UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

PARKINSON'S DISEASE GENETICS IN ADMIXED POPULATIONS: A LATIN AMERICAN STUDY
GENÉTICA DA DOENÇA DE PARKINSON EM POPULAÇÕES ADMIXADAS: UM ESTUDO LATINO-AMERICANO

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.

ABSTRACT

INTRODUCTION: Parkinson's disease (PD) is a neurodegenerative disorder influenced by both genetic and environmental factors, with approximately 15% of cases attributed to monogenic forms, and *GBA1* as the major risk factor. While monogenic cases are relatively rare, the majority of PD cases are influenced by polygenic factors, where genome-wide association studies (GWAS) have identified common variants contributing to PD risk through polygenic risk scores (PRS). Understanding the genetic landscape of PD is crucial for risk prediction, personalized treatment, and improving clinical outcomes. However, most genetic studies have focused on European populations, leaving Latin American groups underrepresented.

OBJECTIVE: To describe the genetic landscape of PD in Latin America.

METHODS: We conducted a systematic review to assess the current knowledge of monogenic PD in the region, followed by a cross-sectional study to evaluate the frequency and distribution of PD-related genes in a cohort of PD patients from southern Brazil and Santiago, Chile, using a next-generation sequencing panel. Finally, we conducted PRS calculations across seven ancestries, including Latin Americans, and compared their performance.

RESULTS: **Article 1**: *"Frequency of Hereditary and GBA1-Related Parkinsonism in Latin America: A Systematic Review and Meta-Analysis"*. This systematic review assessed the frequency and distribution of genetic parkinsonism in Latin America. Among 7,668 Latin American patients, pathogenic variants were identified in 19 genes. The frequencies of pathogenic variants were: *LRRK2* (1.38%, 95% CI: 0.52-2.57), *PRKN* (1.16%, 95% CI: 0.08-3.05), and *GBA1* (4.17%, 95% CI: 2.57-6.08).**Article 2**: *"Genetics of Parkinson's Disease in South America: a cross-sectional pilot study of Southern Brazil and Central Chile"*. We recruited 285 PD patients, including 162 from Brazil and 123 from Chile. After quality control, 230 samples were analyzed. Potential disease-causing variants were identified in 26 patients (11.3%), with *GBA1* accounting for 79% of cases in Brazil and *LRRK2* variants comprising 83% in Chile. Other pathogenic variants included *DJ1* p.T154A and *SQSTM1* p.P308L. Additionally, 53 variants of uncertain significance, including eight novel variants, were identified. No pathogenic bi-allelic variants were identified in *PRKN*, or *PINK1*. **Article 3**: *"Insights into Ancestral Diversity in Parkinson's Disease Risk: A Comparative Assessment of Polygenic Risk Scores"*. We constructed 105 PRS across individual-level data from seven diverse ancestries. A cross-ancestry conventional PRS comparison utilized the 90 known European PD risk loci, with weighted effects from European, East Asian, Latino/Admixed American, and African/Admixed summary statistics. A refined best-fit PRS approach was also applied using multi-ancestry meta-analyzed summary statistics

and p-value thresholding to enhance prediction in a global setting. Despite an AUC of 0.62, the Latin American population showed limited discriminative ability, with sensitivity (0.99), specificity (0.01), and a balanced accuracy of 0.51 using the conventional model, which outperformed the best-fit PRS.

CONCLUSION: Our findings highlight the significant genetic diversity of PD patients in Latin America. Despite ongoing research and collaboration, further efforts are needed to address underrepresentation and improve understanding of genetic risk in this population.

Key Words: Parkinson's disease, genetics, genotype-phenotype correlations, latino population, monogenic forms, gene panel.

RESUMO

INTRODUÇÃO: A Doença de Parkinson (DP) é um transtorno neurodegenerativo influenciado por fatores genéticos e ambientais, com cerca de 15% dos casos atribuídos a formas monogênicas, sendo o gene *GBA1* o principal fator de risco. Embora os casos monogênicos sejam relativamente raros, a maioria dos casos de DP é influenciada por fatores poligênicos, onde estudos de associação genômica ampla (GWAS, do inglês, *genome-wide association study*) identificaram variantes comuns que contribuem para o risco de DP através de escores de risco poligênico (PRS). Compreender o panorama genético da DP é crucial para a predição de risco, tratamento personalizado e melhora dos desfechos clínicos. No entanto, a maioria dos estudos genéticos tem se concentrado em populações europeias, deixando os grupos latino-americanos sub-representados.

OBJETIVO: Descrever o panorama genético da DP na América Latina.

MÉTODOS: Realizamos uma revisão sistemática para avaliar o conhecimento atual sobre DP monogênica na região, seguida de um estudo transversal para avaliar a frequência e distribuição de genes relacionados à DP em uma coorte de pacientes do sul do Brasil e Santiago, Chile, usando um painel de sequenciamento de nova geração. Finalmente, realizamos cálculos de PRS em sete ascendências, incluindo latino-americanos, e comparamos seu desempenho.

RESULTADOS: *Artigo 1:* "Frequência de Parkinsonismo Hereditário e Relacionado ao *GBA1* na América Latina: Uma Revisão Sistemática e Meta-Análise". Esta revisão sistemática avaliou a frequência e distribuição do parkinsonismo genético na América Latina. Entre 7.668 pacientes latino-americanos, foram identificadas variantes patogênicas em 19 genes. As frequências de variantes patogênicas foram: *LRRK2* (1,38%, IC 95%: 0,52-2,57), *PRKN* (1,16%, IC 95%: 0,08-3,05) e *GBA1* (4,17%, IC 95%: 2,57-6,08). *Artigo 2:* "Genética da Doença de Parkinson na América do Sul: um estudo piloto transversal no sul do Brasil e no centro do Chile". Recrutamos 285 pacientes com Doença de Parkinson, sendo 162 do Brasil e 123 do Chile. Após o controle de qualidade, 230 amostras foram analisadas. Variantes potencialmente causadoras da doença foram identificadas em 26 pacientes (11,3%), com *GBA1* representando 79% dos casos no Brasil e variantes de *LRRK2* correspondendo a 83% no Chile. Outras variantes patogênicas incluíram *DJ1* p.T154A e *SQSTM1* p.P308L. Além disso, foram identificadas 53 variantes de significado incerto, incluindo oito variantes novas. Não foram identificadas variantes bialélicas patogênicas em *PRKN* ou *PINK1*. *Artigo 3:* "Perspectivas sobre a Diversidade Ancestral no Risco de Doença de Parkinson: Uma Avaliação Comparativa de Escores de Risco Poligênico". Construímos 105 PRS com dados de nível individual de sete ancestralidades diferentes. Uma comparação de PRS entre ascendências usou os 90 *loci* de risco de DP europeus conhecidos, com efeitos ponderados de estatísticas sumárias de europeus, asiáticos orientais, latinos/mestiços

miscigenados e africanos/miscigenados. Um modelo refinado de PRS com o melhor ajuste foi aplicado usando meta-análises multiancestrais e limiares de p-valor para melhorar a predição em um contexto global. Apesar de uma área sobre a curva de 0,62, a população latino-americana mostrou capacidade discriminativa limitada, com sensibilidade (0,99), especificidade (0,01) e uma precisão balanceada de 0,51 no modelo convencional, que superou o PRS de melhor ajuste.

CONCLUSÃO: Nossos resultados destacam a significativa diversidade genética de pacientes com DP na América Latina. Apesar das pesquisas em andamento e das redes de colaboração, são necessários mais esforços para enfrentar a sub-representação em estudos genéticos e melhorar a compreensão do risco genético nessa população.

Palavras-chave: Doença de Parkinson, genética, correlações genótipo-fenótipo, população latina, formas monogênicas, painel de genes.

LIST OF ABBREVIATIONS AND ACRONYMS

AAC: African Admixed

AAO: Age of onset

ACMG: American College of Medical Genetics

AFR: African

AJ: Ashkenazi Jewish

AMR: Latino/Admixed American

ASAP: Aligning Acience Across Parkinson's

AUC: Area Under the Curve

CADD: Combined Annotation Dependent Depletion

CARD: Center for Alzheimer's Disease and Related Dementias

CAS: Central Asian

CETRAM: Centro de Estudios de Trastornos del Movimiento

CHCHD2: Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 2 gene

CI: Confidence Interval

CNV: Copy Number Variation

ClinVar: Public archive of interpretations of clinically relevant variants

DD: Disease Duration

dbSNP: Database for Single Nucleotide Polymorphisms

DJ1: Oncogene DJ1 gene

DNA: Deoxyribonucleic Acid

DZNE: German Center for Neurodegenerative Diseases

EAS: East Asian

EOPD: Early Onset Parkinson's Disease

EUR: European

ExAC: Exome Aggregation Consortium

FREEMIX: Sequence-only estimate of contamination (0-1 scale)

GBA1: Glucosylceramidase Beta 1

gnomAD: Genome Aggregation Database

GP2: Global Parkinson’s Genetics Program

GWAS: Genome Wide Association Study

HCPA: Hospital de Clinicas de Porto Alegre

HPC: High Power Computer

HWE: Hardy-Weinberg equilibrium

IRB: Institutional Review Board

LARGE-PD: Latin American Research Consortium on the Genetics of Parkinson´s Disease

LD: Linkage disequilibrium

LILACS: Latin American and Caribbean Health Sciences Literature

LRRK2: Leucine Rich Repeat Kinase 2 gene

MAF: Minor Allele Frequency

MAPT: Microtubule-associated protein tau

MDS: Movement Disorders Society

ML: Machine Learning

MLPA: Multiplex Ligation-dependent Probe Amplification

MMSE: Mini-Mental State Examination

MOCA: Montreal Cognitive Assessment

MR: Mendelian Randomization

MT: Mutation Taster

NBIA: Neurodegeneration with Brain Iron Acummulation

NGS: Next Generation Sequencing

NIA: National Institutes of Aging

NIH: National Institutes of Health

NPJ: Nature Parkinson's Journal

OR: Odds Ratio

PARKIN: parkin RBR E3 ubiquitin protein ligase

PCA: Principal Components Analysis

PCR: Polymerase chain reaction

PD: Parkinson's Disease

PINK1: Pten-Induced Putative Kinase 1 gene

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRS: Polygenic Risk Score

PolyPhen: Polymorphism Phenotyping

QC: Quality Control

QSBB: Meaning not found

RBD: REM sleep behavior disorder

REDCAP: Research Electronic Data Capture

ROC: Receiver Operator Curve

ROPAD: Rostock International Parkinson's Disease

RefSeq: Reference sequence

SD: Standar Deviation

SE: Standar Error

SIFT: Sorting Intolerant From Tolerant

SNCA: Alpha-Synuclein gene

SNP: Single Nucleotid polymorphism

SNV: Single Nucleotid Variant

SPECT: Single-photon emission computed tomography

TBI: Traumatic Brain Injury

TCLE: Termo de Consentimento Livre e Esclarecido

UK: United Kingdom

URP: Underrepresented populations

USA: United States of America

USUHS: Uniformed Services University of the Health Sciences

VCP: Valosin Containing Protein

VPS35: Vacuolar Protein Sorting 35 gene

VUS: Variant of Unknown Significance

WES: Whole Exome Sequencing

1.INTRODUCTION

Parkinson's disease (PD) is a complex neurodegenerative disorder, with an estimated global prevalence of 9.4 million people in 2020 [1]. Understanding the global prevalence of PD is crucial for public health planning and resource allocation, as prevalence varies significantly across different regions and demographic groups. Globally, PD prevalence shows notable geographic variability. Higher prevalence rates are observed in North America, Europe, and Australia compared to Asia and Africa. Among individuals aged 70-79, the prevalence is estimated to be 1,601 per 100,000 in North America, Europe, and Australia, while it is 646 per 100,000 in Asia[2–4]. Specific regions such as Norway and the USA have shown pronounced increases in PD prevalence over the past decades [5,6]. These findings underscore the importance of examining regional variations in PD prevalence, particularly in regions like Latin America, where unique demographic and genetic factors may contribute to the observed disease burden. A recent study [7] reported that the prevalence in Latin America and the Caribbean is 1,251 per 100,000 individuals, rising to 2,181 per 100,000 for individuals over 80, which is higher than in all other studied regions, including East Asia and Pacific, Europe and Central Asia, and Middle East and North Africa.

A. Pathophysiology

The histopathological hallmark of PD is the loss of dopaminergic neurons from the substantia nigra, accompanied by the presence of intraneuronal inclusions called Lewy bodies. These inclusions largely consist of aggregated forms of the protein alpha-synuclein, which misfolds to form beta-sheet rich amyloid fibrils [8–11]. According to Braak staging [12], Lewy pathology follows a predictable progression, starting in the olfactory bulb and medulla oblongata (early stages 1-2), advancing to the substantia nigra in the midbrain (stages 3-4), and eventually affecting the cortical regions (late stages 5-6) as the disease progresses. This pattern correlates with the onset of motor symptoms and, in later stages, cognitive decline. Motor symptoms typically appear when 70%-80% of striatal dopamine is depleted [13].

B. Risk Factors

PD arises from a complex interplay between genetic and environmental factors. Age is the primary risk factor, with the majority of cases emerging in the sixth decade of life, although environmental exposures also contribute to disease onset. Significant environmental risk factors include pesticide exposure, particularly paraquat and rotenone(OR ~1.4–1.6), as well as organic solvents like trichloroethylene (OR ~1.4), traumatic brain injury (TBI) (OR ~1.6), lead exposure (OR ~1.5), chronic air pollution (OR ~1.1–1.2), hepatitis C infection (OR ~1.2–1.5), and dairy consumption, particularly milk (OR ~1.3–1.6), have also been associated with increased risk of PD [14]. Familial forms of PD account for 5–15% of cases [15,16], particularly in early-onset PD (EOPD), commonly defined as an onset after 21 years but before 50 years [17].

C. Clinical Diagnosis

The diagnosis of PD is primarily based on clinical evaluation, involving a detailed patient history and neurological examination. Essential diagnostic features include bradykinesia, accompanied by either resting tremor or muscle rigidity [18–20] The Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD outline a systematic method for diagnosing PD. These criteria require confirmation of parkinsonism (defined as bradykinesia plus either resting tremor or rigidity), along with supportive features and the absence of exclusion criteria or concerning red flags [18].

Non-motor symptoms, such as REM sleep behavior disorder, hyposmia, and constipation, often emerge years before motor symptoms, representing an early or prodromal stage of PD [20,21]. When the diagnosis is uncertain, ancillary tests like dopamine transporter single-photon emission computed tomography (DaT-SPECT) may be helpful in distinguishing PD from other Parkinsonian syndromes, although they are not part of the routine diagnostic process [20]. A positive response to levodopa, characterized by a significant reduction in motor symptoms, further supports the diagnosis of PD [22], but is also seen in some other neurodegenerative diseases [23].

D. Differential Diagnosis of Parkinsonian Disorders

Given the overlapping clinical features among various parkinsonian syndromes, accurate diagnosis is essential to ensure appropriate management and avoid misclassification, which can lead to ineffective treatment strategies. Essential Tremor is characterized by postural and action tremor rather than at rest, although it can occasionally include resting tremor and rigidity, adding complexity to the clinical picture[24]. Multiple System Atrophy is an atypical form of parkinsonism that presents with autonomic dysfunction, cerebellar ataxia, and poor response to levodopa, with imaging techniques like F-FDG PET helping differentiate it from PD by revealing distinct regional glucose metabolism patterns[25]. Progressive Supranuclear Palsy, another tauopathy, is identified by early postural instability, vertical gaze palsy, and axial rigidity, and can be distinguished from PD through clinical and imaging signs[25,26]. Similarly, Corticobasal Degeneration, also a tauopathy, presents with asymmetric rigidity, dystonia, and cortical sensory deficits, making its differentiation from PD based on clinical and imaging characteristics essential[25,26]. Dementia with Lewy Bodies differs from PD primarily in the timing of cognitive decline relative to motor symptoms, with early cognitive impairment and hallucinations[25]. Vascular Parkinsonism, often associated with cerebrovascular disease, typically presents with lower body parkinsonism and can be identified through neuroimaging, which reveals vascular lesions[27]. Drug-induced parkinsonism, commonly caused by medications such as antipsychotics, resolves upon discontinuation of the offending drug, differentiating it from neurodegenerative causes[28]. Functional parkinsonism, characterized by inconsistent, variable symptoms that deviate from typical parkinsonian patterns, often requires clinical diagnosis supported by the absence of neurodegenerative markers[29]. To improve diagnostic accuracy, the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine recommend dopaminergic imaging[30] to distinguish these conditions from idiopathic PD, especially in complex cases.

E. Genetic Contributions to Parkinson's Disease

E.1. Monogenic forms of PD

Monogenic forms of PD—where a single gene variant is the primary determinant of disease risk, along with *GBA1* as the main risk factor —account for about 15% of all PD cases [31,32]. The frequency of monogenic forms is notably higher in early-onset cases, representing over 10% of patients diagnosed before 45 and more than 40% in those with onset before 30 [33]. In contrast, complex genetic forms involve multiple variants with smaller individual effects that interact with environmental factors to influence disease risk [34].

In recent years, next-generation sequencing and high-throughput genotyping have facilitated the identification of numerous genetic variants associated with movement disorders. The International Parkinson and Movement Disorder Society (MDS) has developed an updated genetic nomenclature that includes only confirmed disease-causing genes with substantial evidence of a genotype-phenotype relationship. For hereditary parkinsonism, they established a clinical correlation and classified the genes into five scenarios: classical parkinsonism, early-onset parkinsonism, atypical parkinsonism, combined phenotypes, and other diseases presenting with parkinsonism. Genes with the prefix "PARK" fall under the categories of classical, early-onset, or atypical parkinsonism[35,36]. To avoid confusion, we will refer to these "PARK" genes by their specific gene names, without using prefixes or previous locus classifications. Figure 1 provides a simplified summary of these genes, according to phenotype and mode of inheritance, and frequency and distribution in recent articles in Table 1.

E.1.a) <u>Classical parkinsonism - autosomal dominant inheritance</u>

Pathogenic variants in the leucine-rich repeat kinase gene, *LRRK2*, are the commonest cause of autosomal dominant PD, accounting for up to ~40% of all PD cases in selected populations, e.g., North African Berber and Ashkenazi Jewish[37]. There are at least 7 reported pathogenic variants (p.N1437H, p.R1441C/G/H, p.Y1699C, p.G2019S, and p.I2020T) with significant heterogeneity between ethnic and regional groups[38] . *LRRK2* has incomplete penetrance, which varies according to age, estimated at 28% at 59 years and 51% at 60 years, reaching up to 75% at 80

years of age[34]. The mean age of onset for carriers is 57 years, ranging between 47 to 65 years[37]. Clinical features bear the closest resemblance to PD, although there can be intrafamilial heterogeneity. DAT/PET scans are usually abnormal. Other distinguishing clinical features include leg predominant tremor at onset, little cognitive decline, slower progression, milder phenotype, fewer non-motor symptoms and prominent psychiatric symptoms unrelated to treatment. Different clinical features are associated with variable neuropathologic findings. The classic primarily motor phenotype is associated with absence of Lewy bodies pathology, while the broader syndrome with motor and non-motor symptoms is related to the presence of Lewy bodies[39]. *LRRK2* variants have been identified in PD patients around the world: North and South America, North Africa, the Middle East, Europe, Asia and Australia. One LRRK2 mutation, the p.G2019S substitution, is the most common variant and would account for 3-6% of familial and ~1% of sporadic PD patients across European-descended individuals in the United States [40]. It is most common in two populations, the Ashkenazi Jews, where its prevalence can be as high as 30% in familial cases and 13% in sporadic ones, and in North African Arabs, with a prevalence up to 40%. Research by Zabetian and co-workers in 2006 established that these two cohorts share a common ancestor (a 'founder effect') that resided in the Middle East in the 13th century[41].

Genetic variants in the alpha-synuclein gene, *SNCA*, are a rare cause of autosomal dominant PD. This finding was a landmark discovery in 1998 being the first to confirm that PD could be inherited as a single gene disorder[42]. Subsequent work identified that the Alpha-synuclein protein was a major component of the Lewy body [43]. The clinical picture, DAT SPECT scans, and histopathology are broadly similar to PD although there are other distinguishing clinical features including an earlier age of onset (mean 45 years), a non-tremulous presentation, early cognitive decline, autonomic dysfunction, and a rapidly progressive disease course. A total of 5 single nucleotide variants (SNV) have been reported as pathogenic; A53T [42], A30P [44], E46K [45], H50Q [46,47] and G51D [48,49]. Multiplications (duplications and triplications) of the Alpha-synuclein gene can cause autosomal dominant PD, but both are rare, with a frequency that ranges from 0.045% to 1.1% in recent studies [50,51,52]. Many affected patients share an ancestral founder that can be traced to the Peloponnese (Greece)-Salerno (Italy) trade route.

Genetic variants in the vacuolar protein sorting-associated protein 35 (*VPS35*) gene were first identified in an Austrian family as a cause of familial PD by whole-exome sequencing [53]. To date, only one pathogenic mutation has been identified (D620N), and it's a rare mutation, with an overall prevalence of 0.115%, but as high as 1% in autosomal dominant PD [54]. The clinical phenotype associated with *VPS35* variants closely resembles idiopathic PD. Reduced penetrance has been observed. Dementia, although reported, is not a prominent feature of the presentation. Age of onset varies, with some patients presenting with early onset PD.

The *CHCHD2* gene is one of the six newly reported parkinsonism-causing genes by the MDS updated task force [35], and the only one that presents as classical parkinsonism. In 2015 two missense variants (p.T61I, p.R145Q) and a splice-site mutation (c.300+5G>A) in the *CHCHD2* gene were reported in a Japanese family by next-generation sequencing [55]. It is considered a rare mutation, found predominantly in Japanese and Chinese patients, and not replicated among Europeans [56]. The clinical phenotype associated with *CHCHD2* closely resembles idiopathic PD, with a significant response to levodopa.

E.1.b)<u>Classical parkinsonism - autosomal dominant inheritance</u>

The first autosomal recessive locus and the numerically most frequent in juvenile (< 20 years) and early onset parkinsonism (age of onset < 40 years) was identified by the Japanese, in 1998 [57]. Homozygous and compound-heterozygous variants, including genetic rearrangements, in PRKN represent a rather rare cause of parkinsonism over the age of 40 years. The clinical features can mimic that seen in classical PD. *PRKN* also has distinguishing features, including a benign and slow clinical course, normal cognition, and relatively fewer psychiatric symptoms compared to other genetic forms, such as *DJ1* and *PINK1*. Patients with *PRKN* variants generally respond well to dopaminergic treatment, though the phenotype can be heterogeneous. It frequently presents with dystonia, often involving the leg or foot. Cerebellar signs, pyramidal weakness, and/or autonomic involvement may also be present. Unlike classical PD, most cases have normal olfaction. DAT scans are abnormal, and there is usually an absence of Lewy body pathology, although Lewy bodies have been identified in some cases. There are nearly 150 different genetic sequence variants reported in the *PRKN* gene, with most patients carrying

structural variants[58]. Interestingly, heterozygous variants in *PRKN* have been widely explored and are still studied extensively as potential risk variants for sporadic PD, though to date, more evidence disconfirms than substantiates this [59,60].

Another form of autosomal recessive parkinsonism is related to homozygous or compound heterozygous variants in the *PINK1* gene. variants in the phosphatase and tensin homolog-induced putative kinase (PINK1) are the second most common cause of autosomal recessive EOPD, accounting for ~1% to 8% of familial PD with autosomal recessive inheritance and ~1% of early-onset sporadic cases. Genetic variants in *PINK1* were initially described in three consanguineous families from Italy and Spain [61]

PINK1 is clinically similar to *PRKN* and therefore also shows overlap with the clinical picture of classical PD. The disease course is usually slowly progressive, and symptoms are commonly responsive to dopaminergic treatment; though, often resulting in motor fluctuations and levodopa-induced dyskinesias. Psychiatric features like depression and anxiety may be overrepresented in patients with *PINK1*-related PD, whereas cognitive involvement is rare [58]. *PINK1* and *PRKN* function in a common pathway for sensing and selectively eliminating damaged mitochondria from the mitochondrial network.

Similar to *PRKN*, also heterozygous variants in *PINK1* have been widely explored and are still studied extensively as potential risk variants for sporadic PD, although again, to date, there is more disconfirming than substantiating evidence. Genetic variants in the *DJ1* gene are very rare and found only in ~1% of early-onset patients with Parkinsonism. The genetic locus was discovered in a consanguineous family in 2001 [62]. The clinical phenotype is comparable to *PRKN* and *PINK1*-related PD with a rather classical presentation, slow progression, and levodopa-responsiveness. However, dystonic and psychiatric features seem to be overrepresented.

E.1.c) Atypical parkinsonism or complex phenotypes -Autosomal dominant inheritance forms

The dynactin-1 (*DCTN1*) gene, is a rare cause of autosomal dominant atypical parkinsonism. It is also called Perry syndrome. Ten different heterozygous missense variants have been described worldwide [63,64]. The clinical picture is rapidly progressive parkinsonism that can be levodopa-responsive, accompanied by non-motor features like depression, weight loss, and progressive respiratory changes [65,66]. Pathological findings differ from PD. Lewy bodies are not frequent, and TDP43-positive inclusions and selective loss of putative respiratory neurons can be found in the ventrolateral medulla and in the raphe nucleus [54].

The *SLC20A2* gene contributes to the primary familial brain calcification genetic conditions that have been recently reclassified by the MDS updated task force in parkinsonism, according to its predominant movement disorder phenotype [35]. The clinical picture is of an atypical parkinsonism with cognitive impairment and headaches. Other less common features are dystonia, chorea, and ataxia. Calcifications are most frequently found in basal ganglia, followed by thalamus, cerebellum, and white matter [67,68].

E.1.d) Atypical parkinsonism or complex phenotypes -Autosomal recessive inheritance forms

Genetic variants in the *DNAJC6* gene can cause atypical parkinsonism associated with dystonia and occasionally, mental retardation and seizures [69], while genetic variants in the *FBXO7* gene are linked to early onset (atypical) Parkinsonism with pyramidal signs [70]. The *JAM2* gene is part of a group of genes that have been linked to primary familial brain calcifications. These calcifications are most common in the basal ganglia, cerebellum, and white matter, and they may or may not cause a certain phenotype. If clinically symptomatic, patients can present with atypical parkinsonism with cognitive deficits [67,71,72]. *SYNJ1* phenotype includes a wider spectrum of neurological manifestations, such as seizures, cognitive decline, abnormal eye movements, and dystonia [73,74].

Genetic variants in the *VPS13C* gene have recently been identified to cause early-onset atypical parkinsonism [35]. The disease course is characterized by often rapid and severe progression and loss of response to levodopa during the disease course. Additionally, early cognitive impairment potentially leading to dementia seems to be common.[64,75–77].

Patients with genetic variants in this *ATP13A2* can present with a broad and variable clinical spectrum including several movement disorders. It has therefore been recently assigned a "MxMD"-prefix (mixed movement disorder). One typical clinical presentation is the Kufor-Rakeb syndrome, a rare form of usually juvenile-onset atypical dystonia-parkinsonism, although often with a good response to levodopa. The complex phenotype can also include supranuclear gaze palsy, myoclonus, pyramidal signs, dementia, dysphagia, dysarthria, and olfactory dysfunction. The disease is commonly rapidly progressing [78–81]. Neuroimaging can be helpful, and there is often markedly reduced dopamine transporter on DAT SPECT scans, and on MRI, there is a loss of grey matter volume and evidence of iron accumulation in the basal ganglia. Other forms of clinical presentations can be adult-onset complex hereditary spastic paraplegia with often cognitive impairment, psychiatric symptoms, axonal neuropathy, and MRI features like thin corpus callosum and ear of the lynx sign and adult-onset progressive ataxia and action myoclonus.

The phenotype of *POLG* variants is similar to *ATP13A2*, patients with genetic variants in this gene can present with a broad and variable clinical spectrum including several movement disorders; it has therefore been recently assigned a "MxMD"-prefix (mixed movement disorder). This gene is associated with multiple syndromes that often present with progressive external ophthalmoparesis and variable other neurological manifestations. There are a few cases reports describing rare presentations of parkinsonism attributed to genetic variants in this gene [82–84]. 18F-dopa PET scans in some subjects have confirmed nigrostriatal dysfunction, but there is an absence of Lewy body pathology in post-mortem examinations.

E.1.e) Atypical parkinsonism or complex phenotypes -X-linked recessive inheritance forms

The *RAB39* and *WDR45* are genes with X-linked inheritance. Genetic variants in the recently identified *RAB39B* gene have been linked to early-onset (atypical) parkinsonism with delayed psychomotor development and impaired intellectual development (also referred to as Waisman syndrome) [85–87]. Genetic variants in the *WDR45* gene are linked to neurodegeneration with brain iron accumulation (NBIA), particularly the so-called Beta-propeller protein-associated neurodegeneration (BPAN). Clinically, patients present with atypical parkinsonism, associated with a broad range of possible additional clinical features, such as developmental delay and/or intellectual disability, progressive cognitive decline, seizures, spasticity, neuropsychiatric symptoms, sleep disorders, and bowel/bladder incontinence [88].

E.2. Complex Genetic factors in PD

In sporadic PD, genetic factors, while individually modest, interact with environmental influences to shape disease susceptibility. Genome-wide association studies (GWAS) have identified common variants that collectively contribute significantly to heritability, underscoring the complexity of PD and revealing critical loci and biological pathways[16,89,90].

GWAS findings also highlight the role of genes linked to familial PD in sporadic cases. For instance, SNCA, a key gene in PD pathology, harbors common variants influencing risk and age at onset. Similarly, LRRK2 includes rare and common variants, such as the G2019S mutation, which is highly prevalent in Ashkenazi Jewish and North African populations[91,92,93]. Variants in GBA1 are associated with monogenic and idiopathic PD, contributing to increased risk, earlier onset, and more aggressive progression[94,95].Other loci, including *MAPT* (linked to tau pathology) and *TMEM175* (involved in lysosomal function), emphasize the centrality of lysosomal dysfunction in PD pathogenesis[96,97]

Meta-analyses of GWAS have identified independent risk signals across genomic regions. For example, Nalls et al. (2019) reported 90 risk signals across 78 genomic regions, including 38 novel signals, accounting for 16–36% of PD's heritable risk[90]. Integrative studies combining

methylation and gene expression data have pinpointed functional targets within these loci. Additionally, fine-mapping has uncovered rare variants, such as those in *SYT11* and *FGF20*, that operate independently of nearby genes like *GBA1*, illustrating the complexity of PD's genetic architecture[99].

Multi-ancestry GWAS have revealed population-specific loci. For instance, studies in Asian populations identified *SV2C* and WBSCR17, which are absent in European cohorts[100]. In Latino populations, *SNCA* rs356182 has shown genome-wide significance in PD risk prediction, while African and African-admixed populations have revealed novel *GBA1* variants linked to reduced glucocerebrosidase activity[101,102,103]. A multi-ancestry meta-analysis further identified 78 genome-wide significant loci, including 12 potentially novel loci, emphasizing the importance of genetic diversity and population-specific models[104]. These findings highlight the importance of inclusive research approaches to capture the genetic diversity of PD.

E.3. Polygenic Risk Scores

Polygenic risk scores (PRS) quantify genetic predisposition to PD by integrating the cumulative effects of multiple GWAS-identified variants. PRS have been linked to earlier onset, faster disease progression, and key biological pathways, such as mitochondrial and lysosomal dysfunction [105–108]. The interaction between PRS and lifestyle factors presents opportunities for personalized prevention, while studies on polygenic resilience suggest the presence of protective genetic factors that could mitigate PD risk[109,110]. Pathway-specific PRS—focusing on genetic variants within key biological pathways such as mitochondrial and lysosomal pathways—has also shown promise in predicting both PD risk and progression [111].

These scores provide deeper insights into the biological mechanisms driving PD and offer potential therapeutic targets. Moreover, the application of PRS has influenced personalized medicine in PD by enabling genetic risk stratification. For instance, polygenic hazard scores can predict the onset of PD, integrating genetic effects on both disease risk and age at onset [105]. Patients with high mitochondrial PRS may exhibit earlier disease onset and could benefit from targeted treatments such as ursodeoxycholic acid[108].

However, most research on PD has focused on populations of European ancestry, limiting the PRS applicability in non-European groups. Genetic heterogeneity highlights the need for ancestry-specific analyses. For example, the SNCA variant rs356182 explains the most trait variance in PD PRS models for Latinos, demonstrating the distinct genetic architecture within this population. Ignoring ancestry in genetic studies can obscure gene-phenotype associations due to differences in allele frequencies and linkage disequilibrium patterns, reducing the predictive accuracy and utility of PRS models in diverse populations.

PRS derived from European datasets have shown some predictive ability in non-European groups, but their accuracy is highly variable. For example, the VA Million Veteran Program demonstrated similar predictive abilities for PD in African and Hispanic populations, while other studies reported substantial heterogeneity in risk estimates across ancestries, including East Asian, African, and Latino populations[100,101,114]. In the Chinese Han population, PRS had moderate predictive power (AUC = 0.61), whereas in a Latino PD cohort (LARGE-PD), the PRS achieved an AUC of 0.67, with variability largely driven by admixture patterns and biases from European-derived PRS[101,115]. These findings underscore the need for ancestry-specific PRS models to improve accuracy and ensure equitable application across diverse populations.

Developing ancestry-specific PRS is essential for improving predictive accuracy and ensuring equitable healthcare applications. Beyond individual risk prediction, PRS contribute to understanding the pathogenesis of sporadic PD by identifying biological pathways involved in disease development. This dual utility highlights the critical need to address population diversity in genetic studies, which is necessary for advancing fundamental research and enabling personalized medicine. By incorporating diverse populations, genetic studies can reveal population-specific variants, enhance the effectiveness of PRS, and guide preventive and therapeutic interventions.

E.4. Personalized medicine

Recent advances in personalized therapies targeting specific genetic variants in PD hold significant promise. For example, *LRRK2* kinase inhibitors are in clinical trials for both mutation carriers and idiopathic PD patients [95,116]. Therapies targeting *GBA1*-related PD, such as molecular chaperones like ambroxol, are being developed to enhance glucocerebrosidase activity and reduce alpha-synuclein levels[38,98]. Meanwhile, approaches targeting *SNCA* aim to reduce alpha-synuclein levels through RNA-based therapies[97].

Despite these advancements, challenges remain, particularly in low-resource settings where access to genetic counseling, advanced diagnostics, and specialized therapies is limited [31]. Ethical concerns, such as genetic discrimination and psychological impacts, must also be addressed to ensure equitable application of genetic advances [117]. Policies to protect individuals from discrimination are essential as genetic testing becomes more widespread.

A. The Latin American Perspective

Despite advances in PD genetics, Latin American populations remain underrepresented, creating gaps in understanding the disease's genetic architecture[118]. Latin America's rich genetic diversity—shaped by Indigenous, European, and African ancestries—provides a unique opportunity to uncover gene-phenotype associations that may be specific to or more prevalent in these populations. Such diversity can reveal novel genetic variants associated with PD that might be overlooked in studies focused primarily on populations of European descent.

Differences in allele frequencies and genetic backgrounds can impact both the discovery of disease-associated genes and the accuracy of predictive models. Incorporating Latin American populations in genetic studies can also improve the development of PRS that are applicable across diverse groups, ensuring these models are relevant and effective beyond European contexts.

This thesis aims to address this gap by conducting a systematic review of hereditary parkinsonism in Latin America, characterizing the frequency of PD-related genetic variants in

two admixed populations, and evaluating the effectiveness of PRS models across different ancestries. By exploring the unique genetic landscape of Latin American populations, this work aims to identify novel gene-phenotype associations, enhance the accuracy of PRS, and provide a more comprehensive understanding of PD pathogenesis. Ultimately, these efforts will contribute to more inclusive and effective global health strategies, ensuring that diverse populations benefit from advancements in PD genetics.

Figure 1. Hereditary Parkinsonism genes organized by clinical scenario and mode of inheritance

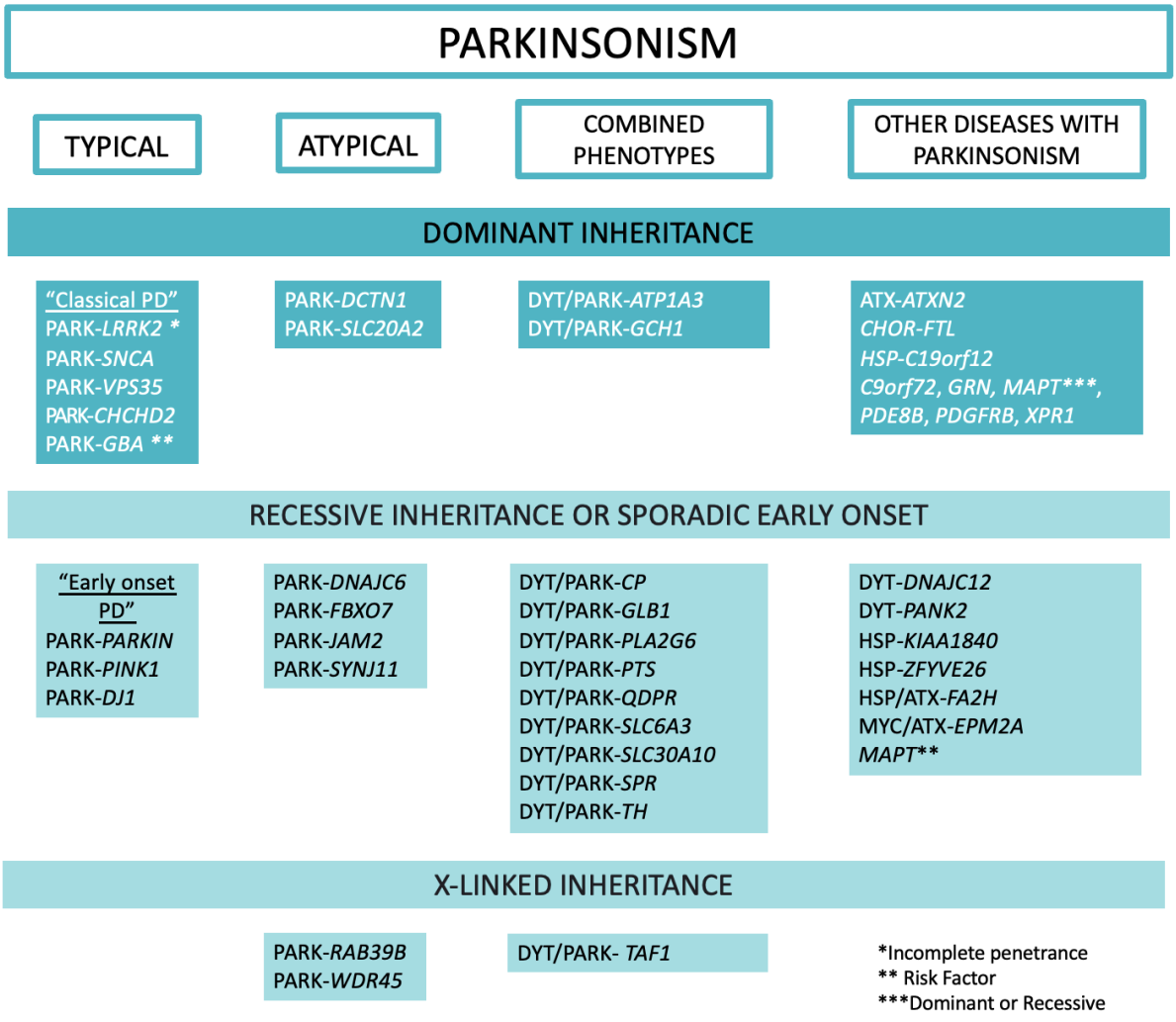


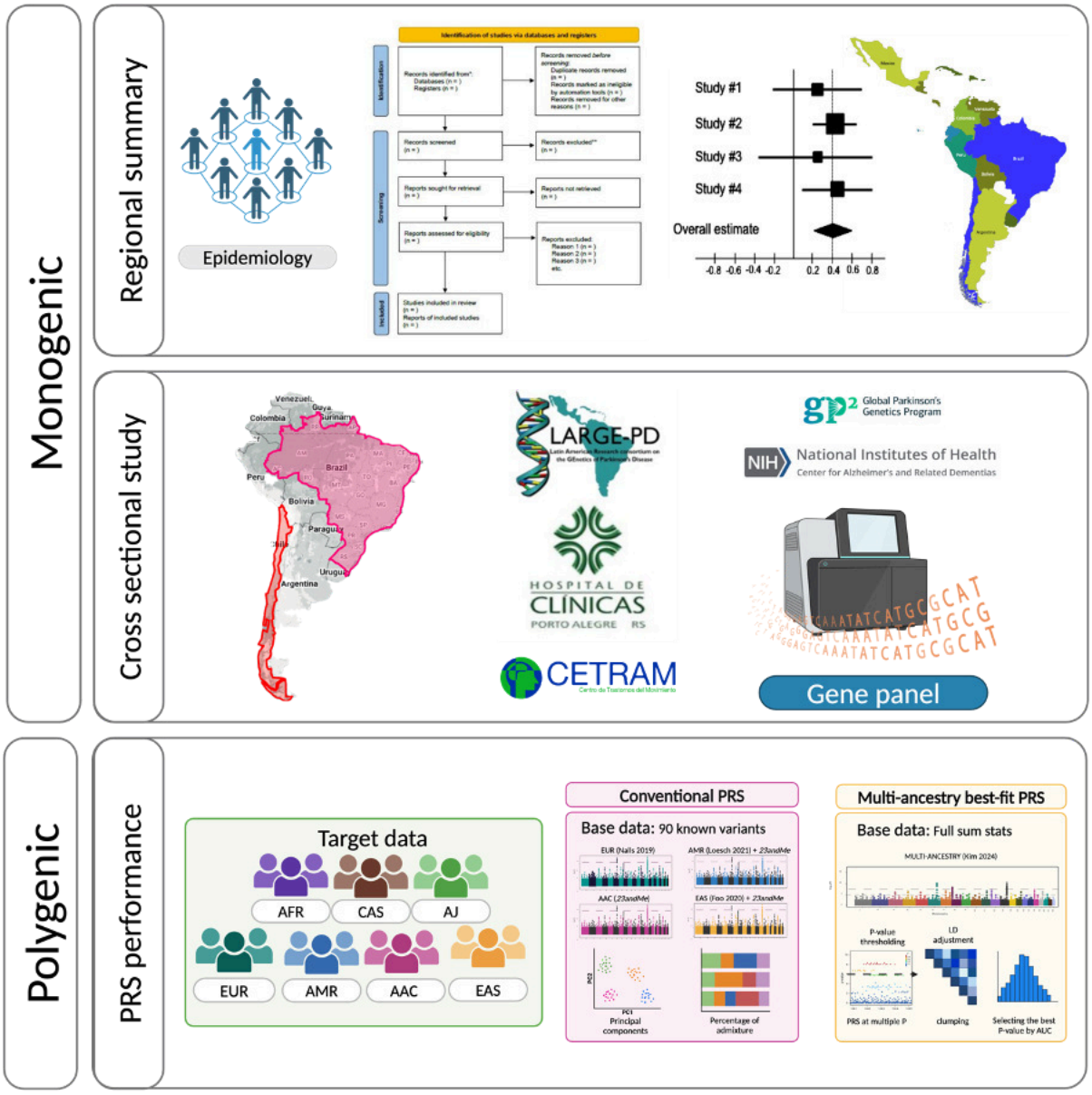
Table 1. Summary of recent findings on Parkinson's Disease genetics in two large multicentric cohorts, and one smaller from Central and South America

Study Name	**Relevance of Genetic Testing in the Gene-Targeted Trial Era**[32]	**Parkinson's disease variant detection and disclosure: PD GENEration, a North American study**[31]	**Parkinson's Disease Gene Screening in Familial Cases from Central and South America**[119]
Geographical Focus	Europe, Middle East, North & South America	North America (US, Canada, Dominican Republic)	Central and South America
Sample Size	12,580 PD patients	10,510 participants (8,301 with results)	468 PD patients from Central and South America
Genes Tested	50 genes, including *LRRK2, GBA1, PRKN, PINK1, SNCA, VPS35, CHCHD2*	7 major PD genes: *LRRK2, GBA1, PRKN, SNCA, PINK1, PARK7, VPS35*	26 genes related to neurodegenerative parkinsonism
Testing Method	Next-generation sequencing (NGS)	NGS	NGS
Filtering Criteria	ACMG guidelines were applied, but additional filters such as MAF < 2% and pathogenicity scores were used; CADD scores likely used	ACMG guidelines, but variant prioritization also used allele frequency, CADD score, and additional in silico predictions; P, LP, and VUS classified	Variants with MAF >1% or CADD score <15 were excluded, prioritized by missense, frameshift, splicing
Variant Inclusion (Heterozygous/Homozygous)	Heterozygous variants in autosomal dominant genes, homozygous/compound heterozygous variants in recessive genes	Heterozygous variants in dominant genes, homozygous/compound heterozygous variants in recessive genes	Heterozygous variants in dominant genes (e.g., GBA1), biallelic variants in recessive genes
GBA1 Variants Included	Included *GBA1* risk variants p.Glu365Lys (E365K) and p.Thr408Met (T408M), pathogenic/likely pathogenic Gaucher variants	Reported *GBA1* c.1093G>A (p.Glu365Lys/E365K), c.1226A>G (p.Asn409Ser/N409S), c.1448T>C (p.Leu483Pro/L444P) variants	Included *GBA1* variants regardless of population frequency, no specific pseudogene validation
Recessive Genes in Diagnostic Yield	Included only if participants had two pathogenic/likely pathogenic variants (homozygous or compound heterozygous)	Included only if participants had two pathogenic/likely pathogenic variants (homozygous or compound heterozygous), but heterozygous variants reported	Included if participants had two pathogenic/likely pathogenic variants (homozygous or compound heterozygous)
Primary Variants Found	*GBA1* 10.4% *LRRK2* 2.9%	*GBA1 7.7%* *LRRK2* 2.4%	*GBA1* 7.7% *LRRK2 1.92%*
Diagnostic Yield	11.7%	13%	9.62%

2. CONCEPTUAL FRAMEWORK

The conceptual framework of this thesis integrates three interconnected components to explore the genetic landscape of PD in Latin America, focusing on both monogenic and polygenic aspects. Firstly, a systematic review is conducted to assess the prevalence and distribution of hereditary parkinsonism in Latin American countries, identifying gaps in regional genetic studies and establishing a foundation for research in this area. Secondly, a cross-sectional study characterizes the frequency and distribution of PD-related genetic variants in two Latin American admixed populations, providing region-specific insights. Lastly, PRS are developed by constructing and comparing two models across diverse populations to evaluate the accuracy of genetic risk prediction. Collectively, these components form a comprehensive framework that addresses both the epidemiological assessment and genetic analysis of PD, contributing to a better understanding of its genetic factors in Latin American populations.

Figure 2. Conceptual framework for investigating genetic contributors to Parkinson's Disease in Latin America: Monogenic and Polygenic Perspectives



3. RATIONALE

Despite significant global advancements in PD research, the genetics of PD remains underexplored in Latin America—a region with rich genomic diversity that offers unique opportunities to uncover novel insights into the disease's genetic architecture. This moment represents an ideal opportunity to deepen our understanding of region-specific hereditary contributors. By investigating rare Mendelian variants linked to early-onset PD, alongside common variants incorporated into polygenic risk scores (PRS), we can clarify individual disease susceptibility and address critical knowledge gaps. Exploring the genetic landscape of these populations will expand our understanding of PD in diverse groups and ultimately advance precision medicine, paving the way for more targeted and effective treatments for all patients.

4. OBJECTIVES

4.1 Primary objective

To explore the genetic contributors to Parkinson's Disease in Latin America by investigating the frequencies of PD-related genes and genetic risk factors, with a focus on populations from South Brazil and Chile, and evaluating polygenic risk score performance for PD across diverse ancestries.

4.2 Secondary objectives

1. To synthesize evidence regarding the frequency and distribution of PD-related genes and genetic risk factors in Latin America;
2. To determine the frequency and distribution of PD-related genes and genetic risk factors in Southern Brazil and Santiago, Chile;
3. To describe the molecular findings and diagnostic yield of a multi-gene NGS panel PD patients in Southern Brazil and Santiago,Chile;
4. To analyze genotype-phenotype correlations in Parkinson's Disease patients carrying disease causative variants;
5. To calculate polygenic risk scores in Latin American populations and compare their predictive performance with those derived from European populations.

5. RESULTS

REVIEW

Frequency of Hereditary and *GBA1*-Related Parkinsonism in Latin America: A Systematic Review and Meta-Analysis

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ABSTRACT: Background: Identifying hereditary parkinsonism is valuable for diagnosis, genetic counseling, patient prioritization in trials, and studying the disease for personalized therapies. However, most studies were conducted in Europeans, and limited data exist on admixed populations like those from Latin America.
Objectives: This study aims to assess the frequency and distribution of genetic parkinsonism in Latin America.
Methods: We conducted a systematic review and meta-analysis of the frequency of parkinsonian syndromes associated with genetic pathogenic variants in Latin America. We defined hereditary parkinsonism as those caused by the genes outlined by the MDS Nomenclature of Genetic Movement Disorders and heterozygous carriers of *GBA1* pathogenic variants. A systematic search was conducted in PubMed, Web of Science, Embase, and LILACS in August 2022. Researchers reviewed titles and abstracts, and disagreements were resolved by a third researcher. After this screening, five researchers reanalyzed the selection criteria and extracted information based on the full paper. The frequency for each parkinsonism-related gene was determined by the presence of pathogenic/likely pathogenic variants among screened patients. Cochran's Q and I^2 tests were used to quantify heterogeneity. Meta-regression, publication bias tests, and sensitivity analysis regarding study quality were also used for *LRRK2*-, *PRKN*-, and *GBA1*-related papers.
Results: We included 73 studies involving 3014 screened studies from 16 countries. Among 7668 Latin American patients, pathogenic variants were found in 19 different genes. The frequency of the pathogenic variants in *LRRK2* was 1.38% (95% confidence interval [CI]: 0.52–2.57), *PRKN* was 1.16% (95% CI: 0.08–3.05), and *GBA1* was 4.17% (95% CI: 2.57–6.08). For all meta-analysis, heterogeneity was high and publication bias tests were negative, except for *PRKN*, which was contradictory. Information on

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the number of pathogenic variants in the other genes is further presented in the text.
Conclusions: This study provides insights into hereditary and *GBA1*-related parkinsonism in Latin America. Lower *GBA1* frequencies compared to European/North American cohorts may result from limited access to gene sequencing. Further research is vital for regional prevalence understanding, enabling personalized care and therapies.

Key Words: *GBA1*; hereditary parkinsonism; *LRRK2*; Parkinson's Disease; *pRKN*

Parkinson's disease (PD) is a common neurodegenerative movement disorder.[1] Although the majority of PD cases are sporadic and multifactorial, resulting from a combination of environmental and polygenic factors, ~5% to 15%[2–6] of cases are attributed to pathogenic variants in a single gene, known as monogenic or hereditary parkinsonism.[7,8] Nevertheless, this definition is not univocal, as some genes have low and incomplete penetrance (*LRRK2*, *GBA1*),[9] thus being considered by some as risk factors, and others have a controversial role when monoallelic (*PRKN*).[10] Despite these issues, identifying monogenic forms of the disease is valuable for achieving a definitive diagnosis, which can enable genetic counseling and clinical trial selection and can also lead to a better understanding of disease pathogenesis and personalized therapies.[11]

The study of monogenic forms of PD has been enhanced due to advancements in genetic technologies.[7,12] However, most of the published data on monogenic PD and related parkinsonian syndromes derived from patients of European and Asian ancestry.[11,13–16] The frequency of monogenic parkinsonism in populations such as those in Latin America is understudied, with only 10% of all research on the genetics of parkinsonism being conducted in this region.[17,18] Latinos are a heterogeneous population that typically exhibits a three-way admixture pattern, resulting from contributions from African, European, and Native American ancestry. Previous studies have shown differences in the frequency of specific monogenic parkinsonism between the Latino population and others.[19,20]

In an effort to comprehensively evaluate the reported studies of hereditary and *GBA1*-related parkinsonism in Latin America, we conducted a systematic review and meta-analyses aiming to determine the frequency and distribution of these disorders, considering hereditary parkinsonism as those caused by the genes outlined in the Nomenclature of Genetic Movement Disorders recommended by the International Parkinson and Movement Disorder Society (MDS) and its updated version,[21,22] and additionally considering heterozygous carriers of *GBA1*, as newer insights have been revealed after the MDS update.[23,24]

To ensure adherence to the MDS categorization framework and maintain consistency within the systematic review, we placed *GBA1* and *ATP13A2* in line with their recommended classification categories: "other diseases with parkinsonism" for the former and "mixed movement disorders" for the latter.

Patients and Methods

Design

We conducted a systematic review with a meta-analysis of (1) PD patients reported as having hereditary parkinsonism (2) caused by the genes outlined by the MDS Nomenclature of Genetic Movement Disorders[21,22] (summarized in Figure S1) and additionally including heterozygous carriers of *GBA1* pathogenic variants (3) reporting results among Latin American patients and (4) published in English, Spanish, or Portuguese. We excluded reports focusing on functional, epigenetic, biomarkers, risk factors, and heterozygous carriers of pathogenic variants in other recessive genes with controversial impact and noncausative pathogenic variants on parkinsonism genes. Studies conducted on animal models or in silico were also excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the elaboration of this review.[25]

Information Sources and Search Strategy

The systematic literature search was done by two independent researchers (P.S.A. and D.T.) in four databases (PubMed, Web of Science, Embase, and LILACS) until August 2022. The search strategy consisted of a list of parkinsonism-related genes, Latin American countries, and terms for parkinsonism and Parkinson's disease. The full search strategy for each database is described in Table S1.

Selection Process

All articles obtained were imported to the Rayyan software,[26] which was used for recording decisions. Three reviewers participated in the study selection. First, articles were screened by two researchers (P.S.A. and D.T.) who blindly assessed titles and abstracts based on inclusion and exclusion criteria. Disagreements were resolved by consensus with a third reviewer (A.F.S.S.).

After the first screening, included articles were randomly assigned to five investigators (P.S.A., AF.S.S., D.T., B.L.S.-L., and S.C.) who reanalyzed the selection criteria and extracted the information requested based on a structured template. The data collected from each individual study are presented in Table S2. Reports that deserved further discussion were screened again by two reviewers who solved the discrepancies (A.F.S.S. and P.S.A.). Multicentric studies that did not report specific data on Latin American patients or reported PD genes with conflicting evidence[27] (eg, *UCHL1*, *GIGYF2*, *EIF4G1*, and *DNAJC13*) were excluded at this stage of the review.

Data Analysis and Synthesis

The frequency of monogenic forms of PD was determined as the number of PD patients carrying variants classified as pathogenic in the genes listed by the MDS update on Nomenclature of Genetic Movement Disorders.[22] Variant pathogenicity was determined based on the guidelines of the American College of Medical Genetics and Genomics[28] and checked in the VarSome platform.[29] Heterozygous monoallelic variants in recessive genes with controversial roles were not counted. We performed three separate meta-analyses of mutational screening studies to determine the frequency of the most extensively studied genes associated with PD, namely *LRRK2*, *PRKN*, and *GBA1*.[22] A quality assessment tool based on guidelines for evaluating prevalence studies was used to determine study quality.[30] It is based on eight criteria that determine the rigor of clinical assessment, quality of the statistical analysis, and representativity of the sample for the target population. A score ranging from 0 to 8 was calculated for each mutational screening study, giving 1 point for each positive applicable criterion.

A meta-analysis of single proportions was performed using R statistical software, version 3.5.1 (R Core Team 2018), using the *meta* package. The random effects model was used on the overall results by estimating both a within-study and between-study variance and weighing each study on its contribution to both variances.[31] The Cochran's Q and the Higgin's & Thompson's I^2 and its 95% confidence intervals (CI) were used to quantify the heterogeneity between studies.[32] Meta-regressions regarding the number of parkinsonism patients and study quality were conducted. We also performed a sensitivity analysis based on the median study quality score; a score of 5 or more indicated high quality and a score less than 5 low quality. Publication bias was investigated using the Begg[33] and Egger[34] tests.

Results

This review assessed 3014 studies, of which 73 met the inclusion criteria.[20,35–106] The process detailing the step-by-step inclusion and exclusion criteria is summarized in the PRISMA flow diagram[107] shown in Figure S2. Sixteen Latin American countries were represented, with most of them from Brazil (50.7%), followed by Colombia (20.5%), Mexico (11%), and Argentina (11%). Most publications (52.1%) were mutational screening studies.

A total of 7668 patients with parkinsonism were included in the analysis, and 306 pathogenic variants were identified in 19 different genes. The most frequent genetic forms of dominant and recessive "classical PD" were *LRRK2* (84) (p. G2019S, p.R1441G being the most frequent) and *PRKN* (93) (p.Cys212Tyr, IVS1 + 1G/T and Ex4del being the most frequent). For the "atypical parkinsonism" subgroup, *SLC20A2* (6) was the most frequent gene with pathogenic variants. Only one patient carrying an *SNCA* pathogenic variant was identified among all studies, and no patients with pathogenic variants in *VPS35*, *CHCHD2*, or *DJ1* were reported. Table 1 summarizes the information on all included studies, with *LRRK2*, *PRKN*, and *GBA1* subgroups. The number of studies and parkinsonism patients evaluated and the frequency of all pathogenic variants identified among them are presented in Table 2. See Table S3 for more details of each study, methodology, and laboratory technique used for genetic analysis. The pathogenic variants for *LRRK2*, *PRKN*, and *GBA1* are summarized in Table S4.

Meta-Analysis of the Frequency of Parkinsonism Related to *LRRK2*, *PRKN*, and *GBA1* Pathogenic Variants

When considering only mutational screening studies, there were 7368 patients, and 226 pathogenic variants were found. Regarding the most common genes with pathogenic variants, the frequency of parkinsonism linked to *LRRK2* was 1.38% (95% CI: 0.52–2.57, I^2: 78% [64%–86%], $P < 0.01$; Figure 1), *PRKN* was 1.16% (95% CI: 0.08–3.05, I^2: 76% [57%–86%], $P < 0.01$; Figure 2), and *GBA1* was 4.17% (95% CI: 2.57–6.08, I^2: 75% [56%–86%], $P < 0.01$; Figure 3).

The meta-analyses showed considerable heterogeneity across all genes. Meta-regressions demonstrated that there was no correlation between the frequency of pathogenic variants in each gene with the quality assessment, or sample size (of parkinsonian patients), except for quality assessment in *GBA1* studies ($P < 0.0001$). Additionally, sensitivity analyses using study quality showed no statistically significant difference between high- and low-quality studies for all genes. The *PRKN* meta-analyses revealed two clear visual outliers that, when excluded, led to an improvement in heterogeneity. However, the same exclusion procedure did not result in lower heterogeneity for *GBA1* or *LRRK2* meta-analysis. The publication biases were contradictory for *PRKN* (Begg's test positive, $P = 0.0197$; Egger's test negative;

TABLE 1 *Overall information on the studies included with* LRRK2, PRKN, *and* GBA1 *subgroups*

	All studies (n = 73)	*LRRK2* (n = 23)	*PRKN* (n = 23)	*GBA1* (n = 15)
Study type				
Case reports and series	34 (46.6%)	7 (30.4%)	9 (39.1%)	3 (20.0%)
Mutational screening	39 (53.4%)	16 (69.6%)	14 (60.9%)	12 (80.0%)
Patients count and prevalence				
Parkinsonism patients	7668	4682	1796	2197
Control patients	4502	2493	972	1259
Number of pathogenic variants	306	84	93	99
Parkinsonism type*				
Typical	46 (63%)	–	–	–
Atypical	10 (13.7%)	–	–	–
Combined phenotypes	6 (8.2%)	–	–	–
Other diseases with parkinsonism	15 (20.5%)	–	–	–
Mixed movement disorders	4 (5.5%)	–	–	–
Inheritance				
Dominant	7 (9.6%)	–	–	–
Recessive	4 (5.5%)	–	–	–
Both	62 (84.9%)	–	–	–
Familial incidence				
Sporadic	14 (19.2%)	7 (30.4%)	4 (17.4%)	6 (40.0%)
Familial	28 (38.4%)	6 (26.1%)	10 (43.5%)	2 (13.3%)
Both	31 (42.5%)	10 (43.5%)	9 (39.1%)	7 (46.7%)
Disease onset**				
Early	30 (41.1%)	7 (30.4%)	17 (73.9%)	5 (33.3%)
Late	2 (2.7%)	2 (8.7%)	0	0
Both	41 (56.2%)	14 (60.9%)	6 (26.1%)	10 (66.7%)
Genetic identification methods*				
Sanger sequencing	27 (37%)	11 (47.8%)	8 (34.8%)	7 (46.7%)
Real-time PCR (RT-PCR)	27 (37%)	10 (43.5%)	8 (34.8%)	5 (33.3%)
Quantitative RT-PCR	7 (9.6%)	3 (13%)	5 (21.7%)	0
NGS/gene panel	5 (6.9%)	0	1 (4.4%)	1 (6.7%)
Whole-exome sequencing	4 (5.5%)	0	2 (8.7%)	0
RFLP	15 (20.6%)	4 (17.4%)	5 (21.7%)	4 (26.7%)
Other methods	18 (24.7%)	6 (26.1%)	12 (52.2%)	2 (13.3%)
Not informed	5 (6.8%)	3 (13%)	0	1 (6.7%)

Data are presented as their frequency.
Abbreviation: NGS: next generation sequencing, RFLP: restriction fragment length polymorphism.
*More than one answer was permitted.
**Defined by the study investigators.

$P = 0.1378$) and negative for *LRRK2* or *GBA1*. Unfortunately, due to overlapping CIs, substantial heterogeneity, and insufficient data for a pooled estimate when restricted to high-quality studies, a meta-analysis comparing the frequencies of *LRRK2*, *PRKN*, and *GBA1* between Latin American countries was not possible.

TABLE 2 *Number of studies, parkinsonism patients, and pathogenic variants found for each gene among all studies*

	Number of studies	Number of parkinsonism patients	Number of pathogenic variants
Typical			
LRRK2	23	4682	84
SNCA	10	1570	1
VPS35	2	259	0
CHCHD2	1	122	0
PRKN	23	1796	93
PINK1	9	1441	2
DJ1	4	515	0
Atypical			
DCTN1	3	5	4
SLC20A2	3	27	6
DNAJC6	1	1	1
FBXO7	0	0	0
JAM2	0	0	0
SYNJ1	1	31	0
RAB39B	0	0	0
WDR45	1	1	1
Combined phenotypes			
ATP1A3	1	1	1
GCH1	3	125	3
CP	0	0	0
GLB1	0	0	0
PLA2G6	1	1	1
PTS	0	0	0
QPDR	0	0	0
SL30A10	0	0	0
SPR	0	0	0
TH	0	0	0
TAF1	0	0	0
Other diseases with parkinsonism			
ATXN2	0	0	0
FTL	0	0	0
C19orf12	0	0	0
C9orf72	0	0	0
GRN	0	0	0
MAPT	2	507	3
PDGFRB	0	0	0
XPR1	0	0	0
GBA1	14	2197	99
DNAJC12	0	0	0
PANK2	0	0	0
KIAA1840	0	0	0
ZFVE26	0	0	0
FA2H	0	0	0
EPM2A	0	0	0
MXMD			
ATP13A2	5	303	7

Abbreviation: MXMD, mixed movement disorders.

Discussion

This study presents a comprehensive overview of hereditary and *GBA1*-related forms of parkinsonism in Latin America. Among 7668 Latin American patients evaluated in 73 studies, 306 pathogenic variants were identified in 19 different genes. Pathogenic variants in the *LRRK2*, *PRKN*, and *GBA1* genes were found in 1.38%, 1.16%, and 4.17% of parkinsonism patients, respectively, highlighting their importance as genetic causes and/or risk factors for PD in Latin America.

The most promising genetic targets for PD treatments are *LRRK2*, *GBA1*, and *PRKN*, with knowledge of their prevalence in different populations of particular interest.[108] In Latin America, our study found a frequency of 1.38% for *LRRK2* pathogenic variants—most of them *p*.G2019S, which is similar to the estimated frequency of sporadic *LRRK2* *p*.G2019S across different ethnicities.[15,109] However, the frequency of *LRRK2* pathogenic variants can be much higher in Ashkenazi Jews and North African Arabs, where it ranges from 28% to 39%.[109] In Latin America, the frequency of p.G2019S has been reported as high as 4.2% in Uruguay[20] but as low as 0.2% in Peru.[20] These disparities in frequencies across countries might be attributed to local ancestry differences. The only Latino PD GWAS (genome-wide association study) meta-analysis[19] reported the highest proportion of European ancestry in Uruguay and the lowest in Peru.

The frequency of *GBA1* in our review was 4.17%, which is lower than the frequencies reported for North American (9.2%),[6] European (5%–15%),[110,111]

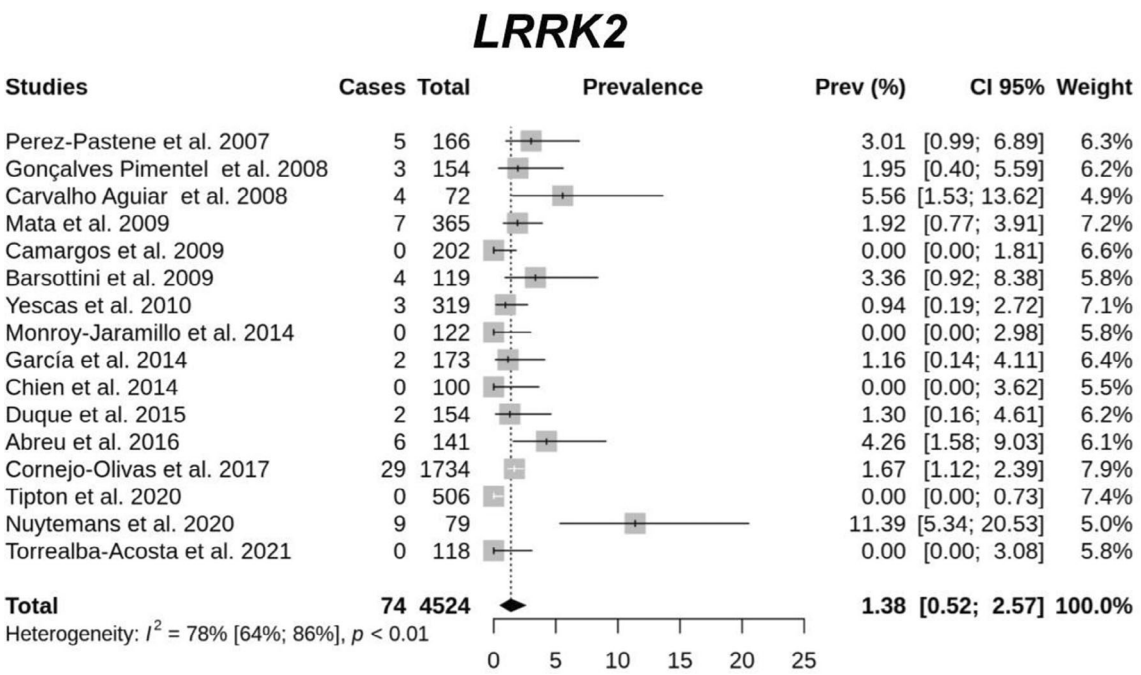

FIG. 1. *LRRK2* mutation frequency meta analysis. [Correction added on 20 December 2023, after first online publication: The figure caption has been revised.]

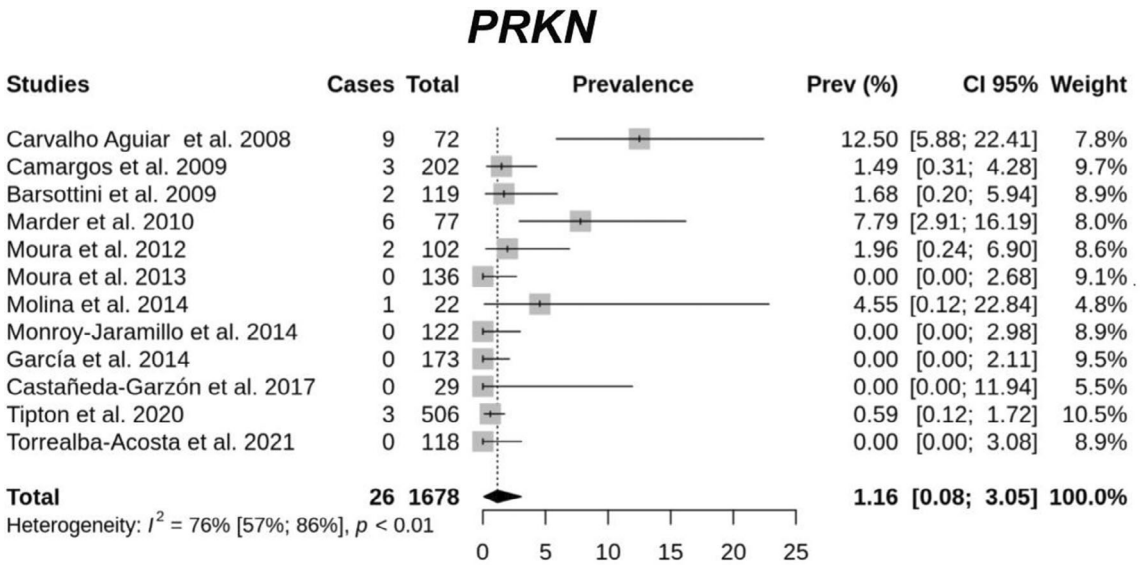

FIG. 2. *PRKN* mutation frequency meta-analysis. Two outliers were removed to obtain the final forest plot for *PRKN* mutations. [Correction added on 20 December 2023, after first online publication: The figure caption has been revised.]

and Ashkenazi Jewish (20%–30%)[111] PD patients. This difference in prevalence might arise because only a third of the included studies in our systematic review fully sequenced the gene (Table S3). Similar findings have been highlighted within our region before,[112] who showed that due to gene complexity, many studies within the region performed incomplete sequencing.

Our study found a frequency of 1.16% for pathogenic variants in *PRKN*, consistent with preliminary results of large multicentric cohorts such as PD GENEration[6] and Rostock International Parkinson's Disease Study (ROPAD),[5,113] which reported *PRKN* frequencies of 2.5% and 1.0%, respectively. Similar to ROPAD, the estimate presented here is based on homozygous or compound heterozygous pathogenic variants, as the clinical relevance of monoallelic pathogenic variants has not been established for the disease.[114–116] Our aim was to determine monogenic forms of parkinsonism, not variant frequency. Although the prevalence of pathogenic variants in *PRKN* among PD patients in

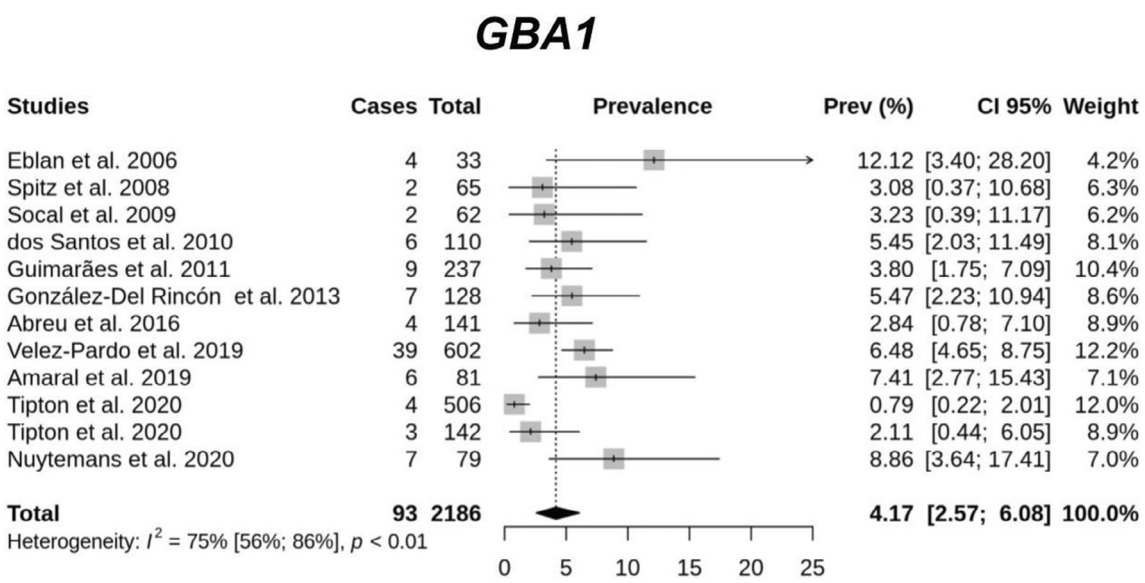

FIG. 3. *GBA1* mutation frequency meta-analysis. [Correction added on 20 December 2023, after first online publication: The figure caption has been revised.]

Latin America is consistent with prior research, the study's generalizability is limited because we observed conflicting results in publication bias tests. Two main factors can account for this result: the high proportion (74%) of studies that screened *PRKN*, where conducted in early-onset PD patients and the potential exclusion of compound heterozygosity due to limited access to genetic analysis.

Another remarkable finding was that 7 patients with *ATP13A2* pathogenic variants were found: 6 from Chile and 1 from Brazil. This gene has a broad phenotypic spectrum combining different degrees of parkinsonism, spastic paraplegia, and/or ataxia.[22] We hypothesize that the finding in our study could be explained as a founder effect—as the gene was first reported in a Chilean family[51]—ancestry related, or correspond to selection bias, as only the Brazilian patient was found in a mutational screening study. Future research could address this question by screening a larger PD population or performing ancestry characterization of this population.

Despite advances in genetic research, monogenic parkinsonism is understudied in Latin America compared with other regions.[18] In recent comprehensive studies on *LRRK2* and *SNCA* variants, involving 49,299 and 24,075 PD patients, respectively, only one study of a Latin American country was included in both reviews.[15,16] A similar scenario is seen in a systematic review with 16,488 *GBA1*-related PD patients, in which there were no Latin American studies among 28 reports.[117] Our systematic review found only 7668 parkinsonism patients in Latin America even though a broad range of genes was included, indicating a disproportionately low representation of the Latino population in genetic parkinsonism research. This disparity in research can also indicate that many Latin American patients do not receive adequate diagnosis, counseling, and treatment, which also limits our capacity to better understand disease mechanisms and modifiers. Likely underlying reasons include limited funding for genetic testing and research,[118–120] lack of knowledge of health professionals,[121–123] and the perception of a lower clinical utility of genetic testing by clinicians.[124]

Understanding the frequency and distribution of monogenic parkinsonism is crucial for the development of clinical trials and targeted medicine. Although previous studies have suggested a worldwide prevalence of ~3% to 5%, or up to 10%, the source of these estimates is unclear.[2–4,125] Unfortunately, there have been a few studies evaluating the prevalence of monogenic parkinsonism or PD, and those that have been conducted are not representative of the entirety of Latin America. Furthermore, the differences in genes analyzed, populations evaluated, and protocols used make calculating a pooled estimate infeasible and potentially misleading. To better understand the prevalence of monogenic parkinsonism in Latin America, there is a need for further multicenter and high-quality genetic screening studies using standardized molecular analysis and a comprehensive set of genes. Initiatives such as the Latin American Research Consortium on the Genetics of PD[126] and the Global Parkinson's Genetics Program (GP2) are, therefore, essential for making advancements in this field.[127]

This study has limitations to be considered. The first is selection bias, as some studies assessed a subpopulation, such as those focused on familial PD or early-onset PD, raising the possibility of a higher frequency of patients with pathogenic variants. Also, samples usually came from specialized medical centers and may not

capture the whole diversity of the Latino admixture population. Second, a low number of studies and a great heterogeneity between them (study design, target population, and genetic techniques performed) made it challenging to analyze the results, make proper estimations, and determine reliable comparisons. Third, the inclusion of low-quality studies and the use of a less-strict quality cutoff than that in other studies that used the same quality evaluation tool[30] may have introduced bias in our analysis, even though sensitivity analyses comparing studies by their quality failed to identify any statistically significant differences between them. Fourth, the lack of specific ancestry data in most studies also limited the investigation of the frequency of different variants in specific populations. Fifth, the interpretation of the frequency of *PRKN* pathogenic variants found must be approached with caution due to conflicting publication bias tests. Finally, data extraction was limited in some multicentric and international studies that did not specify their results of the Latino subpopulations that participated in them. Despite these limitations, this study evaluated a comprehensive number of genes and aimed to provide data with the highest degree of confidence possible by weighing different factors that could influence the quality of the calculated estimates.

In conclusion, the present study can be considered an exploratory investigation aimed at examining the literature and compiling reported data on monogenic parkinsonism in Latin America, thus providing a preliminary overview of the frequency and distribution of monogenic parkinsonism in the region. The identified gap between high-quality and standardized studies limits the interpretation of our results but also highlights the opportunities and challenges for future research on PD genetics in the region. This effort will certainly enhance our knowledge but more importantly will improve the quality of care given to our patients.

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Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

42

5.2 ARTICLE 2

Genetics of Parkinson's Disease in South America: a cross-sectional pilot study of Southern Brazil and Central Chile

Insights into Ancestral Diversity in Parkinson's Disease Risk: A Comparative Assessment of Polygenic Risk Scores

6. DISCUSSION

Medical research has traditionally been conducted by scientists without direct experience in patient care, leading to significant scientific advancements but also creating a disconnect between research questions and real-world medical challenges. Most medical doctors (MDs) are not trained as researchers, which limits the applicability of research to actual clinical issues. Bridging this gap requires MDs who are also researchers, guiding research toward more clinically relevant questions. Personalized medicine is a prime example of this need, promising tailored treatments based on individual genetic, environmental, and lifestyle factors. This approach can revolutionize care for complex conditions like PD, where diverse genetic underpinnings demand precise treatment strategies. However, achieving the full potential of personalized medicine depends on including underrepresented populations (URP) in genetic research. Latin American populations, for example, have largely been neglected, risking the perpetuation of healthcare disparities. Including URP is essential for ensuring equitable healthcare outcomes and reducing health access inequalities.

Before conducting this thesis, GP2 (the consortium funding my PhD) did not return genetic results to patients. However, with the support of my supervisor and co-supervisor, we established a Return of Results (RoR) working group, which conducted a survey to understand the perspectives of medical doctors on returning genetic results. The survey revealed that while most MDs were interested in returning results, many felt uncomfortable or lacked the necessary knowledge to do so (paper in Appendix). To address these challenges, we developed an RoR policy and began training MDs through the GP2 Training Network. These efforts led to the expansion of the PD Generation study to Latin America, a program funded by the Parkinson's Foundation that offer genetic testing for PD free of charge, making RoR both accessible and of high quality. This initiative exemplifies how research can be shaped to directly impact patients' lives by empowering clinicians and integrating patient-centered approaches.

This thesis aimed to bridge some of these gaps by exploring the genetic landscape of PD in Latin America. The systematic review conducted as part of this research revealed significant insights into the genetic diversity of PD in the region, identifying pathogenic variants in 19 genes among

7,668 patients, with GBA1, LRRK2, and PRKN being the most prevalent. During the course of this research, we realized that the quality of studies was low, making it challenging to perform meta-analyses and draw broader conclusions. In our cross-sectional study of PD patients from southern Brazil and Santiago, Chile, disease-causing variants were identified in 33 patients across 64 PD-related genes, resulting in a diagnostic yield of 14.3%. Notably, the *LRRK2* p.G2019S variant was predominantly found in the Chilean cohort, whereas *GBA1* variants were more frequent in the Brazilian cohort. Additionally, novel variants classified as variants of uncertain significance (VUS) were identified, underscoring the unique genetic contributions of Latin American populations. However, there remains a gap in understanding the clinical relevance of these VUS for individual patients, highlighting the need for further functional studies and long-term clinical follow-up.

We also constructed polygenic risk scores (PRS) across seven diverse ancestries, including Latin Americans. Our findings demonstrated the limited applicability of conventional PRS models in non-European populations, with the Latin American cohort showing a lower discriminative ability. This highlights the need for refined, ancestry-specific PRS approaches to enhance prediction accuracy and ensure equitable healthcare benefits across diverse populations. This study serves as a prime example of how a multidisciplinary team can work together to ensure that scientific advancements translate into meaningful health outcomes for patients.

In most healthcare systems, the dual role of being both a practicing physician and a researcher is nearly impossible to maintain due to time constraints and clinical demands. Physicians are often overwhelmed with patient care responsibilities, leaving limited capacity for research activities. This is especially true in underrepresented populations, such as those in southern Brazil and Chile, where economic and structural barriers make it even harder to balance clinical duties and research.

Economic disparities and limited resources mean that funding for research is often scarce and allocated inequitably. In addition to inadequate infrastructure, there is also a lack of high-power computing resources, forcing researchers to rely on cheaper online platforms that are less efficient and more time-consuming. Addressing these barriers requires policies that provide

funding for protected research time for MDs and establish shared workspaces with computational resources to support collaborative research.

A collaborative approach that fosters a common language between clinicians and researchers is essential for advancing precision medicine. By working together in shared work environments and ensuring mutual understanding of each other's expertise, research can be more aligned with real-world medical needs. Such collaboration will help develop accurate genetic models that reflect population diversity, translating scientific findings into tangible health benefits and advancing precision medicine for underrepresented groups.

7. FUTURE DIRECTIONS

To achieve the potential of precision medicine, particularly in underrepresented populations, strong collaborations between clinicians and researchers are essential, between the Global North and South, as well as within Global South countries. Future efforts should focus on:

Building Comprehensive Genetic Databases and Increasing Sample Sizes: Expanding and sharing genetic datasets across underrepresented populations is crucial to improving the accuracy of genetic models used in precision medicine. Collaborative research initiatives should prioritize pooling resources and data to create a reference panel that reflects the diversity of the region. By combining individual research efforts and building larger, more diverse cohorts, we can overcome sample size limitations, improve the statistical power of polygenic risk scores (PRS), and develop more representative and clinically useful models. Incorporating local genetic data, ancestry-specific summary statistics, and an understanding of both global and local ancestries will further enhance the utility of PRS and contribute to precision medicine. Increasing the sample size of PD patients and healthy individuals will also help assess variant frequency and pathogenicity more accurately, enabling better classification of VUS.

Comprehensive Analysis of Genetic Variation: Future research should include copy number variation (CNV) analysis to identify structural variants that may play a role in PD in these populations. Our study has established a foundation by characterizing single nucleotide variants (SNVs), but extending this to CNVs will provide a more complete picture of the genetic landscape of PD in these cohorts. Incorporating CNV data will help refine genetic risk models and identify potential therapeutic targets. We plan to use PennCNV software with data from the Neurobooster array for this purpose.

Validation of Genetic Findings and Return of Results: We aim to validate the identified variants in a CLIA-certified laboratory and return results to patients, providing genetic counseling to ensure comprehensive care. To facilitate this, we have partnered with PD Generation[120] to deliver results and counseling to all patients. Additionally, we plan to apply for funds to conduct long-read sequencing on the most interesting undiagnosed cases.

Leveraging Advanced Technologies for Long-Read Sequencing: Long-read sequencing is particularly important for studying genetically negative PD cases, as it can uncover novel genetic variations, including structural variants and repeat expansions that are missed by short-read technologies. Future work should apply long-read sequencing to these negative cases, as demonstrated in this study, to identify complex variants that may contribute to PD in Latin American populations. Efforts should focus on making these technologies accessible by equipping local research centers and researchers with resources to conduct advanced genomic studies.

Establishing Shared Collaborative Workspaces: To address the challenges of limited computational resources, it is essential to establish shared collaborative workspaces, both physical and digital, equipped with high-power computing capabilities. This will allow researchers in underrepresented regions to work efficiently without relying on less effective, lower-cost online platforms. Collaborative work environments will facilitate real-time communication and efficient resource sharing, ultimately accelerating the pace of genetic research.

Implementing Collaborative Training Programs: Interdisciplinary training programs should be established to equip both MDs and scientists with a foundational understanding of each other's fields. Leveraging the expertise of both clinicians and genetic researchers will help develop clinically relevant research questions and methodologies. Training programs should also include advanced technologies, such as CNV analysis and long-read sequencing, empowering local researchers to conduct cutting-edge investigations and ensuring that research remains aligned with patient care.

Policy and Funding Support for Medical Doctors: Advocate for policies that provide funding and infrastructure specifically aimed at supporting medical doctors who are balancing research and clinical practice. This includes creating grants and funding opportunities that allow MDs to have dedicated, paid time for research without compromising their clinical responsibilities. Ensuring that physicians can maintain both roles is essential for translating genetic research into clinical

practice, particularly in regions like Latin America where time and resource constraints are significant barriers.

By pursuing these strategies, the medical community can move closer to the goal of precision medicine. This approach ensures that advancements in genetic research translate into tangible health benefits for patients, particularly those in underrepresented populations who have historically been excluded from medical innovations. By leveraging expertise from both the Global North and South, and providing shared resources for clinicians and researchers to work collaboratively, we can make meaningful progress in addressing health disparities and advancing precision medicine for all.

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9. APPENDICES

9.1.1: Evaluation protocol (Brazilian version)

NOME

REG: **TIPO •HCRP**

SEXO: •masculino •feminino **DATA NASC:**

Diagnóstico: **• D PARKINSON • CONTROLE sem doença**

Data da coleta do DNA

CÓDIGO LARGE-PD: ***(adicione os 4 últimos dígitos do registro no HCRP)*** **RPP**

REVISÃO DO PROTOCOLO: CHECAR O PREENCHIMENTO CORRETO		
	VERIFICADO	**VERIFICADO POR:**
Assinatura do TCLE		
PARTE 1 PACIENTES - critérios de diagnóstico		
PARTE 2a PACIENTES -antecedentes		
PARTE 2b CONTROLES - antecedentes		
PARTE 3 PACIENTES E CONTROLES dados pessoais e exposição ambiental		
PARTE 4 –MDS-UPDRS		
Extração de sangue ou saliva		
Moca		

9.1.2: Evaluation protocol (Chilean version)

NOMBRE:
SEXO:
FECHA DE NACIMIENTO:
CÓDIGO LARGE-PD:

REVISIÓN DEL PROTOCOLO: VERIFICAR LLENADO CORRECTO		
	VERIFICADO	**VERIFICADO POR:**
Firma del consentimiento informado		
PARTE 1 PACIENTES - criterios diagnósticos • Criterios para definir diagnóstico de Enfermedad de Parkinson (bradicinesia, rigidez, temblor en reposo, etc.). **Paso 1. Criterios de inclusión: afectado(a)** **Paso 2. Criterios de exclusión: afectado(a)** **Paso 3. Criterios positivos prospectivos de apoyo de la enfermedad de Parkinson** (Se requieren tres o más para ser elegible para el estudio)		
PARTE 2a -ESCALA Montreal Cognitive Assessment (MOCA)		
PARTE 2B -ESCALA Hoehn & Yahr		
PARTE 3 PROGRESION DE LA ENFERMEDAD **Datos sobre exposición ambiental** Edad de inicio de los síntomas, progresión de la enfermedad, medicación y respuesta al tratamiento.		
PARTE 4 –HISTORIA FAMILIAR (GENOGRAMA) Antecedentes personales y familiares de enfermedades neurodegenerativas, como Parkinson y otras condiciones relacionadas.¿Cuantos miembros de la familia han sido diagnosticados con EP por un médico?		

9.2.1: Informed consent form (Brazilian version)

Projeto de pesquisa: Caracterização clínica de formas monogênicas da doença de Parkinson na América do Sul

Pesquisadores: Paula Saffie Awad e Artur Francisco Schumacher Schuh.
Pesquisador Responsável: Dr. Artur Francisco Schumacher Schuh.
Serviços de Neurologia - Hospital de Clínicas de Porto Alegre.
Telefones para contato: 33598182

O Serviço de Neurologia deste hospital está promovendo o projeto de pesquisa "Doença de Parkinson Monogênica". A doença de Parkinson não tem causa definida na maioria dos casos. No entanto, em alguns pacientes, a doença pode ser causada por alterações no DNA que ocorrem na família. Pacientes podem herdar as alterações diretamente de um familiar com doença de Parkinson ou quando os pais carregam a alteração, mas sem desenvolver a doença. Nesses casos, os pacientes desenvolvem a doença mais jovens.

Este estudo quer identificar possíveis causas genéticas para pacientes jovens e com familiares que apresentam a doença de Parkinson. Encontrar a causa genética para cada pessoa é importante para entendermos melhor a doença e para o paciente entender as chances de passar a doença adiante na sua família.

O estudo envolverá pacientes em atendimento neste hospital que, ou apresentam familiar de até segundo grau com doença de Parkinson, ou iniciaram os sintomas antes dos 45 anos de idade. Consistirá em uma avaliação clínica na consulta e na realização de um exame físico neurológico. Será, ainda, feita uma avaliação com testes de memória e testes para avaliar sintomas depressivos. Toda a consulta levará em torno de 40 minutos.

Em seguida os pacientes serão encaminhados para coleta de sangue (para extração do DNA).

O material genético que sobrar poderá ser conservado (armazenado) ou não, conforme a decisão da cada paciente. O que ficar armazenado poderá ser utilizado em novos exames: estudo de outros genes em novas pesquisas. No caso de serem propostas novas pesquisas com este material, elas serão avaliadas pelos Comitês de Ética em Pesquisa local e nacional, e somente serão realizadas mediante nova autorização do paciente para aquele estudo específico.

Toda a participação neste estudo é absolutamente confidencial (os dados serão utilizados sem identificação do paciente), bem como os resultados da avaliação clínica e dos exames genéticos. É permitida a desistência em qualquer fase da avaliação, sem qualquer tipo de problema para o participante. O presente projeto foi avaliado e aprovado pelo Grupo de

Pesquisa e Pós-Graduação e pelo Comitê de Ética deste hospital. Os pacientes e familiares serão informados dos resultados da pesquisa.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – PROJETO: Doença de Parkinson Monogênica: Prevalência de Genes e Caracterização Clínica das Famílias com Herança Mendeliana

Eu, _____, declaro que fui informado de que participarei do projeto de pesquisa "Doença de Parkinson Monogênica" acima citado. Fui informado de que minha decisão em participar não comprometerá meu tratamento neste hospital, sendo meus dados e resultados de meus testes absolutamente confidenciais. Além disso, fui informado de que a qualquer momento posso desistir do estudo, sem qualquer problema para meu tratamento. Declaro que aceito participar do estudo e que meus dados sejam incluídos na análise coletiva dos resultados sem identificação.

( ) SIM: autorizo manter meu material genético excedente (DNA) armazenado, sabendo que poderá ser usado em meu benefício diagnóstico direto, no futuro, ou para novas pesquisas, das quais serei informado e poderei novamente optar em participar ou não

( ) NÃO: não autorizo armazenar meu material genético após este exame.

Porto Alegre, ___ de _____ de 201__

Ass: _____

( ) paciente ( ) familiar responsável – nome:

9.2.2: Informed consent form (Chilean version)

Estudio Genético para enfermedades Neurodegenerativas. Un estudio multicéntrico en Latinoamérica (Paciente con enfermedad neurodegenerativa)

Usted está siendo invitado a formar parte como voluntario sano en un estudio multicéntrico llamado: "Estudio Genético para enfermedades Neurodegenerativas. Un estudio multicéntrico en Latinoamérica"

Las enfermedades neurodegenerativas tienen muchas causas, muchas de ellas desconocidas. En algunos casos esta causa es hereditaria. En nuestras células se encuentra el ADN, que almacena nuestra información hereditaria, como si fuera una biblioteca que almacena datos y reciben el nombre de genes. Se ha encontrado que cambios o alteraciones en los genes podrían causar estas enfermedades. Por ejemplo, al menos 12 genes causales de formas monogénicas de EP han sido identificados: los genes SNCA, LRRK2 y VPS35 están asociados a formas dominantes, y variantes en los genes PINK1, DJ-1, PRKN, ATP13A2, FBXO7, PLA2G6 asociados a formas recesivas, y formas ligadas a X como variantes en el gen RAB39B.
Nosotros queremos saber si estos cambios (o quizás otros nuevos) en estos genes están presentes en la población Chilena. Este estudio genético se puede realizar tomando una muestra de sangre. Este estudio formará parte de un trabajo de investigación a nivel de Latinoamérica, por lo que se cuenta con el apoyo de instituciones extranjeras. Este estudio investigativo permitirá avanzar en el entendimiento de las causas genéticas de muchas enfermedades neurológicas.

El estudio se realizará de la siguiente manera:

- Usted será atendido/a por un neurólogo que comprobará si puede participar o no en el estudio. Este proyecto de investigación no incluye ningún tipo de tratamiento médico ni remuneración económica. Si después del estudio, usted necesita apoyo médico, necesitará visitar a su médico particular
- Su tratamiento médico seguirá siendo con su doctor, este proyecto no supone ningún tipo de tratamiento o supervisión médica. Cualquier duda sobre el diagnóstico debe ser clarificado por su médico particular.
- En caso de que forme parte del estudio, se le realizará una punción venosa para extraer una muestra de sangre. Durante este procedimiento, puede sentir cierto malestar en el brazo y es posible que aparezca un hematoma local en su brazo que puede durar dos o tres días después de la extracción. Si alguna de estas situaciones ocurre, los investigadores de este estudio podrán asistirle y orientarle.

- Realizará un cuestionario estándar para recoger información sobre sus antecedentes familiares, exposición a distintos factores ambientales, etc, que no llevará más de 20 minutos. Incluido en este cuestionario se incluye una evaluación cognitiva básica (Test de Montreal, MoCA) que tomará alrededor de 10 min.
- Además, se realizará una evaluación neuropsicológica completa con una duración aproximada de 60 minutos. En esta evaluación se explorarán 5 funciones cognitivas: memoria, lenguaje, atención y memoria de trabajo, habilidades visoespaciales y funciones ejecutivas. Estas tareas se realizarán con cuestionarios de lápiz y papel y con la ayuda de un computador.
- Se extraerá ADN de su muestra de sangre y el ADN será almacenado en el laboratorio de Neurogenética del Dr. Ignacio Mata en el Instituto de Medicina Genómica de la Cleveland Clinic en la ciudad de Cleveland, en Ohio, Estados Unidos de América y utilizada para estudiar las características genéticas de los participantes. El análisis de las muestras de ADN se realizarán en colaboración con una institución internacional de gran experiencia en investigación de las causas genéticas de esta enfermedad, el laboratorio de Neurogenética del Dr. Ignacio Mata en el Instituto de Medicina Genómica de la Cleveland Clinic en la ciudad de Cleveland, en Ohio, Estados Unidos de América que coordina el Consorcio latinoamericano para Investigación en Genética de la Enfermedad de Parkinson o LARGE PD. Para ello se mandará una alícuota de su muestra al susodicho laboratorio.
- Le garantizamos el completo anonimato durante todas las fases del estudio.
- Las muestras de sangre no tendrán ningún dato que permita la identificación personal ya que serán codificadas con secuencias de letras y números antes de llegar al laboratorio. Su nombre no aparecerá en ningún informe ni publicación con los resultados de la investigación. Asimismo la custodia de la información recopilada estará a cargo del investigador principal de este proyecto, el Dr. Pedro Chaná en el Centro de Trastornos del Movimiento (CETRAM), Santiago, Chile. Por ningún motivo identificaremos tu nombre en ningún material, y la información documentada será almacenada en un servidor protegido con contraseña, al cual únicamente tendrá acceso el investigador Principal del estudio en Chile, el Dr. Pedro Chaná. La Comisión de Ética del CETRAM ha aprobado la ejecución de este protocolo. Dicho comité aprueba y supervisan los protocolos y estudios de investigación en humanos. Los datos obtenidos serán utilizados en este protocolo y como parte de futuras investigaciones en publicaciones o presentaciones científicas. En este estudio se han adoptado todas las medidas necesarias para proteger la privacidad e intimidad del paciente. También se utilizará una plataforma en línea segura y confidencial que permitirá colectar de forma de-identificada, la información clínica, demográfica y de exposición ambiental, para su uso exclusivo en investigación por el consorcio LARGE-PD, esta plataforma se llama REDCap. Asimismo, la información recabada en esta plataforma y los datos obtenidos como resultado del análisis de estas muestras y los datos asociados (siempre manteniendo el anonimato) también podrían ser

compartidas en bases públicas de acceso restringido como las de los Institutos Nacionales de Salud de los Estados Unidos.

- Las muestras de sangre y de ADN serán utilizadas únicamente para los propósitos de este estudio y nunca serán utilizadas para transacciones económicas o empresariales.
- Los estudios genéticos, especialmente en enfermedades del sistema nervioso, se realizan continuamente en todo el mundo. Cada día se buscan y encuentran genes involucrado en enfermedades neurológicas. Los resultados se verán mejor en el futuro. Por ello le pedimos permiso para que la muestra de ADN obtenida a partir de su sangre se almacene en nuestro laboratorio. El propósito es seguir investigando no sólo en la enfermedad de Parkinson, sino en otras enfermedades neurológicas que pudieran tener una explicación genética. Un Comité de Ética en Investigación siempre evaluará y autorizará cualquier investigación que se realice en el futuro. Si Ud. desea pueda autorizar con su firma su participación en estudios posteriores: Autorizo que mi muestra de sangre sea utilizada en estudios genéticos posteriores relacionados a enfermedad de Parkinson y enfermedades neurológicas.
- Es importante que sepa que su participación es completamente voluntaria, pudiendo negarse a participar en cualquier momento sin que esto implique algún tipo de consecuencias negativas para Ud. también podrá retirarse en cualquier momento de la investigación. Si Ud. decide no participar o retirarse no tendrá sanción ninguna.
- Su participación no implica ningún riesgo físico ni psicológico para usted, sin embargo, si Ud. así lo requiriera a consecuencia de la participación en esta investigación, se garantizará apoyo y orientación psicológica.
- En caso que Ud. sienta que sus derechos fueron vulnerados en cualquier fase del estudio, podrá recurrir al Comite de Etica de Investigacion Servicio de Salud Metropolitano Norte – San Jose 1053, Comuna Independencia, Santiago - Teléfono: +56 25758506 (Presidente Dr. Dr. Juan Silva Solís)
- Usted puede permitir o no el almacenamiento del material genético si este no ha sido utilizado completamente en este estudio. Si no permite su almacenamiento, el material restante será destruido, respetando las normas estándares de deshechos de material biológico.
- Los resultados serán guardados bajo estricta confidencialidad de acuerdo con los criterios establecidos por las buenas prácticas clínicas y la Declaración de Helsinki. Los resultados serán publicados en revistas científicas. Le garantizamos el anonimato durante todos los procesos del estudio.
- Los datos del estudio pueden enviarse o no a una base de datos nacional de información. Aunque intentaremos mantener la confidencialidad de su identidad y de la muestra, existe el riesgo de que alguien pueda identificarle a partir de la información de la base de datos. La muestra puede enviarse o no a un depósito de los Institutos Nacionales de Salud de los Estados Unidos (NIH). El repositorio de los NIH almacena y distribuye muestras y datos asociados de personas con muchas enfermedades. El propósito de enviar sus datos al

repositorio es hacer que los datos estén disponibles para futuras investigaciones por parte de investigadores no involucrados en este estudio. Los investigadores que utilicen los datos del repositorio de los NIH deben solicitar y recibir la aprobación de los revisores científicos de los NIH y de las juntas de supervisión de la investigación de sus instituciones. Estos investigadores podrán utilizar sus datos en la investigación y la enseñanza. Los investigadores de hospitales, universidades y organizaciones comerciales relacionadas con la salud o los medicamentos pueden utilizar los datos para investigar en áreas similares a esta investigación o en otras enfermedades o áreas no relacionadas.

- Los datos, incluyendo los datos genómicos y fenotípicos, del estudio también serán compartidos con el Programa Global de Genética del Parkinson (GP2). Investigadores de todo el mundo están colaborando a través del GP2 para estudiar la genética de la enfermedad de Parkinson. El propósito de compartir sus datos con el GP2 es hacer que los datos estén disponibles para futuras investigaciones por parte de investigadores no involucrados en este estudio. Los investigadores que utilizan los datos de la GP2 deben solicitar y recibir la aprobación para hacerlo de los revisores científicos de la GP2 y de las juntas de supervisión de la investigación en sus instituciones. Puede encontrar más información sobre la GP2 y los investigadores que dirigen el programa en www.gp2.org.
- La información agregada del estudio (incluidos los resultados del resumen genómico) y los análisis del estudio podrán compartirse en la literatura científica o a través de otros recursos científicos públicos que proporcionen un acceso amplio o sin restricciones a la información.
- Usted tiene derecho de no querer ser informado sobre los resultados de su muestra de sangre. En caso de que quiera conocer los resultados, debe informar al investigador en el momento de extraer la muestra de sangre. Los resultados serán enviados a su doctor quien será en responsable de comunicarle los resultados.
- Su identidad nunca será revelada. Solamente los/las investigadores/as responsables del estudio tendrán acceso a sus datos.
- Tiene derecho a conocer los resultados del estudio
- El estudio es completamente gratuito. Usted no tiene que pagar nada por participar ni recibirá ninguna compensación económica.
- En cualquier fase del estudio, usted podrá comunicarse con los/las investigadores/as del proyecto por cualquier duda que pueda surgirle. El investigador principal en Chile es el Dr. Pedro Chaná, al que puede encontrar en el Centro de Trastornos del Movimiento (CETRAM), Belisario Prats 1597, Independencia, Región Metropolitana Santiago, Chile, en el número de teléfono: (2) 2732 1927 y en esta dirección de correo electrónico: pchana@cetram.org

Declaro:

He sido suficientemente informado sobre el contenido que he leído o me han leído y que describe el "Estudio Genético para enfermedades Neurodegenerativas. Un estudio multicéntrico en Latinoamérica". He hablado con el Dr. Pedro Chaná y/o _____ sobre mi decisión de participar en el estudio.

Tengo claros cuáles son los objetivos del estudio, el procedimiento, sus inconvenientes, riesgos, las garantías de confidencialidad. Tengo claro que mi participación es gratuita y que tendré acceso a tratamiento hospitalario en caso de que sea necesario.

Voluntariamente accedo a participar en este estudio y puedo retirar mi consentimiento en cualquier momento antes o durante el estudio, sin que eso conlleve ninguna falta, pérdida de beneficios o perjuicio de ninguno de mis cuidados médicos en el servicio.

Permito el almacenamiento de mi material genético después de la finalización de este estudio. Si autorizo la conservación del material genético, estoy de acuerdo en permitir el uso del material almacenado para un posterior estudio después de la aprobación del Comité de Ética.

(Participante)

Puesto libremente mi conformidad para participar en el estudio

_____ _____ _____

Nombre completo del participante Firma del participante Fecha:

RUN_____

(Director de CETRAM)

El suscrito toma conocimiento del proceso de CI de esta investigación en el nombre del Director de la institución de Salud donde se realizará el estudio:

_____ _____ _____

Nombre completo del Representante Firma del Representante Fecha:

RUN_____

(Investigador)

Declaro que tengo el consentimiento informado del participante o su representante legal para participar en este estudio

_

_____ _____ _____

Nombre completo del Investigador Firma del Investigador Fecha:

RUN_____

9.3 Appendix 3: STROBE Statement— (Genetics of Parkinson's Disease in South America: a cross-sectional pilot study of Southern Brazil and Central Chile)

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	45	Genetics of Parkinson's Disease in South America: a cross-sectional study of Southern Brazil and Central Chile: a cross-sectional pilot study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	47	
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	48	
Objectives	3	State specific objectives, including any prespecified hypotheses	48	
Methods				
Study design	4	Present key elements of study design early in the paper	49	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	49	
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	49	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	50-51	

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	50-51	
Bias	9	Describe any efforts to address potential sources of bias	-	
Study size	10	Explain how the study size was arrived at	49	convenience sampling
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	52	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	52	
		(*b*) Describe any methods used to examine subgroups and interactions	52	
		(*c*) Explain how missing data were addressed	-	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		
		(*e*) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	53	
		(b) Give reasons for non-participation at each stage	-	
		(c) Consider use of a flow diagram	-	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical,	53	

		social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	53-55
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	53-55
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	56
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	57
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	56-57

Generalisability	21	Discuss the generalisability (external validity) of the study results	56-57
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	46

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

9.4. Other publications produced during the Phd

1. Tan, Ai Huey, Paula Saffie-Awad, Artur F. Schumacher Schuh, Shen-Yang Lim, Harutyun Madoev, Azlina Ahmad-Annuar, J. Solle, et al. 2024. “Global Perspectives on Returning Genetic Research Results in Parkinson Disease.” *Neurology. Genetics* 10 (6). https://doi.org/10.1212/nxg.0000000000200213.
2. Pereira GM, Teixeira-Dos-Santos D, Soares NM, Marconi GA, Friedrich DC, Saffie Awad P, et al. A systematic review and meta-analysis of the prevalence of Parkinson’s disease in lower to upper-middle-income countries. NPJ Parkinson's Dis. 2024 Sep 30;10(1):181.
3. Bandres-Ciga S, Faghri F, Majounie E, Koretsky MJ, Kim J, Levine KS, et al. NeuroBooster array: A genome-wide genotyping platform to study neurological disorders across diverse populations. Mov Disord [Internet]. 2024 Sep 16; Available from: https://movementdisorders.onlinelibrary.wiley.com/doi/abs/10.1002/mds.29902
4. Tan AH, Cornejo-Olivas M, Okubadejo N, Pal PK, Saranza G, Saffie-Awad P, et al. Genetic Testing for Parkinson’s Disease and Movement Disorders in Less Privileged Areas: Barriers and Opportunities. Mov Disord Clin Pract. 2024 Jan;11(1):14–20.
5. Mata I, Salles P, Cornejo-Olivas M, Saffie P, Ross OA, Reed X, et al. LRRK2: Genetic mechanisms vs genetic subtypes. In: Handbook of Clinical Neurology. Elsevier; 2023. p. 133–54.
6. Saffie P, Chaná-Cuevas P, Mata I. Revolución genética: apertura a nuevos desafíos y oportunidades. Revista médica de Chile. 2023;
7. Alosco, M, Hutchins, E. Saffie Awad, P, et al. Getting Started With Parkinson’s Disease Data [Internet]. Available from: https://zenodo.org/records/11167238
8. Saffie P, Baker B, Billingsley KJ. Protocol: Purification of DNA from Whole Blood using the QIAamp Blood Midi Kit (Spin Protocol) + QC with Qu. 2024 Mar 6 [cited 2024 May 31]; https://www.protocols.io/view/protocol-purification-of-dna-from-whole-blood-usin-n92ldmx3ol5b/v1