

Emerging Links Between Pediatric Lysosomal Storage Diseases and Adult Parkinsonism

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ABSTRACT: Lysosomal storage disorders comprise a clinically heterogeneous group of autosomal-recessive or X-linked genetic syndromes caused by disruption of lysosomal biogenesis or function resulting in accumulation of nondegraded substrates. Although lysosomal storage disorders are diagnosed predominantly in children, many show variable expressivity with clinical presentations possible later in life. Given the important role of lysosomes in neuronal homeostasis, neurological manifestations, including movement disorders, can accompany many lysosomal storage disorders. Over the last decade, evidence from genetics, clinical epidemiology, cell biology, and biochemistry have converged to implicate links between lysosomal storage disorders and adult-onset movement disorders.

The strongest evidence comes from mutations in *Glucocerebrosidase*, which cause Gaucher's disease and are among the most common and potent risk factors for PD. However, recently, many additional lysosomal storage disorder genes have been similarly implicated, including *SMPD1*, *ATP13A2*, *GALC*, and others. Examination of these links can offer insight into pathogenesis of PD and guide development of new therapeutic strategies. We systematically review the emerging genetic links between lysosomal storage disorders and PD. © 2019 International Parkinson and Movement Disorder Society

Key Words: genetics; lysosomal storage disease; movement disorders; Parkinson's disease

The lysosome is a major site for degradation of cellular proteins and organelles and is thus essential for cellular homeostasis. Neurons appear especially sensitive to lysosomal function given that a wide range of

neurological disorders have been attributed to defects in lysosome function. Mutations disrupting lysosomal biogenesis or function lead to accumulation of nondegraded substrates and cause lysosomal storage disorders (LSDs). More than 50 LSDs have been identified, which show either autosomal-recessive or X-linked inheritance. Although LSDs are predominantly pediatric disorders, there is substantial heterogeneity in both clinical presentations and manifestations, with infantile, juvenile, and adult forms recognized in many cases. Emerging evidence highlights links between LSDs in children and adult movement disorders, most notably, Parkinson's disease (PD)¹ (Table 1). Examination of these links can inform our understanding of the different mechanisms of dysfunction that lead to onset of movement disorders and provide novel targets for therapeutic development.

The following review will examine the published links between lysosomal storage diseases in children and adult-onset PD. We have focused on overlaps which display a phenotypic or genetic association with PD and also display evidence of pathological association, namely alpha-synuclein aggregation. Among the links described,

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TABLE 1. Summary of LSD associated with PD

| Affected Protein (Gene) | LSD | Parkinsonism in Patients or Carriers | PD GWAS Hit | Pathogenic Variant Identified | α -Synuclein Pathology Observed | Relevant Mouse Model ^a |
|--------------------------------------------|-----------------------------------------------------|--------------------------------------|--------------|-------------------------------|----------------------------------------|-----------------------------------|
| Glucocerebrosidase (<i>GBA1</i>) | Gaucher | χ^{118} | χ^{119} | χ^{12} | χ^{120} | χ^{121} |
| Acid Sphingomyelinase (<i>SMPD1</i>) | Niemann-Pick disease Type A, B | χ^{36} | | χ^{38} | | χ^{35} |
| Niemann-Pick type C (<i>NPC1</i>) | Niemann-Pick type C | χ^{51} | | | χ^{48} | |
| Galactosylceramidase (<i>GALC</i>) | Krabbe disease | | χ^{70} | | χ^{69} | χ^{69} |
| a-N-acetylglucosaminidase (<i>NAGLU</i>) | Sanfilippo syndrome B | | χ^{79} | | χ^{78} | χ^{122} |
| ATP13A2 (<i>PARK9</i>) | Neuronal ceroid lipofuscinosis/Kufar-Rakeb syndrome | χ^{88} | | $\chi^{b,87}$ | χ^{96} | χ^{123} |
| Hexosaminidase B (<i>HEXB</i>) | Sandhoff disease | χ^{109} | | | χ^{108} | χ^{107} |

^aSpecifically mouse models with evidence of alpha-synuclein pathology or other PD related dysfunction.

^bPD risk in PARK9 mutant carriers is controversial, but regardless can refer to PARK9 causing the related movement disorder, Kufar-Rakeb syndrome, which includes parkinsonism.

only the link between Gaucher’s disease and PD is definitively established. In most of the other cases we review, additional investigation is required, including either genetic confirmation and/or mechanistic follow-up.

Glucocerebrosidase (*GBA1*)

Gaucher’s disease (GD) is an LSD caused by autosomal-recessive mutations in the *GBA1* gene that encodes for the lysosomal enzyme, glucocerebrosidase (GCase). GCase is a hydrolase which catalyzes the breakdown of glucosylceramide to glucose and ceramide (Fig. 1). More than 300 mutations in *GBA1* have been identified, including point mutations, splice-site mutations, deletions, insertions, and mutations resulting from recombination events with the highly homologous pseudogene.² These mutations lead to reduced lysosomal GCase activity attributed to either disrupted translation, misfolding, impaired trafficking, protein instability, or a combination of these defects. Very

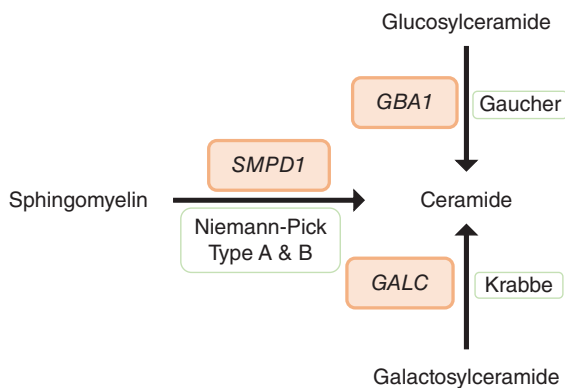


FIG. 1. LSD genes important in ceramide metabolism are also implicated in PD. Mutations in *GBA1*, *SMPD1*, and *GALC* are responsible for Gaucher’s disease, Niemann-Pick disease type A and B, and Krabbe’s disease, respectively. *GBA1* encodes for GCase, which hydrolyzes glucosylceramide to glucose and ceramide; *SMPD1* encodes for acid sphingomyelinase, which hydrolyzes sphingomyelin to phosphocholine and ceramide; and *GALC* encodes for galactosidase, which hydrolyzes galactosyl moieties from lipids, including hydrolysis of galactosylceramide to galactose and ceramide. [Color figure can be viewed at wileyonlinelibrary.com]

rarely, GD can also be caused by mutations in the *PSAP* gene, which encode for Saposin C, an essential protein modulator for GCase.³

Three clinical subtypes of GD are recognized based on age of onset and presence of neurological manifestations. These subtypes are an attempt to categorize what is a phenotypic continuum with presentations ranging from perinatal lethality to nearly asymptomatic.⁴ Type 1 GD is the mildest and most common form of disease (90% of cases in Europe and the United States) which typically presents with hepatosplenomegaly and fatigue. Age at initial presentation of type 1 GD is highly heterogeneous with onset reported in both juvenile and late-adult populations.^{5,6} Type 2 GD is the most severe form of the disease with onset shortly after birth. Type 2 GD manifestations include severe neurological deficits and rapidly progressive neurologic deterioration that is usually fatal by age 3. Type 3 GD includes the symptoms observed in type 1 GD along with more mild central nervous system (CNS) involvement and variable age of onset.⁶

As mentioned above, mutations in *GBA1* lead to reduced GCase enzymatic activity. In general, greater decreases in enzymatic activity correlate with more severe phenotypes. For instance, mutations that result in complete or almost complete loss of enzymatic activity can be perinatal lethal and are more likely associated with the most severe, type 2 form of the disease,^{7,8} whereas mutations with slightly higher residual activity display the least severe, type 1 phenotype. However, exceptions have also been observed.⁸ *GBA1* loss-of-function mutations lead to accumulation of the GCase substrate glucosylceramide (GlcCer), particularly in macrophages, transforming them into classical Gaucher cells. Gaucher cells contain GlcCer aggregates in a characteristic twisted, fibrillar arrangement that are clearly distinguishable by electron microscopy. The monocyte lineage is especially vulnerable because they contain large amounts of glycosphingolipids. As GlcCer accumulates, it is converted to glucosylsphingosine by the enzyme acid ceramidase.⁹ GlcCer and glucosylsphingosine spill over into the

cytoplasm, where they can be further metabolized by neutral GCase2 to ceramide and sphingosine, respectively. Accumulation of glucosylsphingosine and sphingosine also contributes to toxicity in GD.^{10,11}

Heterozygous mutations in the *GBA1* gene are the most common genetic risk factor for PD with a predicted frequency of 7% to 10% in the PD population.¹² This is an example of genetic *pleiotropy*, by which variation in a single gene (*GBA1*) can influence multiple, distinct clinical phenotypes (GD and PD), through autosomal-recessive or dominant inheritance mechanisms, respectively. Overall, GBA-PD exhibits a very similar symptomatic presentation to sporadic PD with a slightly earlier average age of onset. In addition, GBA-PD is characterized by a modest increased risk of cognitive impairment and dementia, and reduced bradykinesia and resting tremor relative to other PD patients.¹²

Although the mechanism by which *GBA1* mutations increase PD risk is not completely understood, GCase enzymatic activity appears to be a critical factor. Individuals with more severe *GBA1* mutations, specifically mutations associated with lower enzymatic activity, have been shown to have increased risk for development of PD and an earlier age of onset.¹³ Specifically, carriers of more severe mutations, such as the c.84dupG or L444P mutation, which are often associated with neuronopathic GD, are more likely to develop PD than carriers of N370S or E326K mutations.^{13,14} Moreover, stronger *GBA1* loss-of-function alleles have also been implicated with more severe motor phenotypes and increased risk of nonmotor manifestations, including hyposmia, cognitive impairment, and dementia.¹³⁻¹⁵ Interestingly, reduced GCase enzymatic activity has also been documented in sporadic PD (without known *GBA1* mutations).^{16,17} Lastly, individuals with GD are also at risk of developing PD. The risk attributed to homozygous *GBA1* loss-of-function alleles is significantly greater than that observed in heterozygous *GBA1* mutations, although most individuals with GD will still not get PD.^{15,18} Together, the accumulating evidence for genotype-phenotype relationships in *GBA-PD* strongly support a dose-dependent, loss-of-function risk model. There is also evidence that GCase unfolding and retention in the endoplasmic reticulum (ER) may also promote toxicity, perhaps through induction of ER stress. Although this mechanism is unlikely to fully account for the GBA-PD link on its own, it could potentially be a relevant modifier contributing to disease heterogeneity.¹⁹ A similar modifier effect may also be driven by genes involved in regulation of GCase, including *SCARB2* and *PSAP*.^{3,20,21}

Work by our lab and others, has shown that reduced GCase activity is associated with lysosomal dysfunction and synuclein accumulation.²²⁻²⁴ This could be attributed to accumulation of the substrate, lysosomal glucosylceramide, which was shown to increase alpha-synuclein

aggregation.²⁵ Recent work has also shown that glucosylsphingosine, which is more abundant in the cytoplasm, might also contribute to alpha-synuclein aggregation.¹¹ More recently, we found that mitochondrial oxidant stress and increased oxidation of dopamine resulted in direct modification of GCase that led to its decreased activity and ultimately lysosomal dysfunction.²⁴ This observation was made in dopaminergic neurons from patients with either idiopathic or familial PD, indicating that this may represent a unifying mechanism linking GCase and PD.²⁴ In support of this hypothesis, we found that mouse models exposed to increased oxidized dopamine displayed alpha-synuclein accumulation, reduced GCase activity, and neurodegeneration in the SN.²⁴ Whereas alpha-synuclein accumulation could inhibit GCase trafficking and lysosomal function in various cell types,²³ our observation highlights one attractive mechanism for the increased vulnerability of midbrain dopaminergic neurons to loss of GCase activity.²⁴

Based on our current understanding, there are several strategies related to GCase ceramide metabolism that could be therapeutic for both GD and PD. Although cellular regulation of ceramide is complex—involving *de novo* synthesis, recycling, and salvage pathways—several feasible strategies might target GCase specifically, including (1) increasing the stability or activity of the remaining GCase enzyme, (2) *GBA1* gene therapy, (3) substrate removal therapy to reduce the accumulation of the glucosylceramide and glucosylsphingosine, or (4) restoring normal levels of ceramide. The first strategy involves the development of molecular chaperones to increase enzyme stability enabling increased trafficking of GCase to the lysosome and/or increasing protein half-life within the lysosome. Alternatively, the development of positive allosteric modulators could directly increase activity of GCase, although this would only be effective if functional GCase is trafficked to the lysosome. The second strategy aims to increase functional GCase protein levels through gene therapy strategies. The third approach targets ceramide synthase in order to reduce accumulation of the GCase substrate, glucosylceramide. This strategy is already approved for use in GD patients and is currently in clinical trials for PD.²⁶ Lastly, we have recently shown that a reduction in ceramide contributes to accumulation of alpha-synuclein in GCase-deficient cells.²² We found that inhibition of acid ceramidase, which catalyzes the hydrolysis of ceramide to sphingosine, could restore normal ceramide levels in the cell and rescue a GCase knockout phenotype.²²

Acid Sphingomyelinase (*SMPD1*)

Niemann-Pick disease (NPD) is a rare autosomal-recessive disorder including neuropathic (Type A) and

non-neuropathic (type B) forms. NPD type A and B are caused by mutations in the gene *SMPD1*, which encodes for acid sphingomyelinase (ASM; sphingomyelin phosphodiesterase). ASM catalyzes the hydrolysis of sphingomyelin to phosphocholine and ceramide in late endosomes and lysosomes (Fig. 1). To date, over 180 mutations in *SMPD1* have been identified, including point mutations (missense and frameshift), small deletions, and splice site mutations.²⁷ These mutations appear to be equally distributed throughout the gene with no specific mutagenic regions identified.

Type A NPD is most common among individuals of Ashkenazi Jewish descent (66% of total type A), although it has also been reported in other populations.²⁸ The most common *SMPD1* mutations are R496L, L302P, and 990delC which account for 90% of type A alleles in the Ashkenazi Jewish population.²⁹ NPD type B is considerably more pan-ethnic than type A with affected populations identified all around the world. Mutations in *SMPD1* that lead to NPD type B display significantly reduced ASM activity, although it is thought that a small amount of residual activity remains, which accounts for the more mild phenotype in NPD type B patients relative to type A.³⁰

Type A NPD is characterized by hepatosplenomegaly, with disease onset beginning months after birth. These individuals also display deteriorating psychomotor development and progressively worsening hypotonia.³¹ In contrast, patients with type B NPD display a significantly milder phenotype with age of onset ranging from infancy to late adulthood. These individuals have normal CNS development, but exhibit hepatosplenomegaly, which can lead to liver failure. In addition, pulmonary function is often compromised and can lead to pulmonary infections, which is the most common cause of death in this population.³¹ Despite the classification of type A and type B, many intermediate cases have also been reported with mild-to-moderated neurological presentations.³² Several of these reported intermediate cases display compound heterozygous mutations, carrying one severe and one mild mutation. This observation highlights a genotype-phenotype association, although patients have also been identified as “intermediate” containing two mild mutations.³²

Mutations in *SMPD1* lead to major loss-of-function of ASM. As a result, patients display accumulation of the ASM substrate sphingomyelin, as well as bis(monoacylglycero) phosphate and lysosphingomyelin within the lysosome.^{33,34} Under stress conditions, ASM is also translocated from the lysosome to the outer leaflet of the plasma membrane, where sphingomyelin hydrolysis leads to reorganization of lipid microdomains.³⁵ As a result, ASM knockout animal models exhibit synaptic dysfunction.^{36,37}

Carriers of *SMPD1* mutations are at increased risk for PD.³⁸ Specifically, heterozygous carriers of more

severe mutations, which cause NPD type A, are implicated. The first mutation identified was L302P, which was found to substantially increase risk for PD (odds ratio estimate = 9.4).³⁸ This was followed by identification of a less common mutation (R591C) in the Chinese population³⁹ as well as the fsP330 mutation.⁴⁰ Interestingly, the R496L mutation, which is one of the most common point mutations in *SMPD1*, was not found to associate with increased PD.⁴¹

Very little is known about the role of ASM and the pathology associated with *SMPD1*-linked PD, because this connection was only recently uncovered and is very rare in the general population. Patients with NPD type B display few neurological symptoms despite having only ~10% residual ASM activity.⁴² This creates uncertainties regarding the mechanism by which *SMPD1* mutation carriers, anticipated to have at least 50% residual activity, would be at risk of PD. In addition, individuals with sporadic PD were found to have normal levels of ASM activity in a dried blood spot analysis.⁴³ However, with the identification of *SMPD1* mutations as risk factors for PD, it is likely that this connection will receive more attention.

Enzyme replacement therapies with ASM are currently in clinical trials for NPD patients. However, because these approaches do not reach the CNS, they are unlikely to be amenable for PD. Additional therapeutic strategies could be aimed at (1) increasing stability or activity of the residual enzyme, (2) reducing the accumulation of the substrate, sphingomyelin, or (3) increasing levels of products (phosphocholine and ceramide). Developing molecular chaperones could increase the stability and levels of protein in lysosomes, whereas positive allosteric modulators might enhance enzymatic activity. These efforts have been aided by the recent publication of the ASM crystal structure.⁴⁴ Augmenting the activity of the similar enzyme, neutral sphingomyelinase, might be one approach to address the accumulation of sphingomyelin in NPD.

Niemann-Pick type C (*NPC1*)

Niemann-Pick type C (NPC) is an autosomal-recessive lysosomal storage disorder primarily caused by mutations in the *NPC1* gene (95% of cases). *NPC1* is a large membrane protein that exists in late endosomes and lysosomes and participates in cholesterol efflux.⁴⁵ More than 260 mutations have been identified in the *NPC1* gene, most of which are missense mutations affecting the luminal domain of the protein, that are associated with onset the disease.^{46,47} Similar to Niemann-Pick type A/B, NPC disease is characterized by hepatosplenomegaly and progressive neurodegeneration, including ataxia, cognitive decline, and seizures. Disease onset usually begins between 2 and 4 years of

age; however, similar to other LSDs, a milder form of the disease displays adult onset with slower progression.^{48,49}

Several case reports have linked *NPC1* to PD. Specifically, the discovery of phosphorylated synuclein pathology at autopsy in the brains of several patients with NPC, with classical Lewy bodies described in the SN from 2 cases.⁵⁰ In addition, several NPC patients and their family members have been reported to present with parkinsonism,⁵¹⁻⁵³ consistent with a possible genetic link similar to *GBA* and *SMPD1*.

Loss of function of *NPC1* leads to accumulation of cholesterol in the late endosome/lysosome of all cells.^{47,54} Cholesterol has been shown to modulate alpha-synuclein/membrane interactions⁵⁵ and thereby promote aggregation and toxicity.^{56,57} *NPC1* mutant cells also accrue sphingolipids including glucosylceramide, glucosylsphingosine, and sphingosine.^{58,59} This is similar to GD and therefore potentially consistent with converging pathogenic mechanisms. The mechanism for accumulation of these additional lipids is unclear, but it could either reflect a direct role for *NPC1* in lysosomal homeostasis or, more indirectly, generalized lysosomal dysfunction following cholesterol accumulation. Further clinical and basic investigation is required to elucidate the potential association between *NPC1* and PD.

One of the pathological hallmarks of NPC is the presence of neurofibrillary tangles comprised of the hyperphosphorylated tau isoform similarly observed in Alzheimer's disease (AD).⁶⁰ Interestingly, presence of the *ApoE4* AD susceptibility allele in *NPC1* patients may be associated with more rapid neurological progression⁶¹ and the coincident development of amyloid plaque pathology.⁵⁰ Although confirmation of these findings in larger, independent cohorts is needed, the observations highlight both the potential role of genetic modifiers in modulating LSD phenotypes and also the possibility of interactions between comorbid brain pathologies. These factors likely contribute to the heterogeneity of disease phenotypes observed in many lysosomal storage disorders.

Galactosylceramidase (GALC)

Mutations in the gene *GALC*, which encodes for galactosylceramidase (GALC), are associated with onset of globoid cell leukodystrophy, also known as Krabbe disease. GALC is a lysosomal enzyme that hydrolyzes galactosyl moieties from lipids, including galactosylcerobroside and galactosylsphingosine (Fig. 1). More than 70 disease-causing mutations in the *GALC* gene have been identified, many of which are compound heterozygous.^{62,63} A large number of these mutations are located outside the catalytic domain, yet still lead to substantially reduced enzymatic activity (~95%).⁶⁴ Therefore,

these mutations are predicted to cause reduced RNA stability, protein stability, or impair protein trafficking.⁶³ Similar to GD, age of onset and disease severity are often dictated by the degree to which enzymatic function is reduced.⁶⁵ Enzymatic activity can be completely lost through splice site and nonsense mutations, whereas more mild, missense mutations show either normal or up to 22% reduced levels of function.^{64,66} Considerable heterogeneity has been described in Krabbe disease, including among individuals with identical mutations, making it difficult to define a genotype-phenotype relationship,⁶⁶ and suggesting the possibility of other genetic or nongenetic modifiers.

Krabbe disease typically presents with infantile onset in the first 6 months of life. The disease commonly manifests as increased irritability, spasticity, and developmental delay along with unexplained fever, blindness, and deafness.⁶² The disease course rapidly progresses with severe motor and mental deterioration.⁶⁷ A small percentage of patients develop juvenile- or adult-onset forms of the disease. These forms are typically less severe, exhibit slower disease progression, and may not involve peripheral neuropathy.⁶⁸

Deficiency of lysosomal GALC leads to rapid accumulation of galactosylsphingosine in patients with Krabbe disease. Accumulation of galactosylsphingosine has been shown to be neurotoxic to oligodendrocytes and Schwann cells⁶⁹ leading to central and/or peripheral demyelination, respectively.⁷⁰ In addition, on neuropathological evaluation, Krabbe disease may reveal cytoplasmic inclusions containing aggregated forms of alpha-synuclein, which are thought to contribute to disease progression.⁷¹ Indeed, sphingolipid accumulation may directly promote and/or accelerate synuclein aggregation.¹¹

In a large genome-wide association study (GWAS) meta-analysis, variants at the *GALC* locus were significantly associated with PD risk.⁷² The causal variant for the association of *GALC* locus with PD risk remains to be defined. Unlike the rare, loss-of-function mutations identified at *GBA1* and *SMPD1*, the most strongly associated variant at *GALC* is a common polymorphism, *rs8005172*, located 12.6 kilobases proximal to the gene promoter and located within an intron of an adjacent gene, *GPR65*. Based on publicly available gene expression data sets,⁷³ this variant is significantly associated with *GALC* gene expression across a large number of tissues, including in brain. Nevertheless, further studies are needed to definitively identify the causal variant(s) and confirm whether *GALC* is indeed responsible for the variant association with PD risk.

Further supporting a role of *GALC* in the onset of PD, a recent study revealed reduced GALC activity and associated sphingolipid accumulation in sporadic PD patients, when compared to healthy controls.⁷⁴ Interestingly, GALC activity was also reduced in aging, which is the strongest risk factor for PD. However, similar to

SMPD1-linked PD, the consideration of PD as part of the phenotypic spectrum of Krabbe disease is difficult to resolve. The disease phenotypes and symptomatic presentations are highly divergent, possibly suggestive of two separate disorders. It is possible that partial loss of *GALC* activity confers increased risk, which, in combination with other factors, leads to the neurodegeneration observed in PD.

The discovery of a possible role of *GALC* in sporadic PD highlights the potential of this protein as a therapeutic target for idiopathic PD. Whereas the current treatment of Krabbe disease is hematopoietic stem cell transplantation,⁷⁵ recent research has identified molecular chaperones that effectively increase *GALC* protein and associated activity.⁶³ These chaperones could potentially be therapeutically beneficial in PD as well. Alternatively, the development of allosteric modulators capable of enhancing *GALC* activity might have promising therapeutic potential in PD.

***α*-N-acetylglucosaminidase (*NAGLU*)**

Sanfilippo syndrome B, also known as mucopolysaccharidosis III disease B (MPS-III B), is an LSD caused by mutations in the *NAGLU* gene encoding *α*-N-acetylglucosaminidase (NAG). NAG is a lysosomal hydrolase, which degrades heparan sulfate glycosaminoglycans. Mutations in NAG lead to accumulation of heparan sulfate within affected individuals.⁷⁶ Sanfilippo syndrome B is characterized by juvenile disease onset with progressive degeneration of the CNS. The rate of MPS-III B progression varies considerably, which appears to correlate, in part, with the level of residual NAG enzymatic activity.⁷⁷⁻⁷⁹

Common genetic variants at the *NAGLU* gene locus were initially discovered in association with PD risk on a candidate basis,⁸⁰ and consistent results recently emerged from GWAS.⁸¹ In addition, examination of postmortem brain tissue from 3 MPS-III B cases revealed accumulations of phosphorylated alpha-synuclein.⁸² Similar pathological findings were also reported in the related LSD, MPS-III A.⁸⁰

There are several possible mechanisms through which impaired NAG activity could promote synuclein accumulation. In vitro studies have found that heparan sulfate dramatically increases the fibrillization of alpha-synuclein.⁸³ Synuclein aggregates can interact with heparan sulfates at the neuronal cell surface leading to cellular internalization.⁸⁴ Thus, it is possible that increased heparan sulfates could accelerate this process enhancing the aggregation and subsequent propagation of alpha-synuclein pathology. Additionally, glycosaminoglycans have been found to inhibit cathepsin D, a major lysosomal protease involved in synuclein

degradation, leading to synuclein accumulation.⁸⁵ Despite these promising observations, more investigation is needed to examine the potential overlap between MPS-III B and PD, including whether targeting NAG might have potential therapeutic benefit.

ATP13A2 (*PARK9*)

ATP13A2 is a transmembrane P5-type ATPase that is involved in active transport of cations across the lysosomal membrane. Currently, only a single homozygous missense mutation in *PARK9* (M810R) has been reported leading to onset of neuronal ceroid lipofuscinosis (NCL) in humans,⁸⁶ although a similar phenotype in canines has more commonly been reported following mutation in a *PARK9* homolog.⁸⁷ NCLs are a heterogeneous group of LSDs resulting from accumulation of lipopigments, predominantly in the brain and retina.⁸⁸ *PARK9*-associated NCL initially presents with learning difficulties in childhood followed by progressive cognitive and motor decline.

Homozygous or compound heterozygous mutations in *PARK9* are also linked to development of Kufor-Rakeb syndrome (KRS). To date, 14 mutations, including deletions, duplications, missense, and splice site mutations, in functionally important domains of the protein have been identified.⁸⁹ KRS, which typically manifests in adolescence or young adulthood, is characterized by parkinsonian motor signs (tremor, bradykinesia, and rigidity) in association with spasticity, supranuclear gaze palsy, and dementia. Pathological features in KRS are unknown because autopsy studies have not been reported.

Heterozygous carriers of *PARK9* mutations have been reported with increased PD risk in some,⁹⁰⁻⁹³ but not all,^{94,95} studies. Interestingly, in one report, *PARK9* variants were implicated to co-occur with either *GBA1* variants or alleles of another PD gene, leucine-rich repeat kinase (*LRRK2*).⁹⁶ Given the rarity of *PARK9* mutations, definitive confirmation of a potential association with PD risk will require sequencing of much larger sample sizes.

Mutations in *ATP13A2* lead to reduced protein expression through nonsense-mediated mRNA decay, reduced protein stability, or impaired trafficking to the lysosome, causing them to undergo ER-associated degradation.⁹⁷ We and others have previously shown that loss of function in *ATP13A2* leads to lysosomal and mitochondrial impairment,^{98,99} possibly attributed to impaired intracellular Zn²⁺ homeostasis.^{100,101} The role of *ATP13A2* in PD is strengthened by the observation that *ATP13A2* mRNA and protein levels are significantly increased in the dopaminergic neurons of patients with sporadic PD.¹⁰² This could indicate that dopaminergic neurons that express higher *ATP13A2*

protein levels are less susceptible to cell death. Potentially consistent with this, loss of *ATP13A2* is associated with impairments in lysosomal function and exosome biogenesis/secretion, both of which may lead to accumulation of alpha-synuclein.^{98,103}

Hexosaminidase B (*HEXB*)

Mutations in *HEXB*, encoding β -hexosaminidase B, cause the recessive disorder, Sandhoff disease (GM2 gangliosidosis). HexB, which is also a lysosomal enzyme, is responsible for the metabolism of GM2 ganglioside. Over 20 mutations in *HEXB*, including both point mutations and deletions, have been described.¹⁰⁴ A juvenile-onset form of Sandhoff disease is caused by severe mutations that nearly abolish enzymatic function (<2% residual activity).¹⁰⁴ These patients present with reduced attention, weakness, and hypotonia, followed by progressive psychomotor impairment.¹⁰⁵ *HEXB* mutations in which slightly higher enzymatic activity is maintained result in a milder, adult-onset form,¹⁰⁶ including muscle weakness, ataxia, and other movement-related symptoms.¹⁰⁷

Although no direct genetic connection has been reported, studies of animal models, human postmortem tissue, along with clinical case reports support a possible link between Sandhoff disease and PD. Notably, *HEXB* knockout mice manifest alpha-synuclein pathology in the SN, along with lysosomal dysfunction.¹⁰⁸ Brain autopsy studies in Sandhoff disease have similarly revealed accumulation of GM2 ganglioside along with alpha-synuclein deposits.^{109,110} Last, several case reports describe the manifestation of parkinsonian motor symptoms/signs in patients with either childhood- or adult-onset Sandhoff disease.¹¹⁰⁻¹¹²

The exact driver of synuclein accumulation in HexB-deficient cells remains unclear. It is possible that accumulation of GM2 ganglioside may directly modulate alpha-synuclein aggregation, or alternatively, this may represent a more indirect consequence of lysosomal dysfunction. Thus, further studies are needed to determine whether modulation of GM2 ganglioside metabolism might be beneficial in PD.

Discussion

The accumulating evidence for genetic connections between LSD and PD has led to the intriguing hypothesis that beyond the pleiotropic effects identified for a handful of genes/variants, a deeper mechanistic link may exist between LSDs and PD.^{113,114} By extension, this would potentially implicate as many as 60 other genes known to cause LSDs. As introduced above, a wealth of evidence including studies of human brain tissue and experiments in numerous animal models,

highlights a clear role for lysosomal dysfunction in PD. Given the rarity of most LSD-causing variants and allowing for the possibility of incomplete- and age-dependent penetrance, definitive assessment of each gene for an association with PD risk will require very large case/control cohorts with sequencing. Based on recent studies in AD,¹¹⁵ it now seems likely that sample sizes including more than 10,000 subjects will be necessary. Although studies of this scope may be possible in the near future, rather than focusing on individual genes where statistical power is more limited, we have pursued a complementary approach examining aggregate genetic risk among 54 LSD genes. Indeed, among ~3,000 PD cases and controls with exome sequencing data, we discovered a significant “burden” of putative damaging variants among this LSD gene set.¹¹⁶ This result was robust to the exclusion of *GBA1* and was consistent in two independent data sets, suggesting that other LSD genes besides *GBA1* likely contribute to PD risk. Importantly, more than half of our PD cohort (56%) had more than one LSD gene variant, and 21% carried two or more potential risk alleles in multiple LSD genes.¹¹⁶ These results therefore support the possibility of an oligogenic risk model for PD, in which multiple genetic hits act in combination to degrade cellular metabolism, enhancing disease susceptibility (Fig. 2). Evidence for the involvement of additional LSD genes in PD risk also comes from a recently completed GWAS, including more than 50,000 cases and 1 million control subjects. This largest-ever study identifies newly significant variant associations at *NAGLU*, *GUSB*, *NEU1*, and *GRN*.⁸¹ Although additional work will be required to confirm whether these genes are in fact responsible for the variant associations, the results of both rare and common variant genetic association studies are converging to implicate significant overlap in susceptibility loci between PD and heterogeneous LSDs.

Despite the genetic, neuropathological, and mechanistic studies implicating lysosomal dysfunction in PD pathogenesis, the involvement of this pathway in disease is not unique to PD. There is abundant evidence of lysosomal dysfunction in several other neurodegenerative disorders, including AD¹¹⁷ and Huntington’s disease,¹¹⁸ suggesting that dysfunction of the lysosomal system is an important contributor to pathogenesis across many neurodegenerative disorders. As a result, lysosomal dysfunction alone cannot explain the preferential neuronal vulnerability in PD, and it is important to consider other responsible factors. In PD, as discussed above, dopamine oxidization may exacerbate lysosomal dysfunction and provide at least a partial explanation for the selective vulnerability of dopaminergic neurons. Increased cytoplasmic oxidation of dopamine may result from synaptic deficits that lead to impaired packaging of dopamine or mitochondrial stress, which increases oxidative potential.^{24,119} In

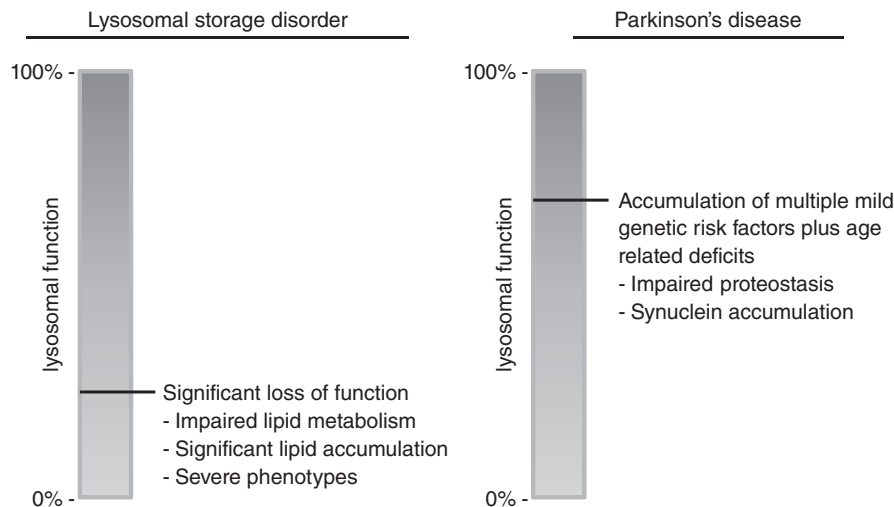


FIG. 2. A hypothetical model for oligogenic risk in PD. Genetic mutations associated with LSDs cause severe impairment in lysosomal function resulting in significant lipid accumulations and leading to the severe phenotypes observed in juvenile-onset LSDs. In cases where mutations result in modest impairments that are associated with PD, lysosomal function is maintained to an extent where lipid metabolism can be relatively normal. However, mild impairments in overall lysosomal protein degradation efficiency caused by one or more LSD genetic variants in combination other genetic and/or non-genetic risk factors as well as aging may further disrupt cellular proteostasis, leading to accumulation of alpha-synuclein and, ultimately, PD.

addition, elevation of alpha-synuclein levels that occurs during lysosomal dysfunction may also explain neuronal vulnerability and could further contribute to lysosomal, mitochondrial, and synaptic dysfunction. Nevertheless, these genetic forms of PD that are linked to lysosomal genes provide a foundation for development of targeted therapies (e.g., activation of GCase in GBA-PD). Despite the potential for complicated interactions and distributed failure of lysosomal, mitochondrial, and synaptic mechanisms in the PD brain, there is promise that targeted approaches, such as activating GCase to enhance lysosomal function, may halt the vicious cycle, enhancing mitophagy, promoting degradation of alpha-synuclein, and blocking accumulation of potentially harmful dopamine oxidation products. ■

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