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ARTICLE

GBA mutations p.N370S and p.L444P are associated with Parkinson's disease in patients from Northern Brazil

Mutações p.N370S e p.L444P no gene *GBA* estão associadas com doença de Parkinson em pacientes do norte do Brasil

Carlos Eduardo de Melo Amaral[1], Patrick Farias Lopes[1], Juliana Cristina Cardoso Ferreira[1], Erik Artur Cortinhas Alves[1], Marcella Vieira Barroso Montenegro[1], Edmar Tavares da Costa[3], Elizabeth Sumi Yamada[3], Fernando Otávio Quaresma Cavalcante[2], Luiz Carlos Santana-da-Silva[1]

ABSTRACT

Mutations of the *GBA* gene have been reported in patients with Parkinson's disease (PD) from a number of different countries, including Brazil. In order to confirm this pattern in a sample of PD patients from northern Brazil, we conducted a case-control study of the occurrence of the two most common mutations of the *GBA* gene (c.1226A>G; p.N370S and c.1448T>C; p.L444P) in a group of 81 PD patients and 81 control individuals, using PCR-RFLP, confirmed by the direct sequencing of the PCR products. In the patient group, three patients (3.7%) were heterozygous for the *GBA* c.1226A>G; p.N370S mutation, and three (3.7%) for *GBA* c.1448T>C; p.L444P. Neither mutation was detected in the control group (p =0.0284). Patients with the c.1448T>C; p.L444P mutation showed a tendency to have an earlier disease onset, but a larger sample number is required to confirm this observation. Our results suggest an association between the *GBA* c.1226A>G; p.N370S and c.1448T>C; p.L444P mutations and the development of PD in the population of patients from the Northern Brazil.

Keywords: Gaucher disease; mutation; Parkinson's disease.

RESUMO

Mutações no gene *GBA* têm sido reportadas em pacientes com doença de Parkinson (DP) em diferentes países, incluindo o Brasil. Com o objetivo de confirmar esse padrão em uma amostra de pacientes com DP provenientes do Norte brasileiro, foi conduzindo esse estudo caso-controle investigando a frequência das duas mutações mais comuns do gene *GBA* (c.1226A>G; p.N370S e c.1448T>C; p.L444P) em um grupo de 81 pacientes com DP e 81 controles, usando PCR-RFLP e confirmado pelo sequenciamento direto de produtos de PCR. No grupo experimental, três pacientes (3,7%) foram heterozigotos para a mutação c.1226A>G; p.N370S e três (3,7%), para a mutação c.1448T>C; p.L444P. Nenhuma das duas mutações foi detectada no grupo controle (p =0,0284). Pacientes com a mutação c.1448T>C; p.L444P demonstraram uma tendência a apresentar os sintomas mais precocemente, porém um número amostral maior é necessário para confirmar essa observação. Nossos resultados sugerem uma associação entre essas duas mutações no gene *GBA* e o desenvolvimento de DP na população de pacientes do norte Brasileiro.

Palavras-chave: Doença de Gaucher; mutação; doença de Parkinson.

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease in humans and it is characterized by muscular rigidity, resting tremor, bradykinesia, and postural instability. These symptoms result primarily from the progressive loss of the dopaminergic neurons from the pars compacta of the mesencephalic substantia nigra and subsequent depletion of the dopamine neurotransmitter in the striatum, a central component of the basal ganglia that is responsible for the instigation and coordination of movements. Parkinson's disease is defined by the presence

[1]Universidade Federal do Pará, Laboratório de Erros Inatos de Metabolismo, Belém PA, Brasil;
[2]Universidade Federal do Pará, HospitalUniversitárioJoão Barros de Barreto,Belém PA, Brasil;
[3]Universidade Federal do Pará, Laboratório de Neuropatologia Experimental, Belém PA, Brasil.
Luiz Carlos Santana da Silva https://orcid.org/0000-0003-1017-6221
Correspondence: Luiz Carlos Santana da Silva; Av. Pedro Miranda, 1807; 66085-024 Belém PA, Brasil; E-mail: lcsantana-pa@hotmail.com

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of Lewy bodies, proteinaceous intracytoplasmic inclusion in the reminiscent neurons in the substantia nigra pars compacta and other regions of the brain. The pathogenesis of PD is still not well understood, although some degree of interaction between environmental factors and genetic predisposition appears to play an important role in the development of the disease[1,2].

Significant advances have been made over the past 20 years in the comprehension of the molecular pathogenesis of PD, which have contributed to the identification of candidate genes with a given pattern of Mendelian inheritance. A number of mutations have been identified in the *SNCA* (alpha-synuclein), *PRKN* (parkin), *DJ1* (oncogene DJ1), *PINK1* (PTEN-induced putative kinase 1) and *LRRK2* (leucine-rich repeat kinase 2)[3,4].

A number of studies have recorded the occurrence of parkinsonian manifestations in patients with Gaucher disease (GD), a lysosomal storage disorder caused by homozygotic mutations in the glucocerebrosidase (*GBA*) gene that codify a glucocerebrosidase enzyme with reduced activity[5,6]. This has led to the suggestion that the presence of mutant alleles of the *GBA* gene may be a risk factor for the development of parkinsonian manifestations[7,8,9]. Indeed, an international and multicenter study with a sample of approximately 5,000 PD patients and equal number of controls has found a strong association between *GBA* mutations and risk of PD with an odds ratio greater than five[10].This finding may support the "loss of function" hypothesis, which postulated that the reduction in enzymatic activity leads to an increase in the levels of glucosylceramide in specific regions of the brain[8].

It seems likely that the presence of the mutant enzyme is a contributing risk factor, but is not a direct cause of PD. One possibility is that the mechanism is related to the defective processing of toxic proteins, which is aggravated by a relative reduction in the activity of the glucocerebrosidase enzyme, and the resulting accumulation of glucocerebrosides[11]. In 2004, Feany suggested that the connection of the alpha-synuclein to lipidic membranes would protect this protein from inadequate and clumped folding[12]. Mutations of the *GBA* gene would alter the lipid composition of the membrane, which would favor a build-up of alpha-synuclein in the cytosol and subsequently in the Lewy bodies[11]. A study has already shown that the affinity of alpha-synuclein for the surface of lipids is sensitive to their composition[13].

The highest frequencies of mutations of the *GBA* gene have been found in PD patients of Ashkenazi Jewish ancestry, with rates of 13.7% to 31.3% in comparison with 4.5% to 6.2% in control groups[7,14,15,16]. The frequencies recorded in PD patients in non-Jewish populations representing other populations, such as Italians, Caucasian Americans, Greeks, Brazilians, British, and Taiwanese, are invariably much lower – 3.5% to 12.0% – while controls from the same populations range from 0% to 5.3%[1,17,18,19,20,21]. The lowest rate recorded to date was 2.3% in Norwegian PD patients, compared with 1.7% in the control[9]. Previously, in North Africa, a study found no association between PD and mutations of the *GBA* gene; however, a more recent African study date suggested a risk association between mutations in the *GBA* gene and PD[22].

The mutations c.1226A>G; p.N370S and c.1448T>C; p.L444P are the most widely analyzed in studies of the association between mutations of the *GBA* gene and the manifestation of PD[7,16,17,21,22,23,24]. Given this, the present study investigated the presence of these two mutations in a population with PD from northern Brazil. In addition to systematic comparisons with previous studies, the primary aim of the study was to contribute to the evaluation of these mutations as a risk factor for the development of PD.

METHODS

Participants

In this cross-sectional study, 81 PD patients (50 male and 31 female) with a mean age of 69.5±10.6 years old (range 44-95) participated, as well as 81 controls (52 male and 29 female) with a mean age of 67.3±14.9 years old (range 34-96), matching in age and gender. All the patients were selected from the João de Barros Barreto University Hospital of the Federal University of Pará, where they were undergoing medical treatment, thus it was a convenience sample. These patients were all diagnosed according to the clinical criteria established by the United Kingdom Parkinson's Disease Society Brain Bank. The patient group covered a heterogeneous group of unrelated people with cases of both early (<50 years old) and late onset of symptoms. The mean age at the onset of the first symptoms was 55.12±11.64 years (range 28-78). All the patients were from the northern Brazilian city of Belém.

The control group comprised individuals with no symptoms of PD or any other neurodegenerative disease, and no family history of PD in first- or second- degree relatives. Their ages varied from 41 to 96 years. Both patients and control individuals were all volunteers, and signed a written informed consent. The study was approved by the Research Ethics Committee of the João de Barros Barreto University Hospital at the Federal University of Pará, under protocol number 2547/06.

Genetic analysis

The DNA of both groups was obtained for analysis of the *GBA* c.1226A>G; p.N370S and c.1448T>C; p.L444P mutations that was conducted in three stages. The first stage consisted of the pre-amplification of a fragment that extends from exon 8 to exon 11 of the *GBA* gene, using the following primers F: 5'-ACAAATTAGCTGGGTGTGGC-3' and R: 5'-TAAGCTCACACTGGCCCTGC-3[25].

The second stage of the analysis involved the use of the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) approach. For the analysis of the *GBA* c.1226A>G; p.N370S mutation, the

internal primers (F: 5'-GCCTTTGTCCTTACCCTCG-3') and (R: 5'-GACAAAGTTACGCACCCAA-3') were used. The products of this PCR were digested with the XhoI restriction enzyme. For the *GBA* c.1448T>C; p.L444P mutation, the internal primers were (F: 5'-TGAGGGTTTCATGGGAGGTA-3') and (R: 5'-AGAGTGTGATCCTGCCAAGG-3'), and the PCR products were digested with the NciI restriction enzyme. Positive and negative controls were included in all assays.

The third stage of the analysis was the confirmation of the presence of the mutations using a direct sequencing reaction with an ABI PRISM BigDye Terminator Cycle Sequencing (Applied Biosystems, USA) kit in an ABI-PRISM 377 (Applied Biosystems, USA) automatic sequencer.

Statistical analysis

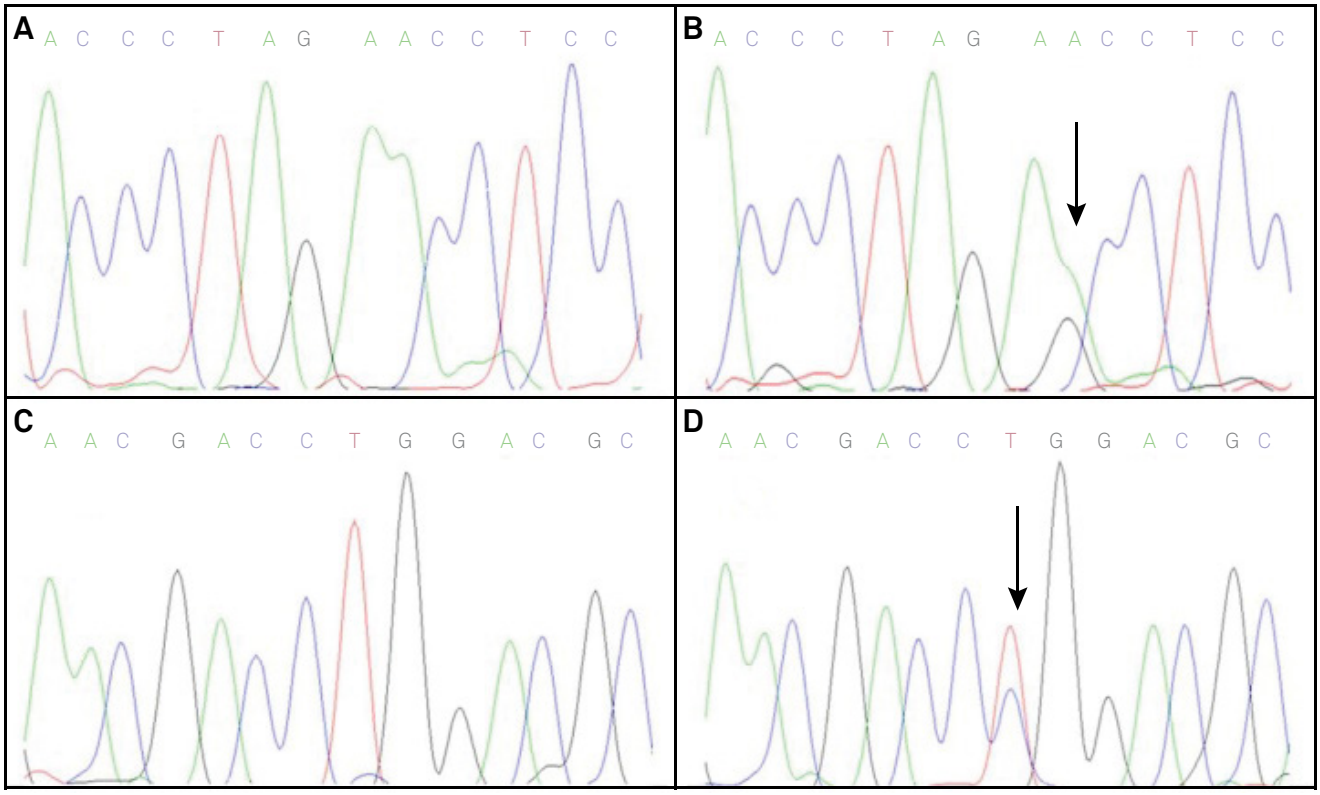
Statistical analyses used Fisher'sexact test.

RESULTS

The analysis of the *GBA* c.1226A>G; p.N370S and c.1448T>C; p.L444P mutations began with digestion by the restriction endonucleases. The presence of the mutations was then confirmed by sequencing analysis (Figure).

Six (7.4%) of the 81 PD patients presented one of the two most common mutations of the *GBA* gene. Half of these six (3.7%) were heterozygous for *GBA* c.1226A>G; p.N370S, and the other half were heterozygous for *GBA* c.1448T>C; p.L444P. By contrast, neither mutation was found in any of the members of the control group. The frequency of the mutant alleles *GBA* c.1226A>G; p.N370S and c.1448T>C; p.L444P (1.85% in both cases) in PD patients was significantly different from that of the control (Fisher's exact test: p = 0.0284).

Clinically, all six PD patients with one of the mutations presented with typical parkinsonian phenotypes, with the onset of symptoms at ages of between 28 and 71 years, and a mean age at the time of the study of 49.6±17.4 years. Three of the patients had suffered an early onset of symptoms, i.e. <50 years old, and two had a family history of PD (Table 1). The initial symptoms were asymmetric in all cases, with tremors reported in four patients, rigidity in one, and an alteration of the walk in the other. Autonomic and cognitive dysfunctions, or psychiatric disturbances were not reported in any of the cases, and most of these patients had responded well to treatment with dopaminergic agonists or levodopa. Overall, the clinical symptoms of these patients were indistinguishable from those of patients with no mutations of the *GBA* gene (Table 2).



A): Normal partial sequence of exon 9 of the GBA gene; B): Partial sequence of exon 9 of the GBA gene, showing the substitution c.1226A>G (N370S) observed in three PD patients in the present study. The position of the substitution is indicated by the arrow; C): normal sequence of exon 10 of the GBA gene; D): Partial sequence of exon 9 of the GBA gene, showing the substitution c1448T>C (L444P) observed in three PD patients in the present study. The position of the substitution is indicated by the Arrow.

Figure 1. sequences of the GBA gene in PD patients, showing the normal sequence (A, C), and those of the N370S (B) and L444P (D) mutations.

Table 1. Clinical characteristics of patients who were *GBA* mutation-positive (+).

Patients (mutation)	Sex	Age of onset	Current age	First symptoms	Familiar history
1 (*N370S*/Normal allele)	M	71	80	Rigidity and weakness in legs	Absent
2 (*N370S*/Normal allele)	F	42	69	Tremor in arm, initially just one side	Absent
3 (*N370S*/Normal allele)	F	67	75	Tremor on left side	Present (mother)
4 (*L444P*/Normal allele)	M	35	52	Impaired gait on left side	Present (paternal grandparents, paternal uncles and father)
5 (*L444P*/Normal allele)	M	28	44	Tremor on right side	Absent
6 (*L444P*/Normal allele)	M	55	65	Tremor on right side	Absent

Table 2. Clinical characteristics of *GBA* mutation positive (+) and *GBA* mutation negative (-) patients.

Variable	Mutation (+)	Mutation (-)	p-value
Total	6 (7.4%)	75 (92.6%)	
Male	4 (66.7%)	66 (88.0%)	
Female	2 (33.3%)	29 (12.0%)	
Age at onset	49.66 ± 17.47	54.96 ± 11.94	0.20
Initial symptoms			
Tremor	4 (66.7%)	47 (62.7%)	0.99
Bradykinesia	0 (0%)	4 (5.3%)	1.00
Rigidity	1 (25.0%)	6 (8.0%)	0.44
Postural instability	0 (0%)	2 (2.7%)	1.00
Family history	2 (3.3%)	6 (8.0%)	0.15

DISCUSSION

We recorded higher frequencies of heterozygous patients (7.4%) *GBA* c.1226A>G; p.N370S and c.1448T>C; p.L444P alleles than those reported in three other studies of Brazilian PD populations[17,24,26]. Spitz et al.[17] found only two (3.1%) of 65 PD patients from southeastern Brazil with mutations of the *GBA* gene (both heterozygous for *GBA* c.1448T>C; p.L444P), while no mutations were recorded in any of the 267 control participants (p = 0.0379). Socal et al.[24] also recorded mutations in only two (3.2%) of 62 PD patients from southern Brazil (one heterozygous for *GBA* c.1226A>G; p.N370S, the other for *GBA* c.1448T>C; p.L444P). Guimarães et al.[26] used a larger sample of 347 PD patients; the frequencies were similar to Spitz et al.[17], with 13/347 mutations in PD patients (3.7%) and 0/341 mutations in controls (0%); with 1.4% being p.N370S carriers and 2.3% c.L444P carriers (Table 3).

Outside Brazil, a number of studies of the mutations of the *GBA* gene have been conducted in a variety of ethnic groups. The Ashkenazi Jews have by far the highest frequencies of these mutations in both PD patients (13.7%–31.1%) and controls (4.2%–6.4%)[7,14,15,16]. Apart from the Norwegian population, the general pattern of significantly-higher frequencies than expected of *GBA* gene mutations in PD patients is repeated throughout most of the World[2,17,18,19,20,21,22,23,24].

Ashkenazi Jews present a relatively high incidence of GD, which affects approximately one in every 10,000 individuals. It thus seems possible that the high frequency of *GBA* mutations observed in Ashkenazi PD patients may be linked to the incidence of GD[17]. In Brazil, however, GD is rare, occurring in one in every 400,000 individuals[27], although the true frequency may be higher, given that not all patients may be diagnosed correctly. This estimate nevertheless indicates that GD is around 40 times less common in Brazil in comparison with the general Ashkenazi population. The incidence observed in Brazil implies that one in approximately 500 individuals may be heterozygous for GD. The relatively high frequency of PD patients in our sample who are heterozygous for mutations of the *GBA* gene reinforces the role of these mutations in the etiology of PD.

While our frequency of PD patients was much lower than those recorded in Ashkenazi Jews, it is consistent with that found in a study of 230 Portuguese patients. In this case, 6.1% of the PD patients were heterozygous for *GBA* mutations, whereas this condition was recorded in only 0.7% (3 of 430) of the control individuals. The *GBA* c.1226A>G; p.N370S is the most common in both Portuguese and Ashkenazi Jewish populations[28].

The higher frequency of heterozygotes in PD patients than in the control group recorded in the present study (7.4%) is also consistent with the results of studies conducted in England (3.5%: 9/259 participants), Greece (10.2%: 21/205), Italy (4.5%: 106/2350), Japan (9.4%: 50/534) and Venezuela (12.0%: 4/33), and in a population of Canadians of Caucasian origin[18,19,20,21,23,29].

The mean age of onset of the disease in PD patients was lower in patients with *GBA* mutations (49.6± 17.4 years) in comparison with those with no mutations (55.1±11.6 years) (Table 2). This finding is consistent with some[2,6,21,22], but not all the other studies of *GBA* mutations in PD patients[7,9,26,30]. These differences may be accounted for by the fact that the modifier genes that contribute to development of the phenotype of the disease may also vary systematically in different populations. Epistatic interactions between genes or specific types of interaction among haplotypes at multiple loci may also contribute to differences in the onset of the disease[2].

Table 3.*GBA* mutation among PD patients in different Brazilian regions.

Studies	Population studied	PD inclusion criteria	Method	Mutation analyzed	Patient mutation frequency	Control mutation frequency	Age of onset	GBA mutated PD and family history
Spitz et al.[17]	65 PD patients and 267 control individuals from southeastern Brazil	Early onset (<55 years)	PCR-RFLP, restriction endonucleases and electrophoresis	N370S and L444P	2/65 (3%); L444P 2/2 (100%); N370S 0/2 (0%)	0/267	Patient 1 at 46 years old and Patient 2 at 42 years old.	The two patients had family history, no statistical test was applied.
Socal et al.[24]	62 PD patients from southern Brazil	All patients diagnosed were included	PCR-RFLP, restriction endonucleases	N370S, L444P and IVS2þ1	2/62 (3.5%); L444P 1/2 (50%); N370S 1/2 (50%)	Not informed	Patients with mutation 37 ± 4 years. Patients without mutation 41.4 ± 10.8 years.	Not informed
Guimarães et al.[26]	347 PD patients and 341 control individuals from southeastern, midwestern and northern Brazil.	All patients diagnosed were included.	direct sequencing	N370S and L444P	13/347 (3.7%); L444P 8/13 (62%); N370S 5/13 (38%)	0/341	Patients with mutation 49.9 ± 11.3 y years Patients without mutation 52.5 ± 13.3 years.	Those with family history and those without family history did not show statistical significance.
Amaral et al. (Present study	81 PD patients and 81 control individuals from northern Brazil.	All patients diagnosed were included	Amplification of the exons 8 to exon 11, PCR-RFLP for N370S and L444P, restriction endonucleases and direct sequencing of N370S and L444P	N370S and L444P	6/81 (7.4%); L444P 3/6 (50%); N370S 3/6 (50%)	0/81	Patients with mutation 49.6 ± 17.4 years. Patients without mutation 55.1 ± 11.6 years.	Of the 6 patients, 2 had family history. No statistical test was used.

PD: Parkinson's disease; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

In both the southeastern and Southern study populations, however, all the PD patients with *GBA* mutations had both a family history of the disease and early onset (<50 years old) (Table 3). In Southeastern Brazil[17], the two patients had onset ages of 42 and 46 years, while in Southern Brazil[24], the ages were 34 and 40 years. Guimarães et al. did not find any significant difference, either in family history or age of onset, among PD *GBA* carriers and non-carriers (Table 3), but this showed a tendency to occur at an earlier age[26]. In the present study, half of the six patients with *GBA* mutations had experienced early onset of the disease, whereas the others suffered their first symptoms at 55 years of age (no family history), 67 years (PD in the mother) and 71 years (no history). Interestingly, the PD patients heterozygous for c.L444P mutation showed a tendency to have an earlier age of onset compared withthose heterozygous for p.N370S mutation (Table 1). Although no statistical test could be used in our study, other studies also observed differences in the PD phenotype according to which mutation is present[15,16]. Another observation was that, among the four Brazilian studies, the mutation c.L444p has been more frequent than the mutation p.N370S (Table 3).

Among our patients, only a third (2 of 6) of the PD patients with mutations of the *GBA* gene had a family history of the disease (Table 3). This corresponds with the pattern observed in some studies[2,9,22,23], but not others, in which most of the patients with *GBA* mutations had a family history[7,17,21,24]. Our results suggest that *GBA* mutations may be related to a greater risk for PD development in patients with family history as well in patients without family with the disease.

It seems reasonable to assume that at least part of the frequency variation among populations is due to differences in sample size and the criteria used to include patients, as well as those in the techniques used to identify the mutations[21,30] (Table 3). The different genetic origins of the populations and varying degrees of interaction with environmental factors may also contribute to observed differences, as suggested by Moraitou et al.[19].

Although less heterogeneous than Brazil, Greek and Italian studies have found significant differences comparing PD patients and controls from urban and rural areas[19], and from the North and South regions[21]. Thus, due to the extremely mixed population of Brazil, research indifferent regions across the country is necessary in order to properly characterize *GBA* mutations in our population. Spitz et al.[17]

and Socal et al.[24] worked with only Southeastern and southern populations, respectively. The population of the Pará State that participated in this study hasa genetic contribution of 60% European ancestry, 12% African ancestry and 28% Amerindian ancestry, whereas Southern Brazil has, almost exclusively, European ancestry[31]. Before this study, only De Guimarães et al. used samples from Northern, along with Southeastern and midwestern samples, but they did not examine the frequencies by regions[26].

This study further reinforces the association of mutations of the *GBA* gene as a factor of genetic susceptibility for the development of PD in the Brazilian population. It also shows a higher frequency of *GBA* mutations in a Brazilian region poorly studied in the neurogenetic field and which has a different ancestry from those Brazilian regions where similar studies have been done. However, the exact molecular and cellular mechanisms involved in the association between the mutations and the development of the disease remain unknown.

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