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The *LRRK2 G2019S* mutation in a series of Argentinean patients with Parkinson's disease: Clinical and demographic characteristics

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HIGHLIGHTS

- The overall prevalence of *LRRK2 G2019S* mutation in this series was 5.45%.
- No R1441G substitution was identified in this series.
- PD in *LRRK2* mutations carriers was indistinguishable for the idiopathic PD.
- Systemic imnuno-mediated disorders were identified in 2 of 3 G2019S carriers.

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ABSTRACT

Objectives: To determine clinical characteristics and frequency of leucine-rich repeat kinase 2 gene (*LRRK2*) mutations in a cohort of patients with Parkinson's disease (PD) from Argentina.
Background: Variation in the *LRRK2* gene represents the most common genetic determinant of PD, only few data are available from Latin-America.
Design/methods: Informed consent was obtained and all studies were approved by the Institutional Review Boards. Fifty five consecutive PD patients were recruited. A structured interview and neurological examination were used to collect demographic and clinical information. Blood samples were obtained and DNA extracted from patient venous blood. All *LRRK2* exons from 25 exon to 51 exon were screened in all patients.
Results: Clinical and molecular data of 55 patients with PD were analyzed. Mean age was 68.8 ± 10.6 years. Jewish and Basque ancestries were found positive in 9 and 7 patients, respectively; family history of PD was identified in 16 patients. The *G2019S* mutation was present in 3 Ashkenazi Jewish subjects (5.45%); all of them reported family history of PD in first-degree relatives. Although Argentina possesses one of the most important Basque communities outside Spain, non *R1414G* mutation was identified in this cohort. Eleven single polymorphisms (SNP) were identified in this cohort. The mean age at onset was higher in *G2019S* mutation carriers than non-carriers (66.67 vs 58.78 years). Asymmetrical tremor as initial symptom and non-motor symptoms occurred at similar frequencies in both groups. The *G2019S* mutation carriers showed a non significant increase in dyskinesias, and 2/3 developed Dopamine Dysregulation Syndrome and visual hallucinations. Systemic disorder identified in *G2019S* mutation carriers included: celiac disease, hypothyroidism, Hashimoto's Thyroiditis and arterial hypertension.
Conclusions: The prevalence of *LRRK2 G2019S* mutation in this Argentinean cohort was similar to other international series, with a higher prevalence in Ashkenazi Jewish. The phenotype was indistinguishable from patients with idiopathic PD. Interestingly, we identified immune mediated disorders in two PD

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patients carrying the *G2019S* mutation. Within this context, recent studies have identified full-length *LRRK2* as a relatively common constituent of many cell types in the immune system including human peripheral blood mononuclear cells. Nevertheless, a casual association could not be excluded and the analysis of more extensive series is required.

1. Introduction

Mutations in the leucine rich repeat kinase 2 gene (*LRRK2*) are considered to be the most frequent monogenic cause of Parkinson disease (PD) [13] and are responsible for 5% familial and 1–2% sporadic PD, approximately, in North American and in most European populations studied [9,12]. Among the different pathogenic *LRRK2* mutations, a glycine to serine substitution located in the highly conserved kinase region of exon 41 (*G2019S*) has been reported as the most common substitution in individuals from Southern Europe and North Africa, accounting for ~20% and up to 40% respectively in these populations [4,6]. On the other hand, the *LRRK2 R1441G* substitution has been observed to be more prevalent in the Basque region of Northern Spain, where it is found in 46% of familial PD and in 2.5% of sporadic PD [21]. Although the penetrance of *LRRK2 G2019S* mutation is clearly incomplete, the phenotype of *LRRK2*-associated PD has been described as indistinguishable from idiopathic PD (iPD) with minor exceptions, including motor and non-motor symptoms [1,9,14,22].

Different genetic studies conducted in our country showed that the average genetic structure of Argentine population contains up to 78% European ancestry [2,7,16], probably as a result of great influence of Spain during the colonial period and the "great European immigration wave" (in the majority of cases from Italy and Spain) during the late 19th and early 20th centuries. Based on that, we hypothesized that occurrence of *G2019S* and *R1441G LRRK2* substitutions in Argentinean individuals could be similar to the previously mentioned European countries.

Data about the prevalence and phenotype of *G2019S* and *R1441G LRRK2* mutations in Latin American and specifically in Argentinean PD patients still scarce [15,17,20,23]. Herein, we conducted the present study to assess the frequency of *LRRK2* mutations (exons: 25–51) in a cohort of patients with PD from Argentina, and to determine clinical characteristics of *LRRK2* mutation carriers.

2. Subjects and methods

The study was approved by the Institutional Review Board (IRB) and local ethics committee.

After signing a written informed consent, 55 consecutive PD patients from 2 Argentinean (Buenos Aires) Movement Disorder Units were recruited between January 2007 and December 2007. Since pathogenic *LRRK2* mutations are clustered among the last five functional domains of dardarin, all patients were screened for mutations within exons 25–51 of the *LRRK2* gene. Genomic DNA was isolated from peripheral blood using standard methods and the mutation screening was performed as previously described [18,19]. Patients were examined by a neurologist specialized in movement disorders. Family history, ethnic and ancestry data were collected. Ashkenazi or Basque ancestries were established by questions about the patients' ancestors' places of birth up to the third generation. Patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for PD; secondary or atypical Parkinsonisms were excluded.

A comprehensive neuropsychological examination was conducted in *LRRK2* mutation carriers, including the following tests: Folstein Mini Mental Status (MMSE), Signoret's memory battery, Trail Making Test-form A (TMT-A) and B (TMT-B), the Digit Span subtest from the Wechsler Adult Intelligence Scale III and the "7-subtraction task" from the Mini Mental State Exam.

The Trail Making Test-form B (TMT-B) and the phonological fluency task were used as measures of executive functioning. In order to avoid any motor confounds on the TMT, a difference score was obtained by subtracting time to perform Part A from time to perform Part B (TMT B-A). This score is considered a purer indicator of executive function.

Every test score was converted to *Z*-score based on the performance of normal control subjects. The executive function score consisted of the mean *Z*-score of performance on TMT B-A and on phonological fluency.

Additionally, social cognition tasks related to Theory of Mind (ToM) were assessed: Faux Pas test (FPT), which evaluates hurtful or insulting social situations and Reading the Mind in The Eyes (RMTE) that was used to assess emotional inference.

3. Results

LRRK2 sequencing was performed in 30 women and 25 men with PD, mean age 68.8 ± 10.6 years (range 44–88 years). Sample composition included 9 Ashkenazi-Jewish patients.

Familial PD (first or second degree relative affected) was reported in 16 patients (29.09% of PD patients); amongst these patients 4 reported Ashkenazi-Jewish ancestry, and 3 Basque ancestry. Clinical and demographic data of the analyzed population are present in Table 1.

The *LRRK2 R1441G* substitution was not present in the population analyzed. And only the *LRRK2 G2019S* mutation and 11 non-pathogenic single nucleotide polymorphisms (SNPs) were identified in this series. Among the familial PD cases, 3 unrelated individuals were found to be heterozygous *G2019S* mutation carriers. It represents the 18.75% of familial cases, 33.33% among patients with Ashkenazi-Jewish ancestry and the 5.45% of the overall analyzed population. All of them had positive family history of PD (Fig. 1) and Ashkenazi-Jewish ancestry with a median age of onset of the disease of 66.67 years (range 65–69), median disease duration of 16 years (range 14–19) and a Hoehn and Yahr scale ranging between 3 and 5. The most frequent symptom at onset in

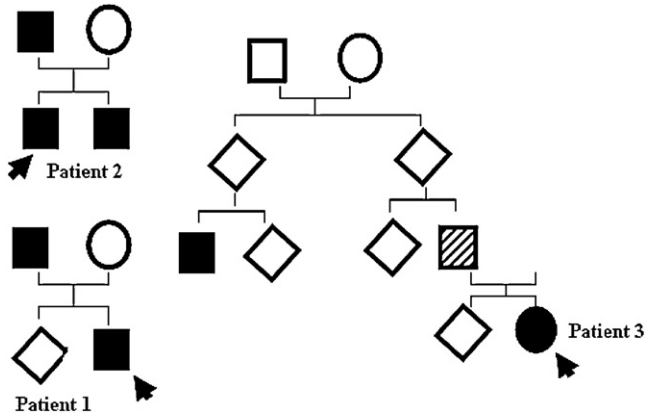

Fig. 1. Pedigrees *of LRRK2 G2019S* mutations carriers. Filled square, circle or diamond = PD; striped = family data about PD were reported indirectly by other family's members.

Table 1
Clinical and demographic characteristics of PD patients. Ref.: AJ: Ashkenazi-Jewish.

	LRRK2 G2019S Carriers	*LRRK2* Non carriers	*p* value
Age at onset, means (SD)	66.67 ± 4.04	58.78 ± 12.45	NS
Age at examination	79.33 ± 2.52	68.19 ± 10.61	0.0353
Disease duration	14.67 ± 2.51	8.94 ± 6.38	NS
Education (university)	2/3	13/47	NS
Female	1/3	29/52	NS
AJ ancestry	3/3	6/42	0.0003
Family history of PD	3/3	13/50	0.0067
Family history of PD in AJ individuals	3/3	1/6	0.0177
Report of hallucinations	3/3	12/48	0.0057
Rest tremor as presenting symptom	2/3	30/48	NS
Motor fluctuations	3/3	31/48	NS
Non motor fluctuations	1/3	16/43	NS

mutation and non mutation carriers was asymmetrical tremor. The sustained L-Dopa response and occurrence of motor fluctuations were similar between the two PD groups (with and without mutation).The mean age at onset was higher in *G2019S* mutation carriers than non-carriers (66.67 vs 58.78 years). Asymmetrical tremor as initial symptom and non-motor symptoms occurred at similar frequencies in both groups. The *G2019S* mutation carriers showed a non significant increase in peak of dose dyskinesias; 2/3 developed dopamine dysregulation syndrome, and all of them reported benign visual hallucinations. At the moment of the present study, executive functions and Theory of Mind (ToM) abilities were evaluated exclusively in *LRRK2 G2019S* mutation carriers: MMSE was abnormal in one patient (MMSE < 24/30). In the other two patients, the extensive neuropsychological battery showed ToM impairment. Clinical and demographic data of PD patients carrying the *LRRK2 G2019S* mutation are shown in Table 2. These patients did not differ clinically from non carriers. Brain MRI of the three patients showed cortical atrophy, gliotic ischemic lesions and leukoaraiosis.

Curiously, two out of these three *LRRK2 G2019S* mutation carriers presented immune mediated disorders: celiac disease (CD) plus hypothyroidism in one patient, and Hashimoto's Thyroiditis in the other one.

One carrier died after 15 years of PD, pathological investigations could not be available.

4. Discussion

The present study represents the first screening focused on identification of the *LRRK2 G2019S* mutation in a series of PD patients from Argentina. Although, heterozygous *LRRK2 G2019S* mutation represents a common monogenic cause of familial and sporadic PD cases regardless of geographic origin and ethnicity [13,18], data about the frequency of this mutations in Latin America countries are scarce [15,17,20,23] and this study contributes to increase our knowledge about this specific mutation in our country.

Herein, *LRRK2 G2019S* mutation was identified in 5.45% of overall PD patients and in 18.48% of familial PD. In our series, non sporadic cases were identified, but it could be related with the small sample analyzed.

Interestingly, these results are in order to that reported in Uruguayan PD patients with an overall estimated frequency of 4.0% and a familial occurrence of 20% [15]. Moreover, both populations reported a higher frequency of a positive family history in the total PD patients (23.2% in the Uruguayan sample and 29.0% in the Argentinean series). Taking into account that both countries possess a similar population composition (with European ancestry, particularly represented by Italian and Spanish people), the similar data observed in both populations contribute to support our results even though our small sample size [15].

On the other hand, our prevalence appears to be higher than the previously reported from others countries of Latino-America such as Chile, Brazil or Peru where the overall prevalence has been estimated of 3% in Chilean PD patients, <2% in those from Brazil and 0.4% in Peruvian population. The discrepancy of frequency, particularly with respect to the Peruvian PD patients may be explained by the influence of Amerindian population, which is extremely rare in the Argentinean population [15,16].

Unexpectedly and despite the high contribution of Spain and Italy to the Argentinean population composition, (≅80% of Argentinean population possesses European ancestry), the overall frequency in our series was higher than it was reported in Italy (2.1–2.9%), and Spain (2.2–7.6%) [6,19].

Moreover, despite the extensive Basque community living in Argentina (around 10% of the Argentine population is of Basque descent) *LRRK2 R1441G* substitution was not present in the population analyzed. Although, these findings agree with the hypothesis of a restricted occurrence of *LRRK2 R1441G* substitution in northern regions of Spain or in restricted areas from Italy [6,21], larger studies are required to confirm this hypothesis.

As in other series, clinical symptoms among *LRRK2 G2019S* mutation carriers were indistinguishable from idiopathic PD, with a typical L-Dopa responsive PD, mild symptoms, slow progression and long disease duration (≅20 years). Nevertheless, as an interesting observation, two of our three patients showed immune mediated disorders.

Although, the pathophysiologic mechanism of *LRRK2*-related mutations is still unknown, *LRRK2* activity does not appear to be restricted to CNS, since sequence variants at or near the *LRRK2* locus have been associated with susceptibility not only to PD but also to Crohn's disease and leprosy [10,24]. Several lines of evidence support the role of inflammation in PD with microglial activation and lymphocytes infiltration [10]. In line with this observation, the full-length LRRK2 has been identified as a relatively common constituent of many cell types in the immune system including human peripheral blood mononuclear cells, and additional experimental studies suggest that it plays an essential role in lysosomal autophagy outside the nervous system [10,24]. Based on these evidences, we could hypothesize about a possible link between *LRRK2* mutations and autoimmune disorders occurring in our patients. This hypothesis could be supported by recent GWAS that confirms a strong influence of *LRRK2* mutation and *HLA* genes in PD [11,13].

Nevertheless, previous epidemiological studies failed to demonstrate a statistically significant association between CD (estimated prevalence in Argentina 0.22%) and PD, since up to 10% of patients with CD could express other neurological symptoms [3,8]. Moreover, the prevalence of thyroid autoimmunity in PD patients was reported similar to that as described in the general population (10.8% in PD patients vs 10% in controls) [5].

Beside those observations, we could not exclude a hazardous co-occurrence of these entities. To the best of our knowledge, our

Table 2
Clinical and demographic information from *LRRK2* mutation carriers. M: male; F: female; ToM: Theory of Mind; NA: not applicable. In patient 1 additional tests were not performed because MMSE < 24.

	Birth date/sex	Symptoms at onset	Neuropsychological examination					ToM	Education years	Immune-mediated disorders	Others disorders
			MMSE	Executive function	Attention	Language	Memory	ToM			
1	1925/M	Pain	<24	NA	NA		NA	NA	18	NA	Coronary heart disease
2	1930/M	Tremor	>24	0.84	0.36	0.62	−1.54	−4.88	18	Celiac disease, anti-tissue transglutaminase, endomysial antibodies and small bowel positive biopsy, hypothyroidism.	Osteopenia/diabetes type II
3	1928/F	Tremor	>24	−1.37	−0.89	−0.34	0.32	−4.14	7	Hashimoto's Thyroiditis; anti-microsomal fraction autoantibodies: 1/102,400).	Osteopenia/blood hypertension.

study is the first to focus and report the occurrence of CD and Hashimoto's thyroiditis in PD patients carrying the *LRRK2 G2019S* mutation. Therefore, we strongly believe that the contribution of these immune-related disorders in the PD pathogenesis is worth of exploring.

One of the limitations of the present study is the absence of a control series, and small size of sample restricted to one specific area of the country. Nevertheless, this is the first clinical data available from Argentinean PD patients, and the frequency observed in this series was similar to that reported in other South American countries with a similar population composition such as Uruguay [15].

In summary, the prevalence of *LRRK2 G2019S* mutation in this Argentinean cohort was similar to other international series, with a high prevalence of Ashkenazi Jewish, and the phenotype was indistinguishable from patients with idiopathic PD. One condition to highlight in these *LRRK2 G2019S* mutation carriers is the association identified among immune-related disorders and PD pathogenesis. However, we concluded that extensive epidemiological studies with a larger number of patients are required to determine the ultimate proof of the association between *LRRK2*-associated PD and immune mediated diseases. These epidemiological studies will allow the identification of environmental and/or additional genetics factors that could modulate the expression, penetrance and phenotype of PD.

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