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Glucocerebrosidase Mutations in Chinese Subjects from Taiwan with Sporadic Parkinson Disease

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Abstract

Background—An association between glucocerebrosidase, the enzyme deficient in Gaucher disease, and the synucleinopathies has been suggested both by the development of parkinsonism in Gaucher probands and carriers, as well as by the presence of mutations in the gene for glucocerebrosidase (GBA) in different series of subjects with synucleinopathies. In this study, an open access Parkinson repository was used to establish the incidence of GBA alterations in a different ethnic cohort with sporadic Parkinson disease (PD).

Methods—The glucocerebrosidase gene was sequenced in samples collected from 92 Chinese Parkinson disease patients from Taiwan along with 92 clinically screened controls, matched for age and ethnicity.

Findings—The frequency of GBA mutations among the Chinese PD probands was 4.3%, in contrast to 1.1% in Chinese controls. Mutant alleles identified included two known mutations, L444P and D409H, and two novel mutations, L174P and Q497R.

Interpretation—These results, ascertained in subjects from Taiwan collected in a standardized and clinically rigorous open access Parkinson disease repository and screened by direct sequencing of GBA, demonstrate that GBA mutations are also encountered in Chinese subjects with sporadic PD at a higher frequency than many other known PD genes. The study demonstrates that the association of GBA mutations with the development of parkinsonian pathology is not related to ethnic origin.

Introduction

Over the past decade, an increasing number of genes have been identified that are associated with the development of parkinsonism. Many of these are causal genes that result in Mendelian-inherited forms of Parkinson disease (PD) and include alpha-synuclein, parkin, *PINK1*, *DJ-1*, and *LRRK2/dardarin* [1–6]. Mutations in certain of these genes are encountered with an increased frequency in specific subsets of patients. For example, among subjects with early onset PD, mutations in parkin are found in 10–20% of sporadic cases [7,8]. Likewise mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene account for 5–6% of familial PD cases [9], and are seen in even higher numbers of both familial and sporadic PD probands in certain ethnic groups such as Ashkenazi Jews [10] and North African Arabs [11].

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Recently, several different findings have implicated a link between parkinsonism and mutations in glucocerebrosidase (GBA), the gene encoding for the enzyme deficient in the autosomal, recessively-inherited lysosomal storage disorder, Gaucher disease. Rare patients with Gaucher disease who develop parkinsonian manifestations have been identified [12,13]. Post-mortem neuropathological evaluations of several of these subjects revealed α -synuclein immunoreactive intra-neuronal inclusions in brain regions typically affected with Gaucher disease [13,14]. Moreover, an increased number of cases of PD was noted among the first-degree relatives of Gaucher probands, many of whom were demonstrated to be Gaucher heterozygotes [15]. Conversely, studies of brain bank samples from subjects with synucleinopathies have demonstrated that between 8–12% carried GBA mutations [16,17]. These studies were criticized initially because of the difficulty in ascertaining the ethnicity of the tissue donors, as well as the absence of ethnically matched controls. However, a subsequent study in a cohort of 99 Ashkenazi Jewish probands with PD from Northern Israel demonstrated that as many as 31% of subjects carried one of six specific GBA mutations, which was five-fold higher than found in the ethnically matched general population controls [18]. A limitation of this series was that the control group comprised subjects of mixed ages who were not specifically evaluated for clinical features of parkinsonism. Additional studies focusing on diverse cohorts with parkinsonism have persistently shown an increased frequency of specific GBA mutations, but the entire GBA gene was not usually evaluated [19–22] (Table 1). To overcome these deficiencies, we screened for GBA mutations by direct sequencing of the gene in PD subjects and in matched controls collected under strict criteria by the Coriell NINDS Genetics Repository Guidelines (<http://ccr.coriell.org/ninds>).

Material and Methods

Samples screened were procured from the Coriell Institute NINDS Genetics Repository. The panels used included panel NDPT003, consisting of DNA from 92 unique and unrelated ethnic Chinese individuals with idiopathic PD from Taiwan, as well as panel NDPT004, the corresponding collection of 92 neurologically normal Chinese controls from Taiwan. All subjects with PD met the UK Brain Bank Criteria for idiopathic PD [23] and no cases had an apparent Mendelian inheritance. Data collected on these subjects included family history, a detailed medical examination and, in most cases, a detailed neurological exam and Folstein Mini-Mental Status testing. The age of the PD onset, defined as when resting tremor, rigidity bradykinesia, gait disorder or postural instability were first noted, ranged from 55–68 years. The age at collection was 56–78 years. The control subjects were volunteers, although two were spouses of affected PD probands. The age at sampling for controls ranged from 55–82 years. All control subjects with any suggestion of neurological disease, or those with a first degree relative with a known neurological disorder, were excluded.

Mutations in GBA were identified by sequencing all 11 exons and flanking intronic regions of GBA as previously described [16]. All identified mutations were confirmed by separate amplification and sequencing. In addition, subjects and controls were genotyped for the *LRRK2* G2019S alteration utilizing a Taqman Assay-by-Design SNP strategy as previously described [9].

Results

The results of GBA sequencing are summarized in Table 2. Among the panel of Chinese subjects with PD from Taiwan, four (4.3%) were heterozygous for GBA mutations. These included one subject each with the known mutations L444P and D409H. The other two subjects each carried a novel alteration, L174P and Q497R, respectively. Both of the novel mutations identified were confirmed by amplification with alternate PCR primers, and neither has been reported in over 500 previously genotyped Gaucher alleles, 400 alleles from subjects with PD

and 300 alleles from screened adult controls. A fifth subject carried an allele with T369M, which, along with E326K, are considered by many to be polymorphisms because they are found in $\geq 1\%$ of the general population [24], and are thus not counted as mutant alleles in our studies. None had the common N370S alteration, perhaps reflecting the rarity of this mutation in Asian populations [25].

The Chinese subjects on the Taiwanese PD plate included 48 males and 44 females and three of the subjects with GBA mutations were male. Four subjects were described with dementia, and one of these carried a GBA mutation (N001064). Only five of the subjects had a positive family history for PD and none of these were GBA carriers. One subject carried *LRRK2* G2019S but did not carry a GBA mutation.

The neurologically normal control panel of Chinese subjects from Taiwan had one subject heterozygous for GBA alteration V460M and none with E326K or T369M. V460M was identified once previously in a subject with type 1 Gaucher disease from Great Britain, but no clinical or further genotype data were provided [26]. In addition, one of the Taiwanese control subjects carried two alterations in the 5' non-coding region of exon 2 that are identical to GBA pseudogene sequence, and presumably are the result of a gene conversion event. However, there were no mutations in the coding regions of GBA in this individual.

Discussion

In the two years since mutations in GBA were first noted in subjects with synucleinopathies, some healthy skepticism has persisted as to the validity of the association. Several of the objections relate to unavoidable difficulties related to banked pathologic samples and appropriately matched controls. However, the finding of an increase in GBA mutations in PD subjects with diverse ancestries (Table 1), the identification of mutations in a spectrum of synucleinopathies [17], and an increased frequency of parkinsonism among Gaucher carriers [15] have encouraged us to explore this association further, using both genetic and cell biological approaches. The current series, obtained from an open access repository, includes subjects of a distinctly different ethnicity than in other published studies, and sample collection proceeded with no specific bias. A uniform system was employed in characterizing clinical features, response to therapy, cognitive deficits and family relationships, and specific guidelines were used in the collection and evaluation of control subjects.

Table 1 compares the incidence of GBA mutations among the different published screened series of patients with parkinsonism. Clearly, the sample size, method of screening for mutations and diagnostic methods differed among the studies reported. What is evident is that this finding is not exclusive to the Ashkenazi Jewish population, where the carrier frequency for Gaucher disease is significantly higher than the general population (4.3% vs. 0.6%) [27]. With the exception of the series from Norway [22], ethnically diverse parkinsonian subjects from four continents have been found to have a greater than anticipated frequency of GBA mutations. This comparison illustrates that the mutations are seen in subsets of patients with varying Parkinson phenotypes including sporadic PD [18,19,22], early onset PD [21,28] and subjects with Lewy body dementia [17].

The other feature that distinguishes this study from most in the literature is the method used for genotyping. We performed direct sequencing of all of the exons and the flanking intronic regions of GBA. In contrast, many of the other published studies focused solely on screening for anywhere between one and seven known Gaucher alleles [18,19,21,22]. Had we examined only the five most common Gaucher mutations, we would have missed half of the mutant alleles in this population. The most common Gaucher allele in Caucasian populations, N370S, is

almost non-existent in Asian patients with Gaucher disease [25], which was reflected by its absence among both the PD and control Chinese subjects in this study.

Our finding that GBA mutations are more frequent in this cohort of Taiwanese subjects with sporadic PD than in clinically screened and age-matched controls (G-test: $P = 0.159$, $\alpha = 0.05$, $\beta = 0.60$), while not statistically significant, continues to be intriguing. Like several of the other reported studies, the current study has insufficient power to detect a statistically significant difference between the GBA mutation frequency in cases and controls. Further studies with larger numbers collected with similar diagnostic criteria and screened by GBA sequencing, will be necessary to better establish these findings. While other genes are associated with familial PD, to date, few have been implicated in sporadic PD among ethnically and clinically diverse populations [29,30]. However, the reported frequencies of GBA mutations reported in different studies of subjects with synucleinopathies are higher than that seen for most other known PD related genes. For example, screening of Caucasian sporadic PD samples for the G2019S variant of *LRRK2* yielded a carrier frequency of only 1.6% [31], and G2019S was absent in a Taiwanese cohort [32]. Previous screening of Chinese PD subjects for the A53T and A30P mutations in the alpha-synuclein gene [33,34], and for S167N, R366W and V380L in parkin [35], revealed no increased frequency of these PD-associated alterations.

The reason for the association of mutant glucocerebrosidase with the development of parkinsonism is still unknown. Since a majority of patients with Gaucher disease, as well as a majority of Gaucher carriers, never develop parkinsonian manifestations, the presence of the mutant protein is likely to be a contributory risk factor rather than a direct cause. Further studies in larger patient cohorts, cell lines, animal models and in families will be necessary to establish the role of this lysosomal enzyme in neurodegenerative disorders.

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Table 1
Incidence of GBA mutations in different studies of subjects with Parkinson disease and/or other synucleinopathies

SERIES (SOURCE)	SCREENING METHOD	SUBJECTS		CONTROLS		G-TEST	METHOD OF DIAGNOSIS	REFERENCE
		N	% GBA mutations	N	% GBA mutations			
Taiwanese (Cortiell)	direct sequencing	92	4.3%	92	1.1%	$P = 0.159^*$	clinical (screened controls)	Current study
USA mixed ethnicities; brain tissue (5 US brain banks)	direct sequencing	57	14%	44	0	$P = 0.002$	pathologic evaluation (subjects & controls)	Lwin <i>et al.</i> (2004) <i>Mol Genet Metab</i>
Ashkenazi Jews (Israeli clinic)	screened for 6 mutations	99	31%	1543	6.2%	$P = 6E-13$	clinical (controls not screened)	Aharon-Peretz <i>et al.</i> (2004) <i>NEJM</i>
Ashkenazi Jews (NYC clinic)	screened for N370S	160	10.7%	92	4.3%	$P = 0.069^*$	clinical (screened controls)	Clark <i>et al.</i> (2005) <i>Mov Disord</i>
Canadian Caucasians; early onset PD and/or PD family history (Toronto clinic)	screened for 7 mutations	88	5.6%	122	0.8%	$P = 0.034$	clinical (screened controls)	Sato <i>et al.</i> (2005) <i>Mov Disord</i> (2005)
UK mixed ethnicities; brain tissue (UK Imperial Brain Bank)	direct sequencing	26	8%	NA [†]	NA [†]	$P = 0.043$	pathologic evaluation	Eblan <i>et al.</i> <i>NEJM</i>
Venezuelan; early onset PD (Caracas clinic)	direct sequencing	33	12%	31	3.2%	$P = 0.170^*$	clinical (screened controls)	Eblan <i>et al.</i> (2005) <i>Mov Disord</i>
Norwegian (Norwegian clinics)	screened for L444P and N370S	311	2.3%	474	1.7%	$P = 0.576^*$	clinical (screened controls)	Toft <i>et al.</i> (2006) <i>Neurology</i>
US subjects; different synucleinopathies (U. Penn. Brain Bank)	direct sequencing	75 total 35 DLB	12% 23%	NA [†]	NA [†]	$P = 0.003$ $P = 0.001$	pathologic evaluation (PD, DLB and MSA)	Goker-Alpan <i>et al.</i> (2006) <i>Neurology</i>

Abbreviations: PD, Parkinson disease; DLB, Dementia with Lewy bodies; MSA, Multiple System Atrophy; NA: not applicable;

[†] GBA mutation frequency in probands may be directly compared with the frequency in the original 44 brain bank controls (0%), the reported GBA mutation frequency in the general population (0.6%) and in the Ashkenazi population (3.4%).

* These studies are unable to detect a statistically significant difference between the proportion of GBA mutations in cases and controls by the G-test of independence. None have sufficient power ($\beta < 0.2$), however, to correctly accept the null hypothesis that proportion of GBA mutations are not different in the two groups.

Table 2

Taiwanese subjects with Parkinson disease and GBA mutations

Patient ID	Genotype	Sex	Age at onset (yrs)	Age at sampling (yrs)	Clinical manifestations	L-Dopa response	Dementia	Family history of dementia
N000559	L174P/wt	M	58	67	tremor, bradykinesia, rigidity, asymmetric onset	+	No	absent
N001064	Q497R/wt	M	63	67	tremor, bradykinesia, rigidity,	+	Yes	absent
N000903	L444P/wt	M	64	65	tremor, bradykinesia, rigidity, asymmetric onset	+	No	absent
N003026	D409H/wt	F	67	78	tremor, bradykinesia, rigidity, asymmetric onset	+	No	absent