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The Expanding Role of Genetics in the Lewy Body Diseases: The Glucocerebrosidase Gene

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In this month's *Archives*, 2 articles describe the association of mutations in the glucocerebrosidase gene (*GBA*) with Parkinson disease (PD) and dementia with Lewy bodies (DLB).^{1,2} These studies add to the growing literature linking mutations in *GBA* to diseases characterized clinically by parkinsonism and pathologically by the presence of Lewy body-related pathology (LRP) (including classic Lewy bodies and abnormal α -synuclein inclusions and neurites). Historically, the link between *GBA* and LRP-associated diseases began with case reports noting clinical parkinsonism in Ashkenazi Jewish patients with Gaucher disease (GD).^{3,4} Subsequent examination of larger samples of patients with GD found a high frequency of parkinsonism and the presence of LRP in some of these patients.⁵ The next question was whether there was an increased frequency of *GBA* mutations in PD, particularly in samples that were not Ashkenazi Jewish. Subsequent studies of multiple PD samples did, in fact, find a higher than expected frequency of *GBA* mutations.^{6–10}

However, until this point the study samples were either small, often with limited control samples, or only evaluated the most frequently observed *GBA* mutations (ie, did not sequence the entire gene). Likely owing to these methodological limitations, the reported frequency of *GBA* mutations in PD samples has been quite variable.

In this month's *Archives*, Mitsui et al² addressed both of these limitations by sequencing all of the coding regions of *GBA* in an impressively large sample of Japanese patients with PD and controls (n = 534 and 544, respectively). They found that almost 10% of their PD group carried *GBA* mutations, whereas these variants were rare in the control group (<1%). It was also reassuring to see that they found no difference in the frequency of non-pathogenic *GBA* variants between the PD and control groups. Given the rather large number of cases of PD with *GBA* pathogenic variants, they were able to examine clinical characteristics of the parkinsonian symptoms and found an earlier age of onset and frequent positive response to dopaminergic therapy (supporting other recent reports of *GBA* mutation-associated PD^{6,11,12}).

In the other *GBA* article in this month's *Archives*, Clark et al¹ examined the frequency of *GBA* pathogenic variants in a sample of patients with DLB. Similar to the article by Matsui et al, they sequenced all of the *GBA* exons. Though the study sample was somewhat smaller (n = 95), this study was notable for the use of pathologically confirmed LRP. They also found a remarkably high frequency of pathologic variants of *GBA* in their sample. Of particular interest was the absence of an association with the pathological changes of Alzheimer disease. Lewy body pathology is frequently observed in Alzheimer disease, even in familial forms,^{13,14} but it is not clear if this type of Lewy body disease is pathophysiologically linked to Alzheimer

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disease or to the more pathologically pure forms of Lewy body disease. These findings would appear to support the former. A caveat in this study was the use of a New York City–area study sample; thus, the relatively high frequency of the N370S variant may have been due to the high representation of Ashkenazi Jewish persons in their sample. One previous study has examined *GBA* mutations in an even smaller sample of pathologically confirmed DLB ($n = 54$), but only evaluated those cases for 2 specific *GBA* mutations rather than sequencing all of the coding regions.⁷ This likely accounts, in part, for the even lower frequency of *GBA* mutations found in this latter study.

These are the largest studies of *GBA* pathologic variants in PD and DLB and not only solidify the *GBA*–Lewy body disease connection, but suggest strongly that *GBA* mutations are, to date, the most common genetic risk factor for Lewy body diseases. One firm conclusion from these studies is that there is a need in genetic studies of *GBA*, and in studies of other susceptibility genes, to perform sequencing of all of the coding regions. As stated by Matsui et al,² “... we should emphasize a paradigm shift from the ‘common disease–common variants hypothesis’ to the ‘common disease–multiple rare variants hypothesis’ in our search for disease susceptibility genes in sporadic PD ...” This, unfortunately, is not a small task, as the technical difficulties, particularly owing to the presence of a highly homologous *GBA* pseudogene (*GBAP*),¹⁵ and the workload associated with detailed sequencing of *GBA* are significant.

The clinical implications of these findings will need to be resolved. Clinical genetic testing and counseling implications will have to be addressed, likely dependent on further research examining the risk for Lewy body disease in patients heterozygous for *GBA* mutations. This may be difficult given the apparent heterogeneous genotype-phenotype correlations with specific *GBA* mutations in GD.¹⁵ Another important clinical question is whether GD biomarkers¹⁶ could assist with the development of biomarkers for PD. There have been some limited attempts up to this point¹⁷; however there has been no correlation to *GBA* genotyping.

Finally, what does this tell us about the pathophysiology of Lewy body disorders such as PD and DLB? A laundry list of potential mechanisms could be and have been hypothesized.¹⁸ Is this a gain-of-function mechanism or related to a modest loss of function? The presence of parkinsonism or PD in GD would appear to support the latter. It does appear, however, that we can have confidence that *GBA* has an important role in the pathophysiology of Lewy body disorders, and that a better understanding of this link should provide new avenues of research and treatment for the Lewy body disorders.

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