PARKINSON DISEASE

New genetic risk factor for sporadic PD

Japanese researchers who have resequenced the glucocerebrosidase (*GBA*) gene conclude that *GBA* variants associated with the rare genetic disorder Gaucher disease markedly increase the risk of Parkinson disease (PD). "Pathogenic *GBA* variants were a strong genetic risk factor for sporadic PD and, more importantly, carriers were 6 years younger at onset of PD compared to non-carriers," observes senior researcher Shoji Tsuji (University of Tokyo Graduate School of Medicine, Japan).

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Previous reports occasionally identified patients with PD within Gaucher disease family groups, and there had been inconsistent observations that variants of *GBA* in the heterozygous state were associated with PD, but most studies had concentrated only on individual variants. "A complete nucleotide sequence analysis was needed to identify all the rare variants associated with PD and our study on the Japanese population has certainly produced some conclusive results," notes Tsuji.

The group undertook the comprehensive resequencing of *GBA* in 534 patients with PD and in 544 healthy controls to compare the frequency of rare *GBA* variants. Of the 27 sequence variants identified, 11 were pathogenic variants linked with Gaucher disease. Possession of one of the pathogenic variants was confirmed in 9.3% of patients with PD but in only 0.37% of the controls (odds ratio 28). In 8 families out of the 34 that had multiple cases of PD, *GBA* variants were shared among the affected family members, confirming that these variants increase susceptibility to PD.

Several hypotheses might explain how *GBA* variants associated with Gaucher disease are involved in the pathogenesis of PD, including the possibility that mutant GBA proteins could be misfolded and neurotoxic. "Haploinsufficiency (decreased activity of glucocerebrosidase) may interfere with the metabolism of glycoconjugates, which is essential for nerve function," says Tsuji. He stresses, however, that cellular and animal models will need to be created to investigate this hypothesis. "It is likely that multiple rare gene variants could be additional risk factors in sporadic PD; more-comprehensive resequencing analysis of many other genes, perhaps eventually all genes, will be required," he predicts.

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