GBA mutations and Parkinson disease

When genotype meets phenotype

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The last 2 decades have seen remarkable advances in our understanding of genetic risk factors underlying the pathogenesis of Parkinson disease (PD). One of the most surprising discoveries was that mutations in *GBA* (glucosidase, beta, acid), coding for the lysosomal enzyme glucocerebrosidase, have a substantial role in PD. While homozygous *GBA* mutations were known for some time as the cause of Gaucher disease, subsequent clinical, neuropathologic, and genetic studies established that heterozygous and occasional homozygous mutations in this gene are also common risk factors for PD, particularly in the Ashkenazi-Jewish population.[1–7]

That is the good news, but of course our story does not end there. There are approximately 300 known *GBA* mutations and determining their exact genotype-phenotype correlations has been challenging.[8] The complexity arises from the fact that not every mutation carrier develops disease, and even if they do, the clinical presentation is highly variable.[9] This clinical heterogeneity is a common theme among neurodegenerative diseases and likely reflects genetic and environmental modifiers at work in the background. From a clinical perspective, it limits our ability to counsel patients and their family members as to their likely risk of developing disease.

In this issue of *Neurology*®, Gan-Or et al.[10] investigate the relationship between 7 common *GBA* mutations in a large Ashkenazi-Jewish PD cohort and risk of developing PD. The authors divided the mutations into severe vs mild mutations based on a frequently used classification in Gaucher disease that distinguishes the 3 clinical Gaucher subtypes (non-neuropathic, acute neuropathic, and chronic neuropathic).[11] What was not known was whether this classification is relevant for PD. Severe mutation carriers had an impressive 10-fold increased risk of developing PD compared with a 2-fold increase in mild mutation carriers. This confirms previous observations by the same group in a smaller Ashkenazi-Jewish cohort.[12] Next, the authors performed a meta-analysis of all relevant published case-control cohorts to evaluate mild vs severe *GBA* mutations in multiple different populations. This led to an impressive cohort of 11,453 patients with PD and 14,565 controls from 31 populations. Again, the data demonstrated that different mutations influenced disease risk and age at onset. There was clear variability across the populations, but, in general, a pattern emerged indicating that severe mutations were associated with a higher risk of disease compared with mild mutations. For example, severe mutation carriers had, on average, 5 years earlier disease onset compared to patients with mild mutations (53 vs 58 years) and the risk for disease was approximately 15 times higher in severe mutation carriers compared with a 3- to 4-fold risk in patients with mild mutations.

The new information provided in this report means that genetic counseling of individuals with a *GBA* mutation can be more refined. This being said, interpretation of disease risk and age at onset is limited to the 7 common founder mutations. Particularly in non-Jewish populations, a large proportion of variants are not covered by these founder mutations and further work is necessary to understand how they influence the phenotypes of patients.

As genetic testing becomes increasingly routine practice in individuals with PD, we have to face a frustrating reality: knowing the genetic cause of parkinsonism does not change clinical management of affected individuals. At least not for now. It is hoped, though, that studying unaffected high-risk individuals and the natural history of affected subjects will reveal important disease modifiers that could lead to new targeted treatments aiming at ameliorating the disease process. Identification of individuals who might benefit from early intervention is also useful in case rational treatments should become available. Stratification of patients enrolled in clinical trials based on their genetic profile may increase the power of such studies to detect therapeutic effects.

From a scientific perspective, the data provided by Gan-Or et al. suggest that the pathobiological mechanisms driving *GBA*-related neurodegeneration are

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likely the same as those in Gaucher disease. Astute clinical observations together with careful molecular characterization of large cohorts, such as this study, may provide important clues to the mechanisms underlying neuronal cell death and may ultimately lead to new therapies.

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REFERENCES

1. Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med 2004;351:1972–1977.
2. Bembi B, Zambito Marsala S, Sidransky E, et al. Gaucher's disease with Parkinson's disease: clinical and pathological aspects. Neurology 2003;61:99–101.
3. Lwin A, Orvisky E, Goker-Alpan O, LaMarca ME, Sidransky E. Glucocerebrosidase mutations in subjects with parkinsonism. Mol Genet Metab 2004;81:70–73.
4. Machaczka M, Rucinska M, Skotnicki AB, Jurczak W. Parkinson's syndrome preceding clinical manifestation of Gaucher's disease. Am J Hematol 1999;61:216–217.
5. Neudorfer O, Giladi N, Elstein D, et al. Occurrence of Parkinson's syndrome in type I Gaucher disease. QJM 1996;89:691–694.
6. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009;361:1651–1661.
7. Tayebi N, Callahan M, Madike V, et al. Gaucher disease and parkinsonism: a phenotypic and genotypic characterization. Mol Genet Metab 2001;73:313–321.
8. Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat 2008;29:567–583.
9. Sidransky E. Gaucher disease: complexity in a "simple" disorder. Mol Genet Metab 2004;83:6–15.
10. Gan-Or Z, Amshalom I, Kilarski LL, et al. Differential effects of severe vs mild *GBA* mutations on Parkinson disease. Neurology 2015;84:880–887.
11. Beutler E, Gelbart T, Scott CR. Hematologically important mutations: Gaucher disease. Blood Cells Mol Dis 2005;35:355–364.
12. Gan-Or Z, Giladi N, Rozovski U, et al. Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. Neurology 2008;70:2277–2283.