Genetics of Parkinson’s disease in Brazil: a systematic review of monogenic forms

Bruno L. SANTOS-LOBATO1,2, Artur SCHUMACHER-SCHUH3,4, Ignacio F. MATA5, Grace H. LETRO6, Pedro BRAGA-NETO7, Pedro R. P.BRANDÃO8, Clécio O. GODEIRO-JUNIOR9, Marcus V. DELLA COLETTA10, Sarah T. CAMARGOS11, Vanderci BORGES12, Carlos R. M. RIEDER13, Vitor TUMAS14 on behalf of the Brazilian Consortium of Parkinson’s Disease

ABSTRACT

Background: Increasing numbers of mutations causing monogenic forms of Parkinson's disease (PD) have been described, mostly among patients in Europe and North America. Since genetic architecture varies between different populations, studying the specific genetic profile of Brazilian patients is essential for improving genetic counseling and for selecting patients for clinical trials. Objective: We conducted a systematic review to identify genetic studies on Brazilian patients and to set a background for future studies on monogenic forms of PD in Brazil. Methods: We searched MEDLINE, EMBASE and Web of Science from inception to December 2019 using terms for “Parkinson's disease,” “genetics” and “Brazil”. Two independent reviewers extracted the data. For the genes LRRK2 and PRKN, the estimated prevalence was calculated for each study, and a meta-analysis was performed. Results: A total of 32 studies were included, comprising 94 Brazilian patients with PD with a causative mutation, identified from among 2,872 screened patients (3.2%). PRKN mutations were causative of PD in 48 patients out of 576 (8.3%). LRRK2 mutations were identified in 40 out of 1,556 patients (2.5%), and p.G2019S was the most common mutation (2.2%). Conclusions: PRKN is the most common autosomal recessive cause of PD, and LRRK2 is the most common autosomal dominant form. We observed that there was a lack of robust epidemiological studies on PD genetics in Brazil and, especially, that the diversity of Brazil’s population had not been considered.

Keywords: Genetics; Parkinson's disease; LRRK2; PRKN.

1Universidade Federal do Pará, Laboratório de Neuropatologia Experimental, Belém PA, Brazil.
2Hospital Ophir Loyola, Serviço de Neurologia, Belém PA, Brazil.
3Hospital de Clínicas de Porto Alegre, Serviço de Neurologia, Porto Alegre RS, Brazil.
4Universidade Federal do Rio Grande do Sul, Departamento de Farmacologia, Porto Alegre RS, Brazil.
5Lerner Research Institute, Genomic Medicine, Cleveland Clinic, Cleveland, OH USA.
6Pontifícia Universidade Católica de Campinas, Centro de Ciências da Vida, Campinas SP, Brazil.
7Universidade Federal do Ceará, Departamento de Medicina Clínica, Serviço de Neurologia e Neurocirurgia, Fortaleza CE, Brazil.
8Universidade de Brasília, Laboratório de Neurociências e Comportamento, Brasília DF, Brazil.
9Universidade Federal do Rio Grande do Norte, Departamento de Medicina Integrada, Natal RN, Brazil.
10Universidade do Estado do Amazonas, Fundação Hospital Adriano Jorge, Manaus AM, Brazil.
11Universidade Federal de Minas Gerais, Departamento de Medicina Interna, Belo Horizonte MG, Brazil.
12Universidade Federal de São Paulo, Departamento de Neurologia e Neurocirurgia, Setor de Transtornos de Movimento, São Paulo SP, Brazil.
13Universidade Federal de Ciências da Saúde de Porto Alegre, Departamento de Neurologia, Porto Alegre RS, Brazil.
14Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Neurociências e Ciências do Comportamento, Ribeirão Preto SP, Brazil.

Conflict of interest declarations: Dr. Santos-Lobato has no conflicts of interest; Dr. Schumacher-Schuh has no conflicts of interest; Dr. Mata has no conflicts of interest; Dr. Letro has no conflicts of interest; Dr. Braga-Neto received fees from Actelion Janssen and Teva for presentation of lectures, and a grant from the Brazilian National Council for Scientific and Technological Development; Dr. Brandão has no conflicts of interest; Dr. Godeiro-Junior received educational support from Roche; Dr. Delia Colleta has no conflicts of interest; Dr. Camargos received fees from Roche and Teva for presentation of lectures, and received support from Roche and Centogene for congress attendance; Dr. Borges received honoraria from UCB Biopharma; Dr. Rieder served on Advisory Boards of Teva Brasil, UCB Biopharma, Medtronic and Roche, received support from Roche for congress attendance, and received a grant from the Brazilian National Council for Scientific and Technological Development; Dr. Tumas received honoraria from Teva Brasil, UCB Biopharma and Ipsen, and travel support from Roche for medical conferences.

Authors’ contributions: Bruno L. Santos-Lobato, Artur Schumacher-Schuh, Ignacio F. Mata, Carlos R. M. Rieder and Vitor Tumas contributed to conception and organization of the manuscript. All authors wrote and critically evaluated the first draft of the manuscript. All authors approved the final version of the manuscript for submission.

Received on August 25, 2020; Received in final form on September 15, 2020; Accepted on September 17, 2020.
INTRODUCTION

Over recent decades, mutations in several genes have been linked to inherited forms of Parkinson’s disease (PD). After alpha-synuclein gene (SNCA) mutations were reported to be a monogenic cause of parkinsonism\(^1\), several other genetic forms of the disease were described, including those with autosomal dominant inheritance, such as with the genes LRRK2, SNCA, VPS35, ATXN2 and GCH1, and others with recessive inheritance, such as with the genes PRKN, PINK1 and DJ1. Some other autosomal recessive mutations cause atypical parkinsonism, such as with the genes ATP13A2, PLA2G6, SYNJ1, SPG11, FBXO7 and VPS13C. Mutations in the X-linked RAB39B gene have also been described as causing parkinsonism\(^1\).

Some of these mutations, such as the LRRK2 point mutation c.6055G>A (p.G2019S), are highly population-specific. While virtually absent among Asians and with low prevalence in Europeans (1–4% of sporadic PD and up to 14% of familial PD cases), LRRK2 mutations can be found in up to 28% of Ashkenazi Jewish and 38% of North-African Arab patients\(^2\).

Brazil is the fifth most populous country in the world, with more than 210 million inhabitants; approximately 14% of the population is aged 60 years or over, and it has been estimated that this proportion will rise to 32% by 2060\(^3\). The Brazilian population has significant genetic variability due to the interactions between Amerindian populations, Portuguese settlers and enslaved African people starting at the beginning of the 16th century; and subsequent interactions with individuals who migrated from other nations (like Italians, Japanese and Germans) in the 19\(^{th}\) century\(^4\). Because of this genetic diversity, the frequency of different monogenic causes of PD can differ from those observed in other regions of the world. This can also vary significantly according to the different regions of the country and between socioeconomic classes.

To identify these gaps in knowledge and lay the foundation for future projects in this country, we conducted a systematic review of previously published studies on monogenic forms of PD among Brazilian patients. Our aims were to provide a broad view of studies describing genetic forms of PD in Brazilian patients, and to perform a meta-analysis to estimate the prevalences of the better-explored monogenic PD mutations in Brazil.

METHODS

Search strategy

We conducted a systematic search of the literature in MEDLINE, EMBASE and Web of Science (from inception to December 2019) using the following algorithms: MEDLINE – “Parkinson’s disease” AND Brazil AND genetics; EMBASE – (parkinson disease/exp OR ‘parkinson disease’) AND (brazil/EXP OR brazil) AND (genetics/EXP OR genetics); Web of Science – ALL=(“Parkinson’s disease” AND Brazil AND genetics). Reference lists of studies that were included were checked to identify any additional studies that might have been missed in the primary search (cross-reference search).

Study selection

We aimed to select any original research study describing Brazilian patients with monogenic forms of PD. Two rounds of selection were performed. In the first round, titles and abstracts were screened and exclusions were made based on these exclusion criteria: (1) studies without a description of the genetic forms of PD in Brazilian patients; (2) studies not conducted on human subjects; and (3) duplicated articles. In the second round, full texts were evaluated and exclusions were made based on other exclusion criteria: (1) review studies; (2) studies on cases of patients with genetic forms of PD that had already described, without making any new
contributions; (3) studies assessing different conditions (such as atypical parkinsonism or dementia with Lewy bodies); (4) conference abstracts; and (5) full text not found. Two reviewers performed each selection round independently and disagreements were resolved by reaching a consensus. The potential pathogenicity of the variants reported was assessed based on the methodology of the International Parkinson Disease and Movement Disorder Society Genetic Mutation Database (https://www.mdsgene.org/methods)\(^5\) and on the ClinVar database of the National Institute of Health, USA (https://www.ncbi.nlm.nih.gov/clinvar/)\(^6\).

Data extraction
Two independent reviewers extracted the data using a spreadsheet, in which the following items were reported: (1) first author’s name; (2) year of publication; (3) Brazilian region involved in the study; (4) study design; (5) studies with family history as an inclusion criteria for patients (defined as any positive family history); (6) studies with early-onset PD (EOPD) as an inclusion criteria (cutoff age at onset ranging from 40 to 55 years between studies); (7) sample size, sex and age of the study population (patients and controls); (7) genes analyzed; (8) number of mutations described; and (9) zygosity of mutations.

Statistical analysis
The number and prevalence of mutations in genes described in Brazilian patients with PD were calculated. We considered that PRKN and LRRK2 were the genes most explored in studies and, hence, we proceeded with further analyses on mutations in these genes. For these analyses, we excluded family case studies and case reports/series due to the high possibility of selection bias. A random-effects model was used to estimate the weighted pooled prevalence of mutations in PRKN and LRRK2. To assess the heterogeneity between the studies, the I\(^2\) test was used, and I\(^2\) above 75% was taken to indicate high heterogeneity. The analyses were performed using MetaXL 5.3 (Epigear International, Sunrise Beach, Australia), which is an add-in for Microsoft Excel.

RESULTS
After pooling the publications from database searches, a total of 343 articles were found. After the first round, 44 articles were selected for full-text examined. From these, a total of 32 articles were finally included and reviewed (Table 1). Twenty-three studies were mutation screenings, seven were family studies, and two were case reports. Twelve studies were international collaborations that included Brazilian groups. Among the studies exclusively conducted in Brazil, only seven involved collaborations between groups in different regions of this country. According to the participation of Brazilian regions in these studies, patients in the Southeastern region were included in 25 studies, in the Southern region in nine studies, in the Central-western region in seven studies, in the Northern region in three studies and in the Northeastern region in three studies (Figure 1). Fifteen studies strictly only included patients with a family history of PD, and 16 studies strictly only included patients with EOPD. Among all these studies, 94 mutations were reported among approximately 2,872 Brazilian PD patients (3.2%). The mean age at evaluation and age at onset were 55.9 and 44.6 years, respectively. Nine genes were analyzed, and mutations in five genes were described (Table 2).

Fifteen studies assessed the prevalence of LRRK2 mutations among 1,556 patients, finding a total of 40 patients (2.5%) carrying LRRK2 mutations. Four of these studies only included patients with familial PD (total of 233 patients; 14.9% of all patients screened for LRRK2 mutations), and five studies only included patients with EOPD (total of 410 patients; 26.3% of all patients screened for LRRK2 mutations). There were no homozygous or compound heterozygous mutations. The mean age at onset was 49.9 years (95% CI, 45.1-54.6) and a positive family history was found among 45.4% of the patients with PD carrying LRRK2 mutations. The most common mutation in the LRRK2 gene was p.G2019S (n = 35), followed by p.Y2189C (n = 2) and p.C2139S, p.R1441C and p.Q923H (each of these last mutations was detected in one patient) (Figure 2). However, nine studies explored only the p.G2019S mutation, and three studies sequenced the whole LRRK2 gene, thus probably overestimating the frequency of this mutation in Brazilian patients with PD. Only p.G2019S and p.R1441C were classified as definitely pathogenic mutations, and the other mutations (p.Y2189C, p.C2139S and p.Q923H) were classified as variants of uncertain significance. In accordance with the methodology described above, we selected eight studies for meta-analysis (n = 1,257). The random-effect model showed that the weighted pooled prevalence of LRRK2 mutations in Brazilian patients with PD was 3.5% (95% CI, 2.2%-5.0%), with moderate heterogeneity between the studies analyzed (I\(^2\) = 37.4%; p = 0.13) (Figure 3A). Comparing only the studies that included strictly EOPD or familial PD patients, the weighted pooled prevalence of LRRK2 mutations was 5.4% (95% CI, 2.7%-9.0%) in three studies that included strictly EOPD patients (n = 208) (Figure 3B), and 5% (95% CI, 1.9%-9.2%) in two studies that included strictly familial PD patients (n = 224) (Figure 3C).

Twelve studies assessed the prevalence of PRKN mutations among a total of 576 patients, finding a total of 48 patients (8.3%) carrying PRKN mutations. Five of these studies only included patients with familial PD (total of 25 patients; 43% of all patients screened for PRKN mutations), and eight studies only included patients with EOPD (total of 559 patients; 97% of all patients screened for PRKN mutations). Among these mutations, 43.7% were homozygous and
Table 1. Main characteristics of 32 genetic studies involving Brazilian patients with PD

| Author, year          | Study design       | Sample size (Brazil) | Gene analyzed       | Analysis method                          | Results                                                                 | Reference |
|-----------------------|--------------------|----------------------|---------------------|------------------------------------------|--------------------------------------------------------------------------|-----------|
| Teive et al., 2001    | Family study       | 10                   | SNCA                | PCR-RFLP                                 | No pathogenic mutations found                                           | [7]       |
| Rawal et al., 2003    | Family study       | 4                    | PRKN                | Sequencing and PCR-RFLP                  | PRKN: Ex4 del - 1, Ex6 del - 1, pAsn52* - 1                              | [8]       |
| Bertolli-Avella et al., 2005 | Mutation screening | 4                    | PRKN                | Sequencing and PCR-RFLP                  | No pathogenic mutations found                                           | [9]       |
| Clarimon et al., 2005 | Family study       | 6                    | PRKN                | Sequencing                              | PRKN: Ex4 del - 1                                                       | [10]      |
| DiFonzo et al., 2005  | Family study       | 9                    | LRRK2               | Sequencing                              | LRRK2; pG2019S - 1                                                      | [11]      |
| Bonifati et al., 2005 | Mutation screening | 8                    | PINK1               | Sequencing                              | No pathogenic mutations found                                           | [12]      |
| Khan et al., 2005     | Family study       | 6                    | PRKN                | Sequencing                              | PRKN: Ex4 del - 6                                                       | [13]      |
| Chien et al., 2006    | Family study       | 10                   | PRKN, PINK1, DJ1    | Sequencing and PCR-RFLP                  | PRKN: IVS1+1G/T - 10                                                    | [14]      |
| DiFonzo et al., 2006  | Family study       | 9                    | LRRK2               | Sequencing                              | No pathogenic mutations found                                           | [15]      |
| DiFonzo et al., 2007  | Mutation screening | 92                   | ATP13A2             | Sequencing                              | ATP13A2: pGly504Arg - 1                                                 | [16]      |
| Lesage et al., 2007   | Mutation screening | ND                   | PRKN                | Sequencing                              | LRRK2; pG2019S - 1; PRKN: Ex3 del/N58QfsX39 - 4, pK211N - 1, Ex11 del/A390EfsX6 - 1, c1286-3G>C - 1 | [17]      |
| Aguiar et al., 2008   | Mutation screening | 72                   | PRKN, LRRK2         | Sequencing and qPCR                      | LRRK2; pG2019S - 4; PRKN: Ex3 del/N58QfsX39 - 4, pK211N - 1, Ex11 del/A390EfsX6 - 1, c1286-3G>C - 1 | [18]      |
| Munhoz et al., 2008   | Mutation screening | 83                   | LRRK2               | PCR-RFLP                                 | LRRK2; p2019S - 6                                                      | [19]      |
| Pimentel et al., 2008 | Mutation screening | 147                  | LRRK2               | Sequencing                              | LRRK2; p2019S - 3                                                      | [20]      |
| Santos-Rebouças et al., 2008 | Case report / series | 1                    | LRRK2               | PCR-RFLP                                 | LRRK2; p2019S - 1                                                      | [21]      |
| Godeiro-Junior et al., 2009 | Mutation screening | 60                   | PINK1               | Sequencing                              | No pathogenic mutations found                                           | [22]      |
| Barsottini et al., 2009 | Mutation screening | 119                  | PRKN, LRRK2         | Sequencing and qPCR                      | No pathogenic mutations found                                           | [23]      |
| Camargos et al., 2009 | Mutation screening | 53                   | SNCA, PRKN, LRRK2, PINK1 | Sequencing                             | LRRK2; pQ923H - 1; PRKN: Dup Ex5 - 1, pP253R - 1, pW54R - 1, pV3I - 1, pAsn52* - 2, pT240M - 2; PINK1: Ex7 del - 1 | [24]      |
| Santos et al., 2010   | Mutation screening | 110                  | ATP13A2             | Sequencing and PCR-RFLP                  | No pathogenic mutations found                                           | [25]      |
| Author, year                  | Study design       | Sample size (Brazil) | Gene analyzed | Analysis method          | Results                                                                 | Reference |
|------------------------------|--------------------|---------------------|---------------|--------------------------|-------------------------------------------------------------------------|-----------|
| Abdalla-Carvalho et al., 2010| Mutation screening | 197                 | LRRK2         | Sequencing               | LRRK2: pT1410M - 4, pG2019 - 2, pC2139S - 1, pY2189C - 2                | [26]      |
| Moura et al., 2012           | Mutation screening | 102                 | SNCA, PRKN, PINK1, DJ1 | MLPA and qPCR           | PRKN: Ex4 del - 1, Ex5-6 del - 1, Dup Ex3 - 1, Dup Ex4 - 1              | [27]      |
| Moura et al., 2013           | Mutation screening | 136                 | PRKN, PINK1   | MLPA, allelic discrimination and PCR-RFLP | PRKN: pT240M - 1                                                        | [28]      |
| Quadri et al., 2013          | Mutation screening | 31                  | SYNJ1         | Sequencing               |                                                                        | [29]      |
| Chien et al., 2014           | Mutation screening | 100                 | LRRK2         | PCR-RFLP                 |                                                                        | [30]      |
| Bertucci-Filho et al., 2014  | Mutation screening | 69                  | PRKN, LRRK2   | Sequencing               | LRRK2: pG2019S - 1, PRKN: Dup Ex2-3 - 1, pAsn52fs - 2, pArg256Cys - 1 | [31]      |
| Longo et al., 2015           | Mutation screening | 154                 | SNCA          | PCR-RFLP                 |                                                                        | [32]      |
| Pimentel et al., 2015        | Mutation screening | 549                 | SNCA          | Sequencing and qPCR      |                                                                        | [33]      |
| Spitz et al., 2015           | Case report / series | 1                   | LRRK2         | Sequencing and PCR-RFLP  | LRRK2: pG2019S - 1                                                      | [34]      |
| Olgiati et al., 2016         | Mutation screening | 39                  | DNAJC6        | Sequencing               | DNAJC6: pThr741= - 2, c1468+83del - 1, c2039+3A>G - 1                  | [35]      |
| Abreu et al., 2016           | Mutation screening | 141                 | SNCA, LRRK2, VPS35 | Allelic discrimination and sequencing | LRRK2: pG2019S - 5                                                      | [36]      |
| Cornejo-Olivas et al., 2017  | Mutation screening | 433                 | LRRK2         | Allelic discrimination and sequencing | LRRK2: pG2019S - 6, pR1441C - 1                                          | [37]      |
| Silva et al., 2017           | Mutation screening | 131                 | LRRK2         | Sequencing and PCR-RFLP  | LRRK2: pG2019S - 5                                                      | [38]      |

MLPA: Multiplex ligation-dependent probe amplification; ND: Not described; PCR-RFLP: Polymerase chain reaction with restriction fragment length polymorphism; qPCR: Quantitative polymerase chain reaction.
Table 2. List of genes investigated and mutations identified in Brazilian patients with PD.

| Genes investigated in Brazilian patients with PD | Genes with mutation identified in Brazilian patients with PD |
|-------------------------------------------------|----------------------------------------------------------|
| ATP13A2                                         | ATP13A2                                                  |
| DJ1                                             | DNAJC6                                                   |
| DNAJC6                                          | LRRK2                                                    |
| LRRK2                                           | PINK1                                                    |
| PINK1                                           | PRKN                                                     |
| PRKN                                            |                                                           |
| SNCA                                            |                                                           |
| SYNJ1                                           |                                                           |
| VPS35                                           |                                                           |

Figure 1. Distribution of monogenic forms of PD described in Brazil. A: Distribution of studies on monogenic forms of PD in Brazil according to states. B: Distribution of LRRK2 and PRKN mutations in Brazil according to regions (depicted in different shades of gray). Studies are represented by symbols, according to the type of study design. Ancestry proportions of each region are represented in pie charts, based on Moura et al., 2015."
12.5% were compound heterozygous. The mean age at onset was 31.8 years (95% CI, 28.5-35.1) and there was a positive family history among 66.6% of the patients carrying PRKN mutations, including copy number variations, single nucleotide variants and frameshift mutations (Figure 4). The most common mutations in PRKN were IVS1+1G/T (n = 10) and a deletion in exon 4 (n = 9). Two mutations were classified as probably pathogenic (p.R256C and c.1286-3G>C), and four as variants of uncertain significance (IVS1+1G/T, p.P253R, p.V3I and p.W54R) due their rarity; all other mutations were classified as definitely pathogenic. We selected four studies for meta-analysis; these studies included strictly EOPD patients, and none included only familial PD patients (n = 296). The random-effect model showed that the weighted pooled prevalence of PRKN mutations in Brazilian EOPD patients was 9.3% (95% CI, 4.4%-15.6%), with high heterogeneity between the studies analyzed (I² = 62.9%; p = 0.04) (Figure 5).

There were descriptions of mutations in other three genes: four patients with DNAJC6 mutations (two patients homozygous for p.T741=, one with compound heterozygosity for c.1468+83del and one with compound heterozygosity for c.2038+3A>G), one patient with PINK1 mutation (homozygous deletion in exon 7) and one patient with an ATP13A2 homozygous mutation (p.G504R). The PINK1 deletion in exon 7 and ATP13A2 p.G504R was classified as probably pathogenic, DNAJC6 p.T741= as possibly pathogenic and DNAJC6 c.1468+83del and c.2038+3A>G as variants of uncertain significance.

**DISCUSSION**

We found in this systematic review that there is a significant number of studies on monogenic forms of PD in Brazilian patients, in which around 3,000 patients were evaluated. Most of these studies were mutation screenings. Mutations in nine genes related to PD were investigated: SNCA, PRKN, LRRK2, PINK1, DJ1, VPS35, ATP13A2, DNAJC6 and SYNJ1; mutations were found in five of them: PRKN, LRRK2, PINK1, ATP13A2 and DNAJC6. The two genes most studied in Brazilian patients were PRKN and LRRK2. This finding was expected, as these monogenic forms of PD are the most common forms worldwide.

The LRRK2 p.G2019S point mutation is the most common associated variant that causes monogenic PD, and it also seems to be the most important cause of LRRK2 PD in the Brazilian population to date. We estimated that the weighted pooled prevalence of LRRK2 mutations was 3.5% among all the Brazilian patients evaluated here, and 5% among familial PD cases. However, considering the low level of inclusion of familial PD patients, and that most studies only screened for the p.G2019S mutation, these prevalences may be imprecise. These Brazilian findings are similar to worldwide data,
Figure 3. Forest plot of prevalence of LRRK2 mutation-positive Brazilian patients with PD and 95% confidence intervals for each study included in the meta-analysis. A: Analysis with all studies. B: Analysis with studies that strictly included early-onset PD cases. C: Analysis with studies that strictly included familial PD cases. Right-hand column shows per-study prevalence of mutation-positive cases for LRRK2 (%), 95% confidence intervals and the weighting (%) of each study. The overall weighted prevalence in the random-effects model is denoted by a blue diamond and dotted line. Blue squares are in proportion to the weighting of each study, and blue bars show confidence intervals.

which LRRK2 p.G2019S point mutations are present in 1-5% of patients with sporadic PD.\(^\text{x}\)

Autosomal recessive homozygous or compound heterozygous loss-of-function mutations were identified in four genes (PRKN, PINK1, ATP13A2 and DNAJC6) in Brazilian patients. PRKN was the most commonly identified gene with pathological mutations in EOPD patients.

In the Brazilian population, as was expected, presence of a family history of PD and earlier age of onset were associated with PRKN mutations. Two-thirds of these patients with PD carrying PRKN mutations in Brazil reported having a family history. As expected, there were different types of mutations in PRKN, including copy number, single nucleotide and frameshift variants. The weighted pooled prevalence in Brazilian EOPD patients (9.3%) was similar to the estimated global prevalence of PRKN mutations in a previous systematic review on EOPD cases (8.6%; 95% CI, 6.0%-12.4%).\(^\text{3,4}\)

SNCA mutations have been found in many countries, comprising 0.2% of sporadic and 1-2% of familial PD cases, but no such patients have been described in Brazil, even though six studies explored this. The lack of mutations in VPS35, DJ1 and SYNJ1 among Brazilian patients was not surprising, since these are rare causes of PD, and only three studies explored these genes.
Figure 4. Schematic representation of Parkin protein domains, and locations of mutations described in Brazilian patients with PD, adapted from the website of the Movement Disorder Society Genetic Mutation Database. Arrows indicate the locations of point mutations, and horizontal lines indicate the locations of copy number variations (deletions and duplications). Definitely pathogenic mutations are indicated in red letters, probably pathogenic mutations in blue letters and variants of uncertain significance in black letters.
Despite the significant number of studies, it was not possible to accurately estimate the epidemiology of monogenic forms of PD in Brazil. We noted that selection bias was present and that only small numbers of patients were included in most studies. Most of the genetic analyses were among individuals in the southern regions of the country, with a strong contribution from European ancestry, which may have given rise to bias of representation within the Brazilian population (the Northern region has the highest proportion of Amerindian ancestry, and the Northeastern region has the highest proportion of African ancestry) (Figure 1B). Therefore, our first conclusion from this systematic review is that there is a lack of robust Brazilian epidemiological studies on the genetics of PD.

We noticed that the level of interactions between Brazilian research groups in different regions of Brazil was low among these genetic studies. It was more common for individual Brazilian groups to participate in collaborative international studies.

Genetic diversity is a major challenge in the field of PD genetics. Like other scientific fields, the majority of the research has been done on individuals with mainly European ancestry. One potential bias in Brazilian studies is that almost all of them were conducted in dedicated tertiary-level referral centers and thus included patients with relatively high a priori likelihood of monogenic disorders.

Another limitation of our analysis was that data from the same patient could have been described in different publications, and this might have caused an overlap between studies. Unfortunately, we were unable to contact the researchers involved in all the original studies in order to gain access to raw data.

In summary, this systematic review showed that there is a lack of robust Brazilian epidemiological studies on the genetics of PD. To date, only five genes associated with monogenic PD have been identified in Brazilian patients with PD (PRKN, LRRK2, PINK1, ATP13A2 and DNAJC6). Studies with larger samples are needed in order to more precisely estimate the frequency of monogenic PD forms in Brazil, a country of continental size and huge genetic variability. We also identified regions of this country that are underrepresented with regard to genetic studies, and we would therefore urge increased representation of these regions in future studies.

ACKNOWLEDGEMENTS

We would like to thank Prof. Márcia Mattos Gonçalves Pimentel, PhD (Universidade do Estado do Rio de Janeiro), for contributing with data from original publications.

REFERENCES

1. Lunati A, Lesage S, Brice A. The genetic landscape of Parkinson’s disease. Rev Neurol (Paris). 2018 Nov;174(9):628-43. https://doi.org/10.1016/j.neurol.2018.08.004
2. Healy DG, Falchi M, O’Sullivan SS, Bonifati V, Durr A, Bressman S, et al. Phenotype, Genotype, and Worldwide Genetic Penetrance of LRRK2-associated Parkinson’s Disease: A Case-Control Study. Lancet Neurol. 2008 Jul;7(7):583-90. https://doi.org/10.1016/s1474-4422(08)70117-0
3. Brazilian Institute of Geography and Statistics [Internet]. Projections of population in Brazil and Federal Units per sex and age: 2010-2060. Rio de Janeiro: IBGE; [cited 2020 Jul 29]. Accessed July 29, 2020.
4. Moura RR, Coelho AV, Babino VQ, Crovella S, Brandão LAC. Meta-analysis of Brazilian Genetic Admixture and Comparison with Other Latin America Countries. Am J Hum Biol. 2015 Sept-Oct;27(5):674-80. https://doi.org/10.1002/ajhb.22846
5. Klein C, Hattori N, Marras C. Closing data gaps in genotype-phenotype correlations of monogenic Parkinson’s disease. J Parkinsons Dis. 2018;8(Suppl 1):S25-30. https://doi.org/10.3233/jpd-181505
6. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018 Jan;46(D1):D1062-7. https://doi.org/10.1093/nar/gkx1153
7. Teive HA, Raskin S, Iwamoto FM, Germiniani FM, Baran MH, Werneck LC, et al. The G20A Mutation in the Alpha-Synuclein Gene in Brazilian Families With Parkinson’s Disease. Arq Neuropsiquiatr. 2001 Sep;59(3-B):722-4. https://doi.org/10.1590/s0004-282x2001000500013

8. Rawal N, Periquet M, Lohmann E, Lucking CB, Teive HA, Ambrosio G, et al. New Parkin Mutations and Atypical Phenotypes in Families with Autosomal Recessive Parkinsonism. Neurology. 2003 Apr;60(8):1378-81. https://doi.org/10.1212/01.wnl.00000561739221.be

9. Bertoli-Avella AM, Giroud-Benitez JL, Akyol A, Barbosa E, Schaap O, van der Linde HC, et al. Novel Parkin Mutations Detected in Patients With Early-Onset Parkinson’s Disease. Mov Disord. 2005 Apr;20(4):424-31. https://doi.org/10.1002/mds.20343

10. Clarimon J, Johnson J, Dogu O, Horta W, Khan N, Lees AJ, et al. Defining the Ends of Parkin Exon 4 Deletions in Two Different Families With Parkinson’s Disease. Am J Med Genet B Neuropsychiatr Genet. 2005 Feb;139B(1):120-3.

11. Di Fonzo A, Rohé CF, Ferreira J, Chien HF, Vacca L, Stocchi F, et al. A Frequent LRRK2 Gene Mutation Associated with Autosomal Dominant Parkinson’s Disease. Lancet. 2005 Jan;365(9457):412-5. https://doi.org/10.1016/s0140-6736(05)17829-5

12. Bonifati V, Rohé CF, Breedveld GJ, Fabrizio E, Dec, Mari M, Tassorelli C, et al. Early-onset Parkinsonism Associated With PINK1 Mutations: Frequency, Genotypes, and Phenotypes. Neurology. 2005 Jul;65(1):87-95. https://doi.org/10.1212/01.wnl.0000176546.39735.82

13. Khan NT, Horta W, Eunson L, Graham E, Johnson JD, Chang S, et al. Parkin Disease in a Brazilian Kindred: Manifesting Heterozygotes and Clinical Follow-Up Over 10 Years. Mov Disord. 2005 Apr;20(4):479-84. https://doi.org/10.1002/mds.20335

14. Chien HF, Rohé CF, Costa MDL, Breedveld GJ, Gostra BA, Barbosa ER, et al. Early-onset Parkinson’s Disease Caused by a Novel Parkin Mutation in a Genetic Isolate From North-Eastern Brazil. Neurogenetics. 2006 Mar;7(1):13-9. https://doi.org/10.1007/s10048-005-0017-x

15. Di Fonzo A, Tassorelli C, Dec, Mari M, Chien HF, Ferreira J, Rohé CF, et al. Comprehensive Analysis of the LRRK2 Gene in Sixty Families With Parkinson’s Disease. Eur J Hum Genet. 2006 Mar;14(3):322-31. https://doi.org/10.1038/ejhg.2005.599

16. Di Fonzo A, Chien HF, Socci M, Giraudo S, Tassorelli C, Iliceto G, et al. ATP13A2 Missense Mutations in Juvenile Parkinsonism and Young Onset Parkinsonism Disease. Neurology. 2007 May;68(19):1557-62. https://doi.org/10.1212/01.wnl.0000260063.8711.08

17. Lesage S, Magali P, Lohmann E, Lacombe L, Teive H, Janin S, et al. Deletion of the Parkin and PDCRG Gene Promoter in Early-Onset Parkinsonism. Hum Mutat. 2007 Jan;28(1):27-32. https://doi.org/10.1002/humu.20436

18. Aguilar PC, Lessa PS, Godeiro Jr C, Barsottini OQ, Felicio AC, Borges V, et al. Genetic and Environmental Findings in Early-Onset Parkinson’s Disease Brazilian Patients. Mov Disord. 2008 Jul;23(8):1228-33. https://doi.org/10.1002/mds.22092

19. Munhoz RP, Wakuuti Y, Manra C, Teive HA, Raskin S, Werneck LC, et al. The G2019S LRRK2 Mutation in Brazilian Patients With Parkinson’s Disease: Phenotype in Moroczygotic Twins. Mov Disord. 2008 Jan;23(2):290-4. https://doi.org/10.1002/mds.21892

20. Pimentel MMG, Moura KCV, Campos Junior M, Rosso ALZ, Nicaretta DH, et al. Parkinson Disease: α-synuclein Mutational Screening and New Clinical Insight Into the p.E46K Mutation. Parkinsonism Relat Disord. 2015 Jun;21(6):586-9. https://doi.org/10.1016/j.parkreldis.2015.03.011

21. Longo GS, Pinhel AL, Gregório ML, Oliveira BAP, Quinhoneiro DQG, Tognola WA, et al. Alpha-synuclein A53T Mutation Is Not Frequent on a Sample of Brazilian Parkinson’s Disease Patients. Arq Neuropsiquiatr. 2015 Jun;73(6):506-9. https://doi.org/10.1590/1679-450820150032

22. Pimentel MMG, Rodrigues FC, Leite MAA, Campos Junior M, Rosso AL, Nicaretta DH, et al. Frequency of the LRRK2 G2019S Mutation in Late-Onset Sporadic Patients With Parkinson’s Disease. Arq Neuropsiquiatr. 2014 May;72(5):356-9. https://doi.org/10.1590/S0004-282x2014000500019

23. Bersch C, Abreu GM, Valença DC, Campos Junior M, Silva CP, Pereira JS, Leite MAA, et al. Autosomal Dominant Parkinsonian Disease: Incidence of Mutations in LRRK2, SNCA and GBA Genes in Brazil. Neurosci Lett. 2016 Dec;635:67-70. https://doi.org/10.1016/j.neulet.2016.10.040
37. Cornejo-Olivas M, Torres L, Velit-Salazar MR, Inca-Martinez M, Mazzetti P, Cosentino C, et al. Variable Frequency of LRRK2 Variants in the Latin American Research Consortium on the Genetics of Parkinson’s Disease (LARGE-PD), a Case of Ancestry. NPJ Parkinsons Dis. 2017 Jun;3:19. https://doi.org/10.1038/s41531-017-0020-6

38. Silva CP, Abreu GM, Acero PHC, Campos Júnior M, Pereira JS, Ramos SRA, et al. Clinical Profiles Associated With LRRK2 and GBA Mutations in Brazilians With Parkinson’s Disease. J Neurol Sci. 2017 Oct;381:160-4. https://doi.org/10.1016/j.jns.2017.08.3249

39. Guedes LC, Ferreira JJ, Rosa MM, Coelho M, Bonifati V, Sampaio C. Worldwide frequency of G2019S LRRK2 mutation in Parkinson’s disease: a systematic review. Parkinsonism Relat Disord. 2010 May;16(4):237-42. https://doi.org/10.1016/j.parkreldis.2009.11.004

40. Kilarski LL, Pearson JP, Newsaway V, Majounie E, Knipe MDW, Misbahuddin A, et al. Systematic review and UK-based study of PARK2 (parkin), PINK1, PARK7 (DJ-1) and LRRK2 in early-onset Parkinson’s disease. Mov Disord. 2012 Oct;27(12):1522-9. https://doi.org/10.1002/mds.26132