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ASHG 2008: Gaucher Disease Mutation Carriers at Higher Risk for Parkinson's Disease

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November 19, 2008 (Philadelphia, Pennsylvania) — A new study has shown that the risk for Parkinson's disease (PD) is 5 times greater in individuals carrying glucocerebrosidase (GBA) gene mutations than in the general population. Age of PD onset is also earlier in patients with GBA mutations. The collaborative study, presented here at the American Society of Human Genetics 58th Annual Meeting, involved researchers and patients on 4 continents.

Since 1965, GBA mutations have been recognized as the cause of Gaucher disease. GBA mutation is relatively common (1 in 100 people in the United States is a carrier of type I Gaucher disease), but it occurs most often among Ashkenazi Jews (1 in 15 is a carrier of type I). Gaucher is an autosomal recessive disease, so a person must inherit 2 mutant copies of the gene to develop the disease.

GBA is an enzyme that breaks down a fatty substance called glucocerebroside. Mutations that impair GBA function allow glucocerebroside to accumulate in the lungs, kidneys, spleen, liver, bone marrow, and brain. This accumulation results in an enlarged spleen and liver, premature destruction of blood cells, bony abnormalities, and neurologic symptoms that can include convulsions, retardation, apnea, or dementia.

Presenter Ellen Sidransky, MD, chief of the Section on Molecular Neurogenetics, National Human Genome Research Institute, National Institutes of Health, in Bethesda, Maryland, explained that clinicians noted the occurrence of PD in Gaucher patients as well as increased PD frequency in their relatives. Conversely, increased occurrence of GBA mutations was reported in brain-bank samples from PD patients.

An international group made up of 15 centers in North America, South America, Europe, Asia, and Israel collected genotypic and phenotypic data on PD patients (4911 non-Ashkenazi; 780 Ashkenazi) and matched controls (4511 non-Ashkenazi; 387 Ashkenazi). All centers were able to genotype for 2 major GBA mutations, N370S and L444P. Israeli centers screened for additional GBA mutations.

Screening for N370S and L444P found that 3.24% of non-Ashkenazi PD patients had 1 or both mutations, as did 15.3% of Ashkenazi PD patients; 0.6% of non-Ashkenazi controls had 1 or both mutations, as did 3.36% of Ashkenazi controls. Odds ratios for these mutations, considered together, were 5.56 (95% confidence interval [CI], 3.69 - 8.37; $P < .0001$) in non-Ashkenazi populations, and 5.18 (95% CI, 2.19 - 9.31; $P < .0001$) in the Ashkenazi population.

"Mutations were over 5 times more frequent in patients than controls," Dr. Sidransky told *Medscape Pathology & Lab Medicine* via email. "This makes GBA mutations the most common genetic risk factor for Parkinson's disease known. We consider it to be a risk factor and not a disease gene because most patients with Gaucher disease (who each carry 2 GBA mutations) never develop parkinsonism. So other factors must also play a role in defining which individuals with GBA mutations go on to have Parkinson's disease," Dr. Sidransky pointed out.

The study also determined that screening for only N370S and L444P would miss at least 22% of the mutant alleles of GBA in Ashkenazi Jewish patients and at least 42% of mutant alleles in non-Ashkenazi patients. Finally, the study showed that the average age of PD onset in patients with N370S or L444P mutations was 54.8 years, whereas in patients with neither

mutation the average age was 58.7 years (*P* = .00000).

Session comoderator Alison M. Goate, DPhil, professor of genetics in psychiatry, professor of genetics and neurology, Washington University School of Medicine, in St. Louis, Missouri, also talked with *Medscape Pathology & Lab Medicine*: "What [Dr. Sidransky] did was to actually get a very large dataset together so that we have a more comprehensive picture and a clearer picture of what the results say."

"And I think...it's pretty clear that she actually saw, in both the Ashkenazi Jewish sample and in the non-Ashkenazi Jewish sample with Parkinson's disease, there was a 5-fold increase in risk for Parkinson's disease associated with being carriers for a variety of mis-sense mutations in this gene," said Dr. Goate.

Dr. Sidransky concluded: "I do believe that understanding the mechanism for this association [between PD and GBA mutations] will ultimately lead to targeted strategies for patients with Parkinson's disease who harbor GBA mutations. Perhaps we will even be able to initiate therapy before symptoms manifest. However," she acknowledged, "this is still a fair way off."

Dr. Sidransky and Dr. Goate have disclosed no relevant financial relationships.

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