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ARTICLE

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

Genética da doença de Parkinson no Brasil: revisão sistemática de formas monogênicas

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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*.

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RESUMO

Introdução: Um número crescente de mutações causando formas monogênicas de doença de Parkinson (DP) tem sido descrito, principalmente entre pacientes da Europa e da América do Norte. Como a arquitetura genética varia entre diferentes populações, entender os perfis genéticos específicos de pacientes brasileiros é essencial para um melhor aconselhamento genético e para a seleção de participantes para ensaios clínicos. **Objetivo:** Revisão sistemática para identificar estudos genéticos brasileiros na área e definir o cenário para estudos futuros das formas monogênicas de DP no Brasil. **Métodos:** Nós pesquisamos as bases de dados MEDLINE, EMBASE e Web of Science desde a criação até dezembro de 2019, usando termos para "Parkinson's disease", "genetics" e "Brazil". A extração de dados foi feita por dois revisores independentes. Para os genes *LRRK2* e *PRKN*, calculamos a prevalência estimada para cada estudo e realizamos uma meta-análise. **Resultados:** Um total de 32 estudos foram incluídos e 94 pacientes brasileiros com DP com mutações causativas foram identificados em 2872 pacientes avaliados (3.2%). As mutações no PRKN causaram DP em 48 de 576 pacientes (8.3%). As mutações no LRRK2 foram identificadas em 40 de 1566 pacientes (2.5%), sendo a mutação mais comum a p.G2019S (2.2%). **Conclusões:** As mutações na PRKN são a causa mais comum de DP autossômica recessiva, e as mutações no LRRK2 a causa mais comum de DP autossômica dominante. Nós observamos uma falta de estudos epidemiológicos robustos em genética de DP, especialmente por não levar em conta a diversidade de nossa população.

Palavras-chave: Genética; doença de Parkinson; *LRRK2*; *PRKN*.

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 19th 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; 4.3% 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	*PRKN*: Prom+Ex1 del - 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]

Table 1. Cont.

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	No pathogenic mutations found	[29]
Chien et al., 2014	Mutation screening	100	*LRRK2*	PCR-RFLP	No pathogenic mutations found	[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	No pathogenic mutations found	[32]
Pimentel et al., 2015	Mutation screening	549	*SNCA*	Sequencing and qPCR	No pathogenic mutations found	[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, c2038+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.

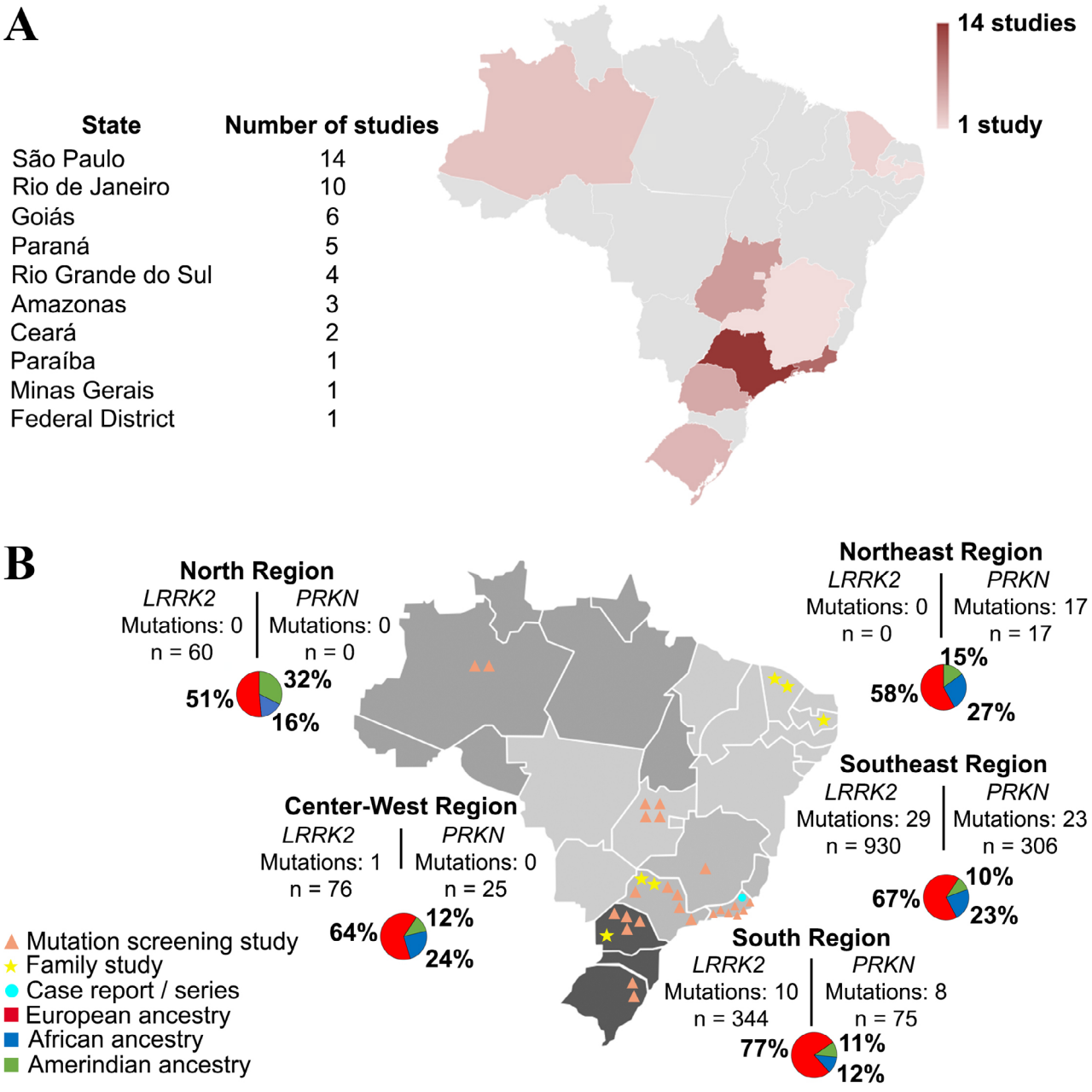

Figure 1. Distribution of monogenic forms of PD described in Brazil. A: Distribution of studies on monogenic forms of PD in Brazil according to states. B: Distribution of *LRRK2* and *PRKN* mutations in Brazil according to regions (depicted in different shades of gray). Studies are represented by symbols, according to the type of study design. Ancestry proportions of each region are represented in pie charts, based on Moura et al., 2015[4].

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	

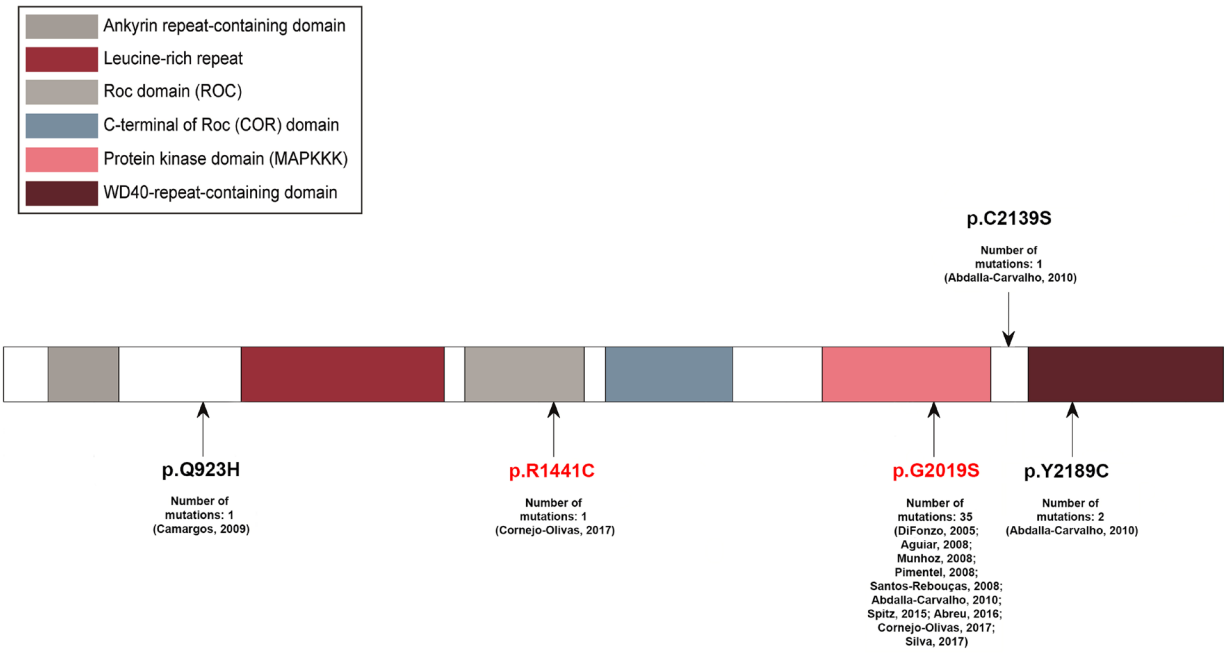

Figure 2. Schematic representation of *LRRK2* protein domains, and locations of mutations described in Brazilian patients with PD, adapted from the website of the Movement Disorder Society Genetic Mutation Database[5]. Arrows indicate the locations of point mutations. Definitely pathogenic mutations are indicated in red letters and variants of uncertain significance in black letters.

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 (I^2 = 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[1].

The *LRRK2* p.G2019S point mutation is the most common associated variant that causes monogenic PD[2], 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, in

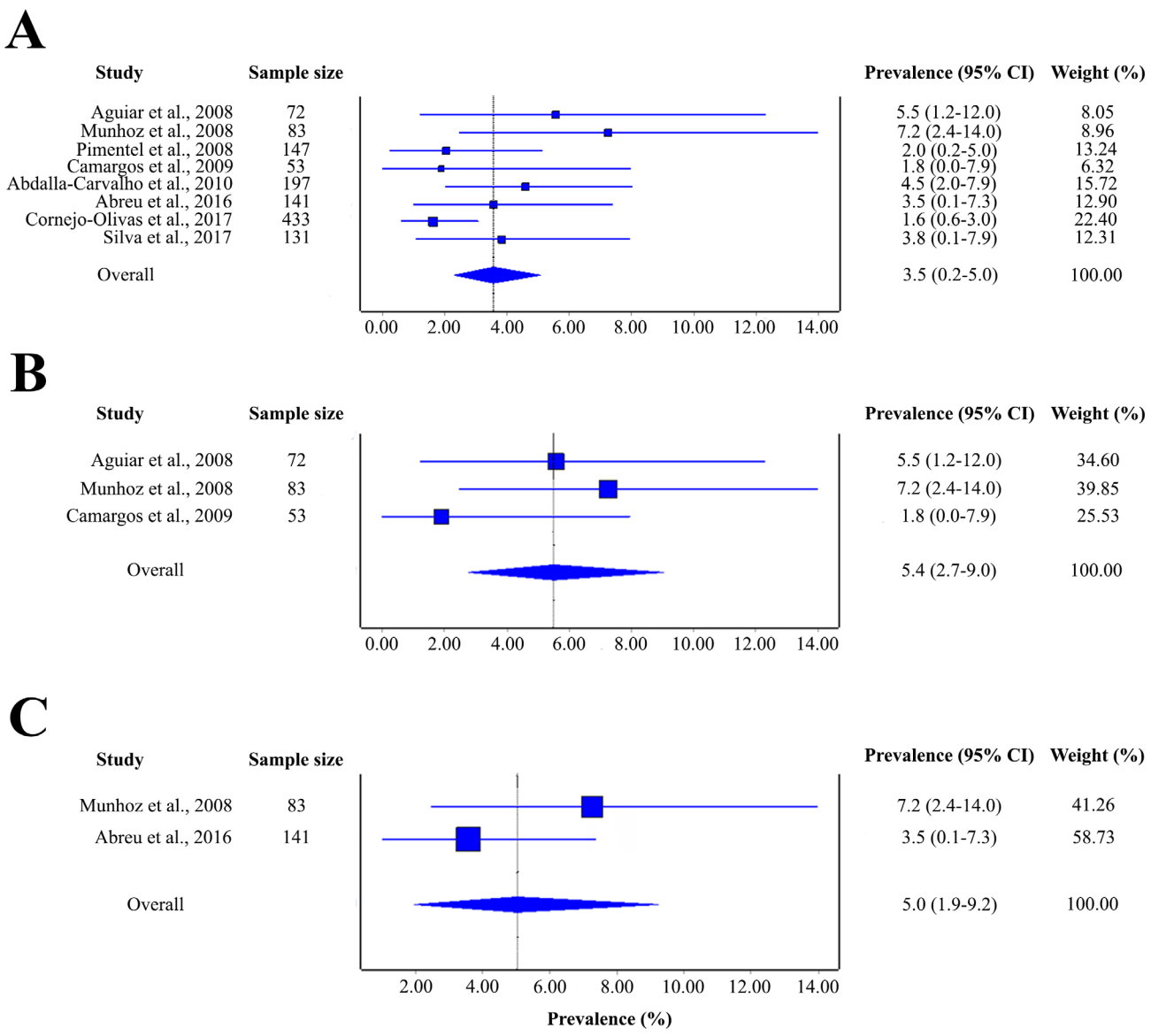

Figure 3. Forest plot of prevalence of *LRRK2* mutation-positive Brazilian patients with PD and 95% confidence intervals for each study included in the meta-analysis. A: Analysis with all studies. B: Analysis with studies that strictly included early-onset PD cases. C: Analysis with studies that strictly 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[2,39].

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%)[40].

SNCA mutations have been found in many countries, comprising 0.2% of sporadic and 1-2% of familial PD cases[1], 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[1], and only three studies explored these genes.

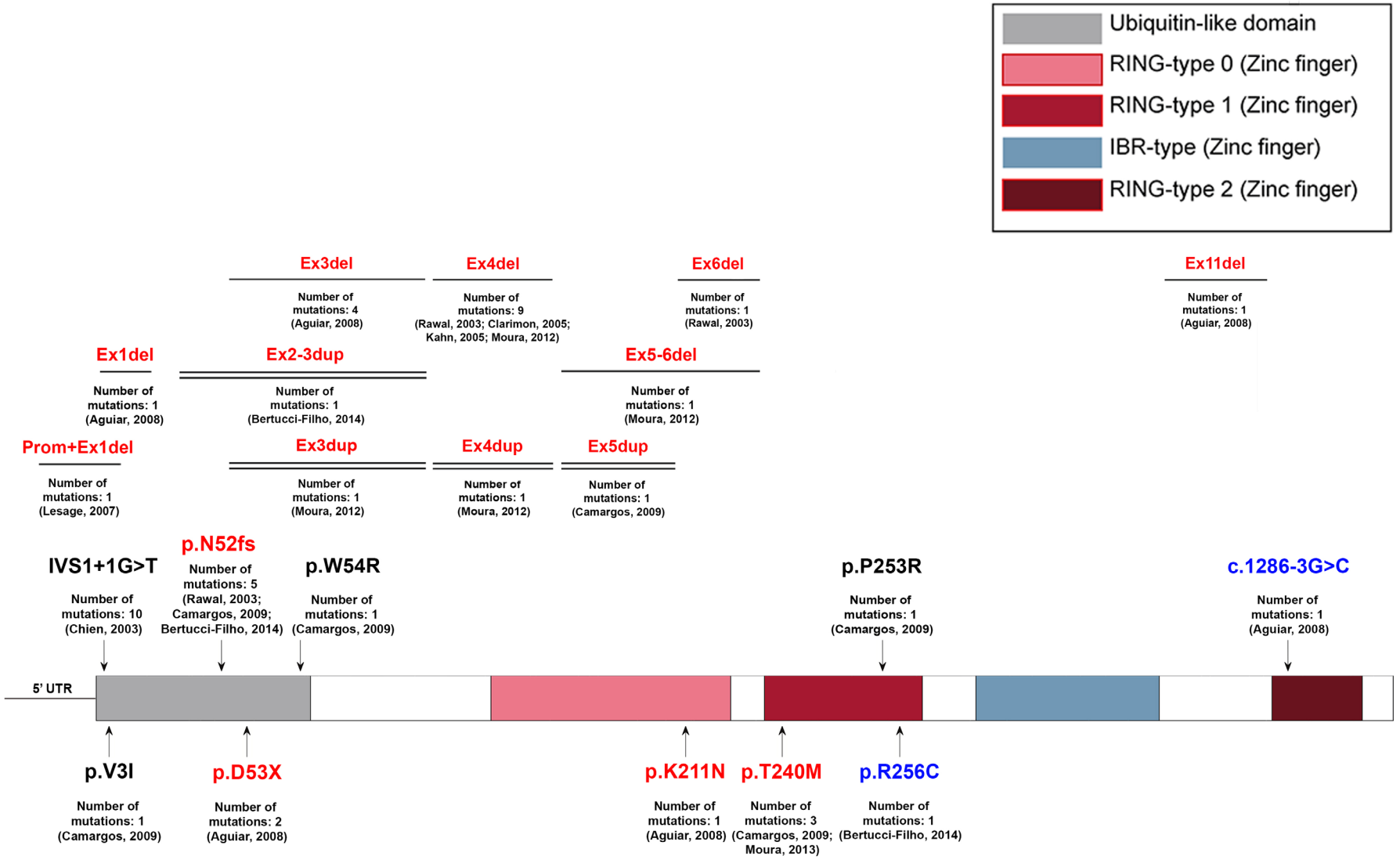

Figure 4. Schematic representation of Parkin protein domains, and locations of mutations described in Brazilian patients with PD, adapted from the website of the Movement Disorder Society Genetic Mutation Database[5]. Arrows indicate the locations of point mutations, and horizontal lines indicate the 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.

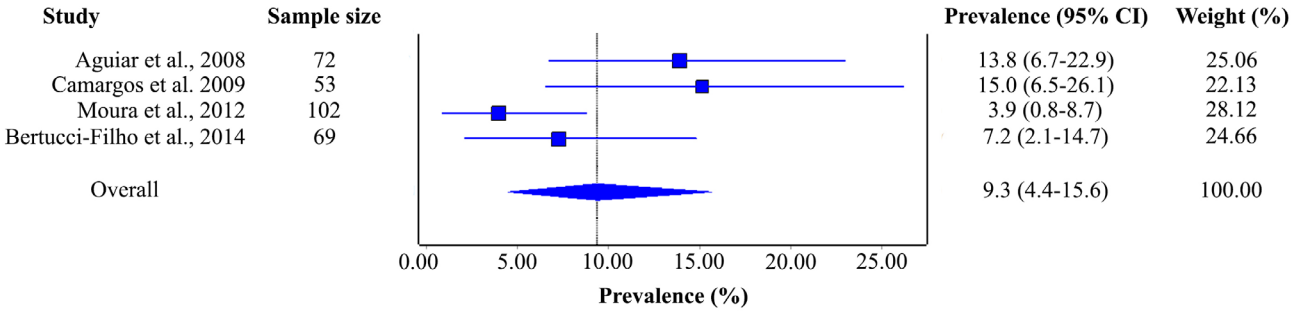

Figure 5. Forest plot of prevalence of *PRKN* mutation-positive early-onset Brazilian patients with PD and 95% confidence intervals for each study included in the meta-analysis. Right-hand column shows per-study prevalence of mutation-positive cases for *PRKN* (%), 95% confidence intervals and the weighting (%) 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.

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)[4]. 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.

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