPEX: immunodysregulation, polyendocrinopathy, enteropathy, X-linked; MPS: mucopolysaccharidoses; GAG: glycosaminoglycans.

reported as a VUS in the original clinical report, reclassification of this variant taking into account cosegregation of the recessive variants placed this variant in the pathogenic category. No other change in this gene was identified. The younger affected brother is a 14-year-old boy with a progressive neurological disease that started with cognitive difficulties in kindergarten followed by seizures and speech dysarthria at the age of 12 years, tremors at 13 years of age, and most recently, gait imbalance. The youngest brother is a 12-year-old boy with a progressive neurological disorder, including cortical involvement with cognitive impairment, epilepsy, dysarthria, and seizure onset at the age of 11 years. There is no other family history of neurological diseases. WES performed for the affected siblings not only confirmed the previously detected *CLN6* variant, but also identified a second in trans missense variant in *CLN6* NM_017882.2(*CLN6*):c.13C > T (p.Arg5Trp), a previously reported pathogenic variant in a patient with neuronal ceroid lipofuscinosis type 6 (OMIM: 601780) [17].

3.3. Patient C

The patient is a 4-year-old girl from Kuwait, born to consanguineous parents, who was referred to Clinical Genomics for evaluation of developmental delay, ataxia and seizures. She was born at term after an uneventful pregnancy. Her early development was unremarkable. At 2 years of age, she started to have myoclonic seizures, gait unsteadiness, and developmental delay. She has a sister with similar symptoms, with myoclonic seizures starting at 15 months of age. At 4 years of age, a brain MRI and spectroscopy were normal. However, when she was 5 years, a repeat MRI was abnormal with volume loss of the gray and white matter. A chromosomal microarray was done and showed a 421 kilobase deletion of uncertain significance in region 15q11.2, which has been described in unaffected individuals [18]. After unrevealing extensive evaluations, WES was performed and detected a likely pathogenic [15] homozygous missense variant in the *KCTD7* gene NM_001167961.2(*KCTD7*):c.422T > C (p.Leu141Pro) in both sisters. *KCTD7* is associated with neuronal ceroid lipofuscinosis type 14 (OMIM: 611726), characterized by progressive myoclonic epilepsy with or without intracellular inclusions.

3.4. Patient D

The patient is a 16-year-old boy from Saudi Arabia, born to consanguineous parents, who was referred for evaluation of chronic diarrhea, failure to thrive and systemic autoimmune disorder. He was born at term after a normal pregnancy and had normal developmental milestones. At 6 months of age, he started having chronic diarrhea that is still an ongoing problem with accompanying failure to gain weight. He had intestinal biopsies that showed villous atrophy and inflammation initially attributed to celiac disease. At approximately 2 years of age, he was started on a gluten-free diet, but there was no improvement. He was diagnosed with juvenile arthritis, vitiligo, and bilateral uveitis at 6 years of age. He continued to have diarrhea and failure to thrive. In addition, he was diagnosed with hypothyroidism and psoriasis. Extensive immunological, genetic and biochemical investigations were all unrevealing. WES was performed and revealed a homozygous truncating variant in the *LRBA* gene NM_006726.4(*LRBA*):c.3985_3986del (p.Asp1329Tyrfs*18), associated with immunodeficiency common variable type 8 with autoimmunity (OMIM: 614700). The patient's father was heterozygous for this variant, while the mother was unavailable for testing.

3.5. Patient E

The patient is a 12-year-old girl, with German and American ancestry, born to non-consanguineous parents, who was referred to Clinical Genomics for evaluation of progressive joint pain, contractures of the hand joints, a radial deviation of her wrist, and corneal clouding.

She was born at term after an uneventful pregnancy, labor, and delivery. During childhood, she experienced frequent ear infections. Corneal clouding was noted at about 5 years of age. She underwent mucopolysaccharidoses (MPS) screening in urine which was normal. She had a stable thickened mitral valve as well as two papillary muscles and trivial to mild mitral stenosis. She has significant pain in her wrists, knees, and ankles and has always had decreased flexibility, including her spine. X rays showed thickened ribs, several shorted vertebrae and hip dysplasia. Given the concern for a lysosomal disorder, another MPS screen was requested which showed a very mild elevation of urinary glycosaminoglycans (GAG) (11.1 mg/mmol creatinine, with normal values below 10 mg/mmol creatinine) and mildly elevated excretion of dermatan sulfate in urine. A lysosomal enzyme panel in blood, including alpha-galactosidase, total hexosaminidase, and alpha-L-iduronidase was normal. WES was performed and identified two novel missense variants, classified as VUS in *ARSB* (NM_000046.3(*ARSB*):c.[310C > A];[928A > G]). Arylsulfatase B in leukocytes was undetectable, confirming the diagnosis of Mucopolysaccharidosis type VI, Maroteaux-Lamy syndrome (OMIM: 253200).

4. Discussion

This paper aimed to raise the awareness that several lysosomal disorders can remain undiagnosed after extensive genetic and biochemical investigations. LD are a large group of over 60 various inherited diseases that, in the majority of cases, result from functional deficits of specific lysosomal enzymes and, in a few cases, from the defective function of non-enzymatic lysosomal proteins or non-lysosomal proteins involved in lysosomal biogenesis. There is a wide phenotypic spectrum of nonspecific manifestations, which may lead to considerable diagnostic delay as well as missed diagnoses. Since there are many lysosomal disorders that do not result from lysosomal enzyme deficiencies detected by clinically available tests, we hypothesized that WES is a tool that can be used to aid diagnoses of this group of diseases. By querying our cohort of WES cases we found that the molecular diagnostic yield of WES in our cohort of previously undiagnosed patients was in accordance with other cohorts worldwide [16]. Also, we revealed a genetic diagnosis of a LD in 8 individuals from 5 different families.

Mutations in *MYO6* can cause isolated sensorineural hearing loss or deafness associated with hypertrophic cardiomyopathy. Besides sensorineural hearing loss, our patient also had seizures, a phenotype shared with three out of six siblings. Since mutations in *MYO6* have never been associated with epilepsy, and patient A has VUSs in genes that have been associated with seizures, we suspect that variants in other genes may have a role in her phenotype but, at this time, we are unable to determine the secondary genetic cause that would explain seizures in the proband and her sisters. *MYO6* encodes for myosin VI which is involved, among other functions, in exocytosis at the Golgi and plasma membrane, as well as trafficking and sorting of cargo at early endosomes [19]. Depletion of myosin VI causes accumulation of autophagosomes, which may cause impairment in the autophagosome maturation and its fusion with the lysosome [20].

Two patients (B and C) had a diagnosis of NCL, a group of currently 13 diseases classically characterized as lysosomal storage disorders, and are the most common degenerative brain diseases of childhood [21]. Clinical enzymatic testing is only available for types 1 and 2, making a multi-gene panels and WES the best techniques for the diagnosis of other types of NCL. Noteworthy, patient B went through a multi-gene panel testing that included *CLN6*, but one of the variants had been missed because exon 1 was not well covered by the customized panel offered by the performing clinical laboratory. Research WES performed by our group had better coverage of the *CLN6* exonic regions, and was able to detect the second causative variant in this family leading to a definitive diagnosis and appropriate genetic counseling for the family. Although, there is no specific treatment approved for NCL6, this

diagnosis qualified the family for consideration in an ongoing gene therapy-based clinical trial (NCT02725580) [22].

Patient C was found to have a pathogenic variant in *KTCD7*, which has been reported in only 12 families so far. All reported patients, including our case, presented with epileptic seizures. Patients with mutations reported close to the N-terminus region of the protein seem to have a more pronounced progressive myoclonic epilepsy phenotype. Brain MRI was either normal or had nonspecific findings and eye examination was normal in most patients [23]. The finding of prominent NCL-type storage material in one out of nine patients' fibroblasts lead Staropoli et al. to classify the disease as NCL type 14 [24]. Even though the disease has no specific treatment, after reaching the diagnosis of our patient, we could provide the family with information regarding the oldest patient with NCL type 14, who is now 25 years old and is able to walk independently [23]; this a very different clinical course compared to the majority of patients with the more common types of NCL.

For patient D, the list of differential diagnoses was wide and included IPEX (immune dysregulation, polyendocrinopathy enteropathy, X-linked) syndrome, and IPEX-like disorders (*CD25*, *ITCH*, *STAT5B* deficiencies, and gain-of-function mutations in *STAT1*), among other immunodeficiency syndromes. After many invasive procedures (such as intestinal biopsies), unsuccessful treatments with high-cost immunotherapies and restrictive diets, and single-gene and multi-gene panel tests that failed to lead to a diagnosis, WES was able to detect a homozygous variant in *LRBA*. This finding introduced the possibility of a bone marrow transplant as an appropriate treatment for his illness [25]. *LRBA* deficiency leads to reduced autophagy and increased susceptibility to apoptosis which is speculated to be the cause of the autoimmune features seen in *LRBA*-deficient individuals [26].

Although the suspicion for a lysosomal disorder for patient E was raised since she was 5 years of age, screening tests failed to result in a diagnosis. For some MPS VI patients, glycosaminoglycan excretion can be normal or only mildly elevated, which can cause a delay in the diagnosis of the attenuated form of the disease [27]. Furthermore, the enzymatic analysis of arylsulfatase B may not be present in all lysosomal screening panels, as in our case. Due to the wide phenotypic spectrum, many patients with attenuated forms, such as MPS I and MPS VI remain undiagnosed after years of clinical investigation when they could benefit from treatment.

Only one third of the classical lysosomal disorders have a clinically available specific enzymatic test that can be used as a diagnostic test. For the others and for the increasing number of lysosome-related heritable diseases, while secondary biomarkers can be helpful, the definitive diagnosis relies on genetic testing. For instance, since the majority of the NCL patients present with overlapping neurological symptoms, a multi-gene panel would be the most cost-effective test for that group of disorders. In our Individualized Medicine Clinic, where many of the patients present with neurological and nonspecific symptoms, WES has been the most effective diagnostic approach.

5. Conclusion

Patients with lysosomal disorders can present with a constellation of nonspecific symptoms. In our cohort, WES had a higher diagnostic yield in individuals born to consanguineous parents, and those who had neurological manifestations, making this technique the most cost and time-effective approach used in the setting of an individualized medicine clinic. Based on our findings, diseases associated with lysosome-related genes may be collectively common, reaching up to 1.5% in a cohort of patients with undiagnosed diseases after extensive metabolic and genetic investigation.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ygm.2017.08.001>.

Take-home message

Lysosome-related disorders may be collectively common, reaching up to 1.5% prevalence in a cohort of patients with undiagnosed diseases presenting to a genetics clinic.

Contributions of individual authors

FPV, NB, CK, PRB, MAC, EC, BCL, RHG, PNP, KNL, DB, and EWK collected and interpreted the data and drafted the manuscript. All authors read and approved the final manuscript.

Competing interest statement

The authors declare that they have no conflicts of interest.

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Informed consent

All procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients (or their parents) included in the study.

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