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Genetic Brief

Pilot Association Study of the β-Glucocerebrosidase N370S Allele and Parkinson's Disease in Subjects of Jewish Ethnicity

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Abstract: Mutations in the β-glucocerebrosidase gene cause Gaucher's disease, one of the most common lysosomal lipid storage diseases in the Ashkenazi Jewish population. The occurrence of parkinsonism in patients with Type 1 Gaucher's disease has been noted previously. In this pilot study, we evaluated a possible association between Parkinson's disease (PD) and the β-glucocerebrosidase gene N370S allele (nt.1226 A>G) in 160 Parkinson's disease patients and 92 controls of Jewish ethnicity. We observed a higher frequency of the N370S genotype in PD cases (NS and SS, 10.7%) compared to controls (NS and SS 4.3%); however, the difference was not statistically significant ($\chi^2 = 3.4$, $P = 0.2$). A total of 17 PD cases carry the N370S allele, including 2 homozygotes and 15 heterozygotes. The N370S allele (nt.1226 A>G) may be associated with PD in patients of Jewish ethnicity and should be examined in a larger study. © 2004 Movement Disorder Society

Key words: N370S; beta-glucocerebrosidase; genetic risk factor; heterozygote; homozygote; Jewish ethnicity

The lysosomal storage diseases are a group of genetic disorders caused by defective lysosomal metabolism, including transport and degradation of glycosphingolipids.[1] Gaucher's disease (GD; MIM 230800), a lysosomal lipid storage disease, is one of the most common genetic diseases reported in the Ashkenazi Jewish (AJ) population and is caused by mutations in the β-glucocerebrosidase gene (GBA). Four mutations in the GBA gene, N370S, L444P, 84GG, and IVS2+1, are prevalent in AJ patients with GD. Typically, the inheritance pattern for GD is autosomal recessive. However, homozygous, compound heterozygous and heterozygous genotypes at the GBA locus have been reported. Furthermore, N370S mutation carriers can have late-onset GD (normally non-neurologic) or no significant symptoms at all.

A spectrum of clinical manifestations has been noted in GD, including hepatosplenomegaly, anemia, thrombocytopenia, and bone manifestations.[2] Typically, GD is classified into three types based on the severity of the associated neurological symptoms.[3] Age at onset of GD

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TABLE 1. *Demographic and clinical characteristics of Jewish study participants*

Variable	PD probands (n = 160)	Control probands (n = 92)	Significance (*P*)
Current age (yr) (mean, SD)	66.5 (10.5)	69.6 (9.6)	0.021
Age at onset of PD (yr) (mean, SD)	59 (12.4)	NA	NA
Gender (male), n (%)	99 (62.3)	54 (60)	NS
Education (yr) (mean, SD)	16 (3.2)	16.4 (2.6)	NS
Family history in first-degree relative, n (%)	25 (15.7)	7 (7.8)	0.08

PD, Parkinson's disease; NA, not applicable; NS, not significant.

can range from less than 1 year to 81 years.[2] In adult onset GD, a range of neurological manifestations has been observed, including epilepsy, myoclonus, supranuclear gaze palsy, cerebellar ataxia, psychiatric symptoms, dementia, and parkinsonism.[4–11] Type 2 GD is associated with a severe central nervous system (CNS) involvement with infantile onset and is usually fatal. Type 3 GD has an onset in early adulthood and a milder CNS involvement. The most common variant of GD is Type 1, which is the least severe of three types of GD, and typically is described as non-neuronopathic.[2] However, several studies report neurological symptoms in patients with Type 1 GD, including Parkinson's disease (PD).[8–10,12–15] In a survey of 55 patients with Type 1 GD (mean age, 46.8 years with 93% Ashkenazi Jewish), 73% reported at least one neurological symptom (sciatica, paraesthesias, muscle weakness, muscle cramps, and tremor [rest tremor or action tremor not defined]).[16] Of 7 patients reporting tremor, 3 were diagnosed with PD.[16] Parkinsonism has also been reported preceding the clinical manifestations of GD,[13] and in a survey of 17 patients with Type 1 GD and parkinsonism, 5 (29%) had a family history of parkinsonism in a first-degree relative.[14]

Pathologically, Lewy bodies and marked loss of pigmented neurons in the substantia nigra has been reported in the brains of four individuals with Type 1 GD and parkinsonism.[14] Furthermore, mutation screening of the GBA gene and measurement of enzyme activity in 57 samples of brain tissue from subjects with a primary pathological diagnosis of PD identified 8 (14%) with functional mutations (including N370S, L444P, K198T, and R329C) in the GBA gene.[17,18]

SUBJECTS AND METHODS

We evaluated a possible association between PD and the GBA N370S allele (nt.1226 A>G), the most common mutation reported in Ashkenazi Jews with Type 1 GD. The N370S allele has only been associated with Type 1 Gaucher's disease.[2] A total of 160 PD patients and 92 controls who reported that all 4 grandparents were Jewish were genotyped. Information about Ashkenazi origin was not specifically obtained; however, ~90% of Jews in the United States are Ashkenazi.[19] Genotypes for the N370S allele were determined by direct sequencing of polymerase chain reaction products as described previously.[20]

Both PD cases and controls were a subset of individuals participating in a study of the genetic epidemiology of PD[21] (GEPD). Cases were recruited from the Center for Parkinson's Disease and Other Movement Disorders at Columbia University; all met research criteria for PD.[22] The majority of controls (99%) were recruited by random digit dialing and were frequency matched by age, gender, ethnicity, and area code/exchange. A total of 1% of controls were recruited from a 50% sample of Medicare recipients ≥65 years of age who resided in the Washington Heights community.[23] All controls underwent the same evaluation as cases and included a medical history, Unified Parkinson's Disease Rating Scale,[24] and modified Mini-Mental State examination.[25]

RESULTS

The demographic and clinical characteristics of study participants are shown in Table 1. A total of 17 PD cases (5 with onset <50 years of age, 12 with onset ≥50 years of age) carry the N370S allele, including 2 homozygotes and 15 heterozygotes. We observed a higher frequency of the N370S genotype in PD cases (NS and SS, 10.7%) compared to controls (NS and SS 4.3%; Table 2); however, the difference was not statistically significant ($\chi^2 = 3.4$, $P = 0.2$).

PD patients carrying a N370S allele reported the following first symptoms of PD: rest tremor (64%), gait impairment (24%), foot cramping (6%), and rigidity (6%). A total of 65% had asymmetry of motor signs at onset. Five patients (29%) were never treated with levodopa. Six cases reported a family history of PD in a first-degree relative. One case, homozygous for N370S, with an age of onset in the range 70 to 75 years, subsequently developed dementia 4 years after onset of motor signs. This proband also had 3 relatives with PD (a parent, sibling, and child; Fig. 1).

TABLE 2. *β-Glucocerebrosidase N370S genotype (nt. 1226 A>G) and allele frequencies in Jewish PD cases and Jewish controls from this study and others*

Sample	PD (n = 160)	Controls (n = 92)	Controls (n = 593)[26]	Controls (n = 1,528)[27]
Genotype				
NN(AA)	143 (89.4)	88 (95.7)	554 (93.4)	1437 (94.0)
NS(GA)	15 (9.4)	4 (4.3)	37 (6.2)	87 (5.7)
SS(GG)	2 (1.3)	0	2 (0.4)	4 (0.3)
Allele				
N(A)	301 (94.0)	180 (98.0)	1145 (96.5)	2961 (96.9)
S(G)	19 (6.0)	4 (2.0)	41 (3.5)	95 (3.1)

The amino acid nomenclature for the N370S genotype is shown; nucleotides at nt. 1,226 are shown in parentheses.
PD, Parkinson's disease.

DISCUSSION

This pilot study suggests that the GBA N370S allele may be associated with PD in the AJ population and should be examined in a larger study. The frequency of the N370S allele in the AJ population is estimated to be between 0.031 and 0.035[26,27] (Table 2). Based on the N370S disease allele frequencies observed in this study, a sample size of 372 (186 cases and 186 controls) would be required to detect a statistically significant difference (80% power, $\alpha = 0.05$). Therefore, we did not have power to detect an association. It is possible that the N370S allele is not causal but is in linkage disequilibrium with disease allele(s) in the GBA gene or neighboring genes. A 70-kb region of chromosome 1q21 spanning the pyruvate kinase gene and the GBA gene shows almost complete linkage disequilibrium in populations worldwide.[28] Alternatively, the N370S allele may be acting in concert (gene–gene interaction) with other causal or risk-raising PD genes, none of which were examined in this study. In this study, we identified 2 PD subjects homozygous for the GBA N370S allele, and it is possible that these subjects have PD coincidentally and that mutation(s) in other gene(s) and not *GBA* contribute to PD pathogenesis in these subjects.

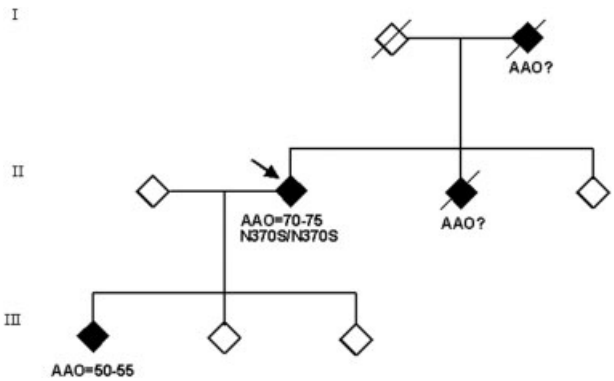

FIG. 1. Pedigree of the proband homozygous for the β-glucocerebrosidase (GBA) N370S allele. Generations are indicated by Roman numerals. Shaded symbols represent individuals with Parkinson's disease. Clear symbols indicate individuals presently unaffected. Age at onset (AAO) and genotype are indicated. To conceal the identify of the family in this study, the gender of family members is not shown (all individuals are indicated by diamond shapes) and a range of AAO is given for affected members. Sibs in generation III were younger than the affected subject. The GBA N370S genotype was not determined for the affected subject III-I as DNA was not available for analysis.

The strengths of this study include that cases were recruited based on age of onset rather than family history of PD and is reflective of PD subjects who are seen at a tertiary medical care center.[21] All cases and controls from GEPD were administered structural neurological examinations and family history interviews that were reliable and valid.[29] Furthermore, we have restricted analysis to Jewish subjects, who are likely to have less genetic heterogeneity than the general US population and to share common disease genes and/or susceptibility alleles.

The identification of disease genes in PD, including α-synuclein, parkin, and UCHL1, and the underlying disease pathological state implicate the ubiquitin–proteasome pathway in disease pathogenesis. The autophagic/lysosomal pathway is an alternative mechanism for regulation and degradation of proteins, in addition to lipids and damaged organelles. Further studies are required in larger patient populations of Ashkenazi Jewish ethnicity to determine whether the N370S allele, or other mutations in the GBA gene, increase susceptibility to Parkinson's disease.

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