



Glucocerebrosidase mutations and parkinsonism: how much does the mutation matter?

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Mutations in *GBA1*, the gene that encodes the enzyme glucocerebrosidase (GCase), are associated with a rare Mendelian disorder [Gaucher disease (GD)] as well as common, complex disorders. GD is an autosomal recessive lysosomal disease that is caused by homozygous mutations in *GBA1*. Deficient or defective GCase prevents the degradation of the glycolipids glucosylceramide and glucosylsphingosine. The subsequent lipid accumulation in lysosomes leads to macrophages with a characteristic, crumpled tissue paper-appearing cytoplasm, known as Gaucher cells. GD presents with vast clinical variability, encompassing both non-neuronopathic (type 1) and neuronopathic (types 2 and 3) manifestations. Genotype-phenotype correlation in this disorder is imperfect, with significant phenotypic heterogeneity among patients sharing the same mutations (1). However, milder mutations like N370S and R496H are associated with type 1 GD, while homozygosity for more severe mutations like L444P, D409H and recombinant or null alleles generally leads to type 2 or type 3 GD, the acute neuronopathic and chronic neuronopathic forms, respectively (2).

Close clinical observation of patients with GD led to the identification of an association between GD and the far more common disorder, Parkinson disease (PD) (3). It has been well established that heterozygous mutations in *GBA1* are the most frequent known genetic risk factor for PD and associated Lewy body disorders. Most studies indicate that, in general, patients with PD carrying heterozygous mutations in *GBA1* display an earlier age of onset of parkinsonian symptoms, greater cognitive deficits, and a

more rapid progression of motor impairment than patients with PD without *GBA1* mutations (4). Furthermore, patients with the diagnosis of dementia with Lewy bodies (DLB) have an even higher likelihood of carrying mutations in *GBA1* than patients with PD, with an odds ratio of over 8 (5). There is some evidence that more severe *GBA1* mutations confer a higher risk of developing PD than less severe mutations (4,6). However, there have been few studies investigating the differential survival between non-mutation carriers, and carriers of mild *vs.* severe mutations. This was addressed in a recent publication by Cilia *et al.*, which focused on the differential impact of “severe” *GBA1* mutations *vs.* “mild” *GBA1* mutations on survival and dementia in subjects with PD (7). Their study included 2,764 patients with PD, of which 123 were *GBA1* mutation carriers. Of these, 67 mutations were described as mild (all N370S) and 56 as severe (mostly L444P). This was a somewhat limited study as the investigators only evaluated mutations in exons 8 and 9, a strategy which may potentially miss as many as 20–25% of mutations in a Caucasian population. Overall, the researchers found dementia in 19.6% of non-carriers compared to 34.1% of *GBA1* carriers. The risk for dementia was determined to be even higher in individuals with severe mutations, where there was a 3-fold greater risk *vs.* those with mild mutations. As seen in previous studies, the average age at PD onset was 5 years earlier in *GBA1* carriers. The authors conducted a survival analysis in the 597 subjects that died, and found that compared to PD-noncarriers, the risk of death was significantly higher ($P=0.012$) in patients with a severe

GBA1 mutation, but this risk did not reach significance for patients with a mild *GBA1* allele. This led the investigators to conclude, as stated in the title of their manuscript, that “The Mutation Matters”. However, exploring other motor and non-motor features of PD, except for the described cognitive findings, there were no other significant differences between the carriers of mild and severe mutations. The analysis also revealed that *GBA1* mutations were associated with a greater mortality risk independent of dementia, suggesting the contribution of other factors to the reduced survival.

Cilia *et al.* also performed single-photon emission computed tomography (SPECT) on a subgroup of 35 *GBA1* mutation carriers (20 with “mild” and 15 with “severe” *GBA1* mutations). All mutation carriers were found to have decreased synaptic activity and reduced blood perfusion in the posterior parietal and occipital regions, an observation previously reported in a study using positron emission tomography (8). Perfusion in the parietal lobe was decreased in carriers of severe mutations compared to those with mild mutations and non-mutation carriers with PD. Dopamine transporter density imaging scans also showed more pronounced reduction of nigrostriatal terminals in carriers of severe mutations. Taken together, these findings led the investigators to conclude that carriers of severe mutations have a phenotype that is similar to DLB, while those with mild *GBA1* mutations are likely to have a PD phenotype. The authors then suggest that their data supports a loss-of-function mechanism to explain *GBA1*-associated parkinsonism, where the more severe *GBA1* mutations lead to less GCase and more severe parkinsonian manifestations.

Some of the strengths of this paper include the large sample size of 2,766 subjects with PD, which permitted the researchers to compare the effects of the different mutation groups with respect to dementia and PD. The large sample size also enabled the researchers to analyze survival data longitudinally. Moreover, the researchers’ use of SPECT and dopamine transporter density imaging to compare the neuroimaging phenotypes in their subgroups complemented their clinical assessments in the study.

However, there are major weaknesses in this study. First, the mutation status of the DLB controls was not described, which is essential, due to the high prevalence of *GBA1* mutations in that population. In a multicenter study of DLB, *GBA1* mutations were identified in 54 of 721 subjects (5). Interestingly, of the 54 mutation carriers identified, the most common mutation found was N370S (n=23). Thus, this “mild” mutation is also associated with DLB, a more

progressive disorder with prominent dementia. In a smaller study of 35 Ashkenazi Jews with a diagnosis of DLB (9), 9 of the 11 patients with *GBA1* mutations carried an N370S allele. In addition, E326K and T369M, alterations in *GBA1* that are often considered to be polymorphisms and do not result in GD, were frequently encountered in DLB (10,11). In a large study of autopsy-proven cases of DLB or LBD/Alzheimer disease (12), the vast majority of *GBA1* alterations identified were N370S, E326K, T369M and R496H, all mild variants. Thus, there is a contradiction between these previous findings and the conclusions of the current study. If more severe *GBA1* mutations are responsible for decreased survival and dementia in subjects with PD, why is it that milder mutations are still implicated in DLB? Furthermore, the current study is limited in that it exclusively reported on mutations located in *GBA1* exons 9 and 10, and *GBA1* alterations on the other nine exons were not considered.

In the same issue of *The Annals of Neurology*, a second paper, by Liu *et al.*, explored whether mutations that result in neuronopathic GD accelerate the cognitive decline in patients with PD. This study yielded results similar to those of Cilia *et al.* (13). In this second study, 2,304 patients with PD from seven centers were followed for a median of 4.1 years. The study found that 10.3% of patients carried a mutation in *GBA1*, identified by sequencing the 11 exons of *GBA1*. Approximately 1.4% were considered to have a “neuronopathic” mutation (including L444P), 0.7% had a complex allele, 1.5% had N370S and 6.6 % had E326K, T369M or E388K. They found cognitive decline to be over 3 times more rapid in subjects with a mutation enriched in neuronopathic GD or a complex allele, while there was no increase in the rate of progression in N370S carriers compared to non-carriers. Again, this does not explain why “non-neuronopathic” mutations are also seen in DLB, and why this subset of mutations might be associated with cognition. In fact, a recent study on spinal fluid of subjects with PD with and without *GBA1* mutations demonstrated that the observed cognitive decline was not associated with cerebrospinal fluid levels of amyloid-beta or Tau (14).

In designing rational therapy for patients with *GBA1*-associated PD, a better understanding of the mechanism underlying this association is necessary. Cilia *et al.* maintain that the stronger connection between severe *GBA1* mutations and cognition lends credence to the hypothesis that a loss of function mechanism, related specifically to decreased levels of GCase activity, explains the association between *GBA1* mutations and parkinsonism. While several

treatment strategies are available that target the enzymatic deficiency or the resultant substrate accumulation, it is not clear that any could play a role in treating the parkinsonian manifestations. In patients with type 1 GD and early type 3 GD, enzyme replacement therapy (ERT) has proved effective in reversing hepatosplenomegaly, cytopenia, and osteopenia (15,16). However, since ERT drugs do not cross the blood-brain barrier, ERT does not address the neurological manifestations of type 2 and type 3 GD. Strategies to target the enzyme to the brain via “trojan horse” delivery systems or gene therapy could be efficacious. Substrate reduction therapy (SRT) has also been proposed to decrease the amount of glucosylceramide substrate that is produced, thereby decreasing the strain placed on GCase to cleave the substrate into its sugar and lipid components. Currently available SRT drugs, while shown to be effective for patients with type 1 GD (17), also do not get into the brain, but other forms of SRT are being developed and are under consideration. This strategy, however, assumes that substrate accumulation is responsible for the development of parkinsonism, but this has not been conclusively established.

Alternate strategies under consideration are small molecule chaperones or activators that increase lysosomal levels of GCase by facilitating proper GCase folding and translocation from the endoplasmic reticulum. Many of these molecules are capable of crossing the blood-brain barrier. Ambroxol, a pH-dependent mixed inhibitor of GCase, appears to help translocate GCase to the lysosome in cellular and mouse models, and a human study is underway (18-20). The efficacy of these inhibitors has been limited because they must outcompete the substrate to facilitate proper folding and translocation of GCase to the lysosome. Non-inhibitory chaperones that bind to a site distant from the active site offer some advantages. Two such chaperones have been identified that increase GCase activity, decrease substrate accumulation, and restore defective chemotaxis in primary macrophages differentiated from GD patient monocytes, as well as from patient-derived induced pluripotent stem cells (iPSC) (21). The same chaperones increased GCase activity, decreased substrate storage, and lowered levels of α -synuclein in iPSC-derived dopaminergic neurons (22). Thus, non-inhibitory chaperones are promising drug candidates that might prove equally useful in patients with parkinsonism carrying either mild or severe *GBA1* mutations, so long as these are not null alleles.

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pathogenesis has been challenging, but will likely prove instrumental in designing the next generation of drugs for patients with parkinsonism. If these efforts to enhance GCase activity prove successful, they may positively impact both survival and dementia in patients with different forms of parkinsonism. However, while the severity of the *GBA1* mutation may contribute to the PD phenotype observed, it appears premature to use the genotype to predict disease outcome, especially with the genotypic and the phenotypic overlap with DLB.

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References

1. Goker-Alpan O, Hruska KS, Orvisky E, et al. Divergent phenotypes in Gaucher disease implicate the role of modifiers. *J Med Genet* 2005;42:e37.
2. Hruska KS, LaMarca ME, Scott CR, et al. Gaucher disease: mutation and polymorphism spectrum in

- the glucocerebrosidase gene (GBA). *Hum Mutat* 2008;29:567-83.
3. Tayebi N, Walker J, Stubblefield B, et al. Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? *Mol Genet Metab* 2003;79:104-9.
 4. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med* 2009;361:1651-61.
 5. Nalls MA, Duran R, Lopez G, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. *JAMA Neurol* 2013;70:727-35.
 6. Gan-Or Z, Amshalom I, Kilariski LL, et al. Differential effects of severe vs mild GBA mutations on Parkinson disease. *Neurology* 2015;84:880-7.
 7. Cilia R, Tunesi S, Marotta G, et al. Survival and dementia in GBA-associated Parkinson's disease: The mutation matters. *Ann Neurol* 2016;80:662-73.
 8. Goker-Alpan O, Masdeu JC, Kohn PD, et al. The neurobiology of glucocerebrosidase-associated parkinsonism: a positron emission tomography study of dopamine synthesis and regional cerebral blood flow. *Brain* 2012;135:2440-8.
 9. Shiner T, Mirelman A, Gana Weisz M, et al. High Frequency of GBA Gene Mutations in Dementia With Lewy Bodies Among Ashkenazi Jews. *JAMA Neurol* 2016;73:1448-53.
 10. Davis MY, Johnson CO, Leverenz JB, et al. Association of GBA Mutations and the E326K Polymorphism With Motor and Cognitive Progression in Parkinson Disease. *JAMA Neurol* 2016;73:1217-24.
 11. Gámez-Valero A, Prada-Dacasa P, Santos C, et al. GBA Mutations Are Associated With Earlier Onset and Male Sex in Dementia With Lewy Bodies. *Mov Disord* 2016;31:1066-70.
 12. Tsuang D, Leverenz JB, Lopez OL, et al. GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology. *Neurology* 2012;79:1944-50.
 13. Liu G, Boot B, Locascio JJ, et al. Specifically neuropathic Gaucher's mutations accelerate cognitive decline in Parkinson's. *Ann Neurol* 2016;80:674-85.
 14. Lerche S, Schulte C, Srujijes K, et al. Cognitive impairment in Glucocerebrosidase (GBA)-associated PD: Not primarily associated with cerebrospinal fluid Aβ and Tau profiles. *Mov Disord* 2017. [Epub ahead of print].
 15. Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency--macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med* 1991;324:1464-70.
 16. Mistry PK, Lopez G, Schiffmann R, et al. Gaucher disease: Progress and ongoing challenges. *Mol Genet Metab* 2017;120:8-21.
 17. Cox TM. Eliglustat tartrate, an orally active glucocerebrosidase synthase inhibitor for the potential treatment of Gaucher disease and other lysosomal storage diseases. *Curr Opin Investig Drugs* 2010;11:1169-81.
 18. Maegawa GH, Tropak MB, Buttner JD, et al. Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease. *J Biol Chem* 2009;284:23502-16.
 19. Bendikov-Bar I, Maor G, Filocamo M, et al. Ambroxol as a pharmacological chaperone for mutant glucocerebrosidase. *Blood Cells Mol Dis* 2013;50:141-5.
 20. Narita A, Shirai K, Itamura S, et al. Ambroxol chaperone therapy for neuronopathic Gaucher disease: A pilot study. *Ann Clin Transl Neurol* 2016;3:200-15.
 21. Aflaki E, Stubblefield BK, Maniwang E, et al. Macrophage models of Gaucher disease for evaluating disease pathogenesis and candidate drugs. *Sci Transl Med* 2014;6:240ra73.
 22. Aflaki E, Borger DK, Moaven N, et al. A New Glucocerebrosidase Chaperone Reduces α-Synuclein and Glycolipid Levels in iPSC-Derived Dopaminergic Neurons from Patients with Gaucher Disease and Parkinsonism. *J Neurosci* 2016;36:7441-52.

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