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Featured Article

Association of glucocerebrosidase polymorphisms and mutations with dementia in incident Parkinson's disease

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Abstract

Introduction: Both polymorphisms and mutations in glucocerebrosidase (*GBA*) may influence the development of dementia in patients with Parkinson's disease.

Methods: Four hundred forty-two patients and 419 controls were followed for 7 years. Dementia was diagnosed using established criteria. Participants were analyzed for *GBA* genetic variants, including E326K, T369M, and L444P. Associations between *GBA* carrier status and dementia were assessed with Cox survival analysis.

Results: A total of 12.0% of patients with Parkinson's disease carried a *GBA* variant, and nearly half (22/53) of them progressed to dementia during follow-up. Carriers of deleterious *GBA* mutations (adjusted hazard ratio 3.81, 95% confidence interval 1.35 to 10.72; $P = .011$) or polymorphisms (adjusted hazard ratio 1.79; 95% confidence interval 1.07 to 3.00; $P = .028$) progressed to dementia more rapidly than noncarriers.

Discussion: *GBA* variants are of great clinical relevance for the development of dementia in Parkinson's disease, especially due to the relatively higher frequency of these alleles compared with other risk alleles.

Keywords: Parkinson's disease; Parkinson's disease with dementia; GBA; Longitudinal; Genetic association

1. Background

Dementia is among the most common and severe nonmotor symptoms of Parkinson's disease (PD), affecting nearly 20% of all patients within the first 5 years of the disease and most patients if they survive for more than 10 years after

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diagnosis [1,2]. Dementia in Parkinson's disease (PDD) has important adverse implications for quality of life, caregiver burden, and health-related costs [3]. The etiology of PDD remains poorly understood, and no neuroprotective therapies are currently available.

Genetic factors undoubtedly play a role in modifying the rate of disease progression in PD, and identifying these is a key to the early identification of patients at greatest risk of PDD. Genetic variants in glucocerebrosidase (*GBA*) have the strongest evidence for association with more rapid cognitive decline in PD. Homozygous mutations in *GBA* cause Gaucher disease (GD), and it is well established that some of the heterozygous mutations are associated with an increased risk of PD [4]. *GBA* variants associated with increased risk of PD chiefly fall into two categories: risk polymorphisms, the most common of which are E326K and T369M [5,6]; and deleterious mutations, such as N370S and L444P, which in a homozygous state cause GD [7].

GBA variants have been shown to increase the risk of PDD in cross-sectional studies [8,9], and longitudinal studies are starting to show how different *GBA* variants affect the rate of the development of dementia during the course of PD. Most longitudinal studies have found that carriers of deleterious *GBA* mutations are at increased risk of earlier PDD onset [10–13] or faster decline in global cognitive function [14]. To date, few studies have considered the effects of *GBA* risk polymorphisms on the development of PDD, and the only longitudinal studies to identify a significant association between *GBA* polymorphisms and progression to PDD did so only after controlling for the effect of *MAPT* genotype [10] or by including both mild cognitive impairment and PDD [6].

Therefore, we analyzed the *GBA* carrier frequencies of three deeply phenotyped, longitudinal PD cohorts of highly uniform design from Northern Europe, each of which uses established criteria for the diagnosis of PDD. Together, the Norwegian ParkWest study [15], the Parkinsonism Incidence in Northeast Scotland (PINE) [16], and the New Parkinson Patient in Umeå (NYPUM) [17] studies represent the largest prospective population-based longitudinal study of PD with age- and sex-matched controls in which the effect of *GBA* variants on PD progression has been addressed. By determining the roles of *GBA* polymorphisms and deleterious mutations in the development of PDD, we provide important insights into the heterogeneity of disease progression in these subgroups.

2. Methods

2.1. Study participants and procedures

The ParkWest study, the NYPUM project, and the PINE study were initiated between 2002 and 2004. All are large, on-going, population-based multicenter studies of newly diagnosed (incident) PD patients, designed to determine the incidence, neurobiology, and prognosis of PD and are described in detail elsewhere [15–18]. Briefly, 212 patients were enrolled in the ParkWest study, 211 in the PINE study, and 182 in the NYPUM study. Of these, 68 had a diagnosis other than PD during follow-up, 57 declined genotyping, 31 have no available DNA sample or DNA was not extractable, and seven did not consent to follow-up. The remaining 442 patients were eligible for this study and underwent comprehensive and standardized clinical examinations before drug treatment was initiated if possible (98% drug-naïve). During the same time, normal control subjects were recruited in the same geographical areas from spouses or friends of PD patients, or unrelated persons [19,20]. They were clinically examined and had no signs of movement disorders or cognitive deficiencies. Two hundred one controls were enrolled in the ParkWest study, 266 in the PINE study, and 56 in the NYPUM study. Of these, 68 had no DNA samples available or DNA was not extractable, 30 declined genotyping, and 6 developed incident PD during follow-up and were excluded. The remaining 419 consented to routine follow-up with a standardized battery of clinical testing. PD patients are currently under continued follow-up, and only those with a confirmed clinical or pathological (if performed postmortem) diagnosis of PD according to the UK brain bank criteria at their latest or final clinical visit were included. All participants signed written informed consent. The Western Norway Regional Committee for Medical and Health Research Ethics, the Regional Ethics Review Board in Umeå, and the Multi Centre Research Ethics Committee for Scotland approved the respective studies.

2.2. Clinical assessments in PD

The data were analyzed with the focus on PD risk, age at symptom onset or diagnosis, and the development of dementia. PD patients were examined at time of diagnosis by experienced study neurologists and research nurses. Clinical evaluations made up to the 7-year visit are included in this study. Motor severity was rated using the motor section (part III) of the Unified Parkinson Disease Rating Scale, and disease stage using the Hoehn and Yahr staging. Global cognitive decline was measured by the Mini–Mental State Examination [21]. Dementia diagnosis was set according to Movement Disorder Society criteria [22] (ParkWest and NYPUM) or DSM-IV [23] (PINE), using a combination of Q3 clinical history from the patient and carer, and cognitive testing. Patients with dementia with Lewy bodies (DLBs), as defined by the development of dementia within 1 year of the onset of the motor features of PD, were not eligible for this study.

2.3. Genetic analysis

Genomic DNA was extracted from peripheral blood samples of eligible participants using standard methods. Large-scale allelic discrimination analysis was performed for all