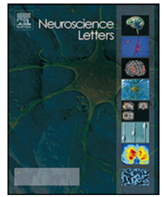
Neuroscience Letters 469 (2010) 155–158

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



PINK1 polymorphism IVS1−7 A → G, exposure to environmental risk factors and anticipation of disease onset in Brazilian patients with early-onset Parkinson's Disease

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ARTICLE INFO

Article history:
Received 10 October 2009
Received in revised form
19 November 2009
Accepted 21 November 2009

Keywords:
PINK1
Early-onset Parkinson's Disease
Environmental exposure
Disease modifier

ABSTRACT

Parkinson's disease (PD) etiology has been attributed both to genetic and environmental factors, although the exact mechanisms of its pathogenesis remains elusive. We investigated Brazilian early-onset PD (EOPD) patients with *PINK1* polymorphisms (SNPs) in order to find possible correlations between SNPs, environmental exposure, and disease age of onset. We enrolled 48 patients and 61 controls. *PINK1* SNPs and environmental exposure (living in rural areas, well-water drinking, exposure to pesticides, herbicides and organic solvents and smoking) were investigated in both groups. We divided our group of patients into four subgroups, according to the presence/absence of *PINK1* SNP IVS1−7 A → G and the presence/absence of environmental factors exposure. We found a significant decrease (ANOVA test: $p = 0.02$) of age at disease onset in those patients that had the IVS1−7 A → G SNP and were exposed to environmental risk factors. Our data suggest that the interaction of *PINK1* SNP IVS1−7 A → G and environmental risk factors together have an important role in EOPD: each of them individually has a minor influence, whereas their interaction is associated with a significant effect in anticipating the disease clinical onset.
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The pathogenesis of Parkinson's disease (PD) remains unclear, despite being the subject of many studies. Most cases of PD may have multifactorial etiologies, involving both genetic and environmental elements [15].

Environmental factors such as rural living, well-water drinking, exposure to pesticides, herbicides, and organic solvents have been implicated in the etiology of PD [9]. Whether they act as causal agents or risk factors for subjects with genetic susceptibility to PD has not been completely clarified. *PINK1* mutations represent a very rare monogenic form of PD and seems to play a role in sporadic or familial EOPD [12,11]. Different studies attempted to associate *PINK1* single nucleotide polymorphisms (SNPs) to PD [7,2,14]. SNPs may lead to slight alterations in *PINK1* gene, and act as a risk factor for the development of PD. It seems that these SNPs do not play a major role in EOPD [7,2], but may be important in sporadic cases of LOPD [14].

Nevertheless, it remains unknown whether SNPs in the *PINK1* gene may influence the clinical presentation of EOPD patients when associated to environmental risk factors. We aimed to address this question evaluating a group of Brazilian EOPD patients.

We prospectively and consecutively enrolled sixty unrelated EOPD Brazilian patients. The control subjects were sixty-one unrelated individuals from the same geographic region and paired by disease age of onset in patients' group. The vast majority of the individuals were from the urban living area of São Paulo, Brazil. Ancestry was assigned according to subjects' information and adjustments for relevant axes of ancestry that varied between the study populations were performed. None of the controls had a clinical evidence of neurological disease or family history of neurodegenerative disorders.

We enrolled PD patients who fulfilled the clinical criteria of the UK Parkinson's Disease Society Brain Bank Criteria. EOPD was considered when age at disease onset was below 50 years. All patients were recruited at the movement disorders outpatient clinic of the Universidade Federal de São Paulo and from movement disorder specialists at Hospital Israelita Albert Einstein between 2004 and 2008.

All patients had already been screened for the presence of mutations in the *PARK2* and *LRRK2* genes [1]. Twelve patients were excluded from our study because they already presented mutations either in *PARK2* or *LRRK2* genes.

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doi:10.1016/j.neulet.2009.11.064

Table 1
Polymorphisms in PINK1 gene*.

Exon	Nucleotide change	Aminoacid change	PD patients (N = 48)	Controls (N = 61)	p-Value#
2	IVS1−7 A → G		15 (31.3%)	24 (39.4%)	0.4
4	C879A(Hom)	V293V	1 (2.1%)	2 (3.3%)	0.8
5	IVS4 −5 G → A		1 (2.1%)	1 (1.6%)	0.6
6	IVS6+43 C → T		1 (2.1%)	0	0.9
6	C1230T(Hom)	A410A	1 (2.1%)	0	0.9
8	A1562T(Het)	N521T	1 (2.1%)	1 (1.6%)	0.6
8	3′+36 A → T		1 (2.1%)	0	0.9

* Nucleotide and protein changes are in accordance with the nomenclature guidelines available from the Human Genome Variation Society (HGVS). The A of the translation initiation codon ATG is designated base 1. Het, heterozygous; Hom, homozygous.
# Chi-square test with Yates' correction.

Our patients had also been screened for the presence of *PARK2* SNP Val380Leu, which was considered a disease modifier when interacting with an environmental factor, well-water drinking. Patients with at least one Leu allele showed a later age of onset, suggesting this allele might have a protective effect in the presence of an environmental putative risk factor. Only four patients of our group presented this SNP. On the other hand, eleven patients presented *PARK2* Val380Val, which was related to an earlier age of onset [1].

All experiments were conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written consent of the subjects, approved by review board of our institution.

Patients and controls underwent an interview and a physical exam, including Unified Parkinson's Disease Rating Scale (UPDRS) and Hohen and Yahr scale. The following clinical data were assessed: gender; age of onset; age at current evaluation; disease course.

Exposure to environmental risk factors (living in rural areas, well-water drinking, and exposure to pesticides, herbicides or organic solvents) was defined as household contact or occupational exposure to a given factor for at least two continuous years on a regular basis, at a minimum frequency of 1 day per month. Environmental factors known to induce cytotoxicity due to oxidative stress (pesticides, herbicides, and organic solvents) were analyzed in a single group. Smoking is considered an environmental protective factor for PD and we measured exposure when used for at least two continuous years on daily use.

Genomic DNA was extracted from peripheral whole blood using the Puregene® DNA Purification kit (Gentra Systems) or cheek swab using the ChargeSwitch gDNA Buccal Cell kit® (Invitrogen). DNA was amplified by PCR (primers and conditions available upon request). All eight *PINK1* exons and exon-intron boundaries were screened by standard dideoxy nucleotide sequencing on a MegaBACE 1000 DNA Sequencer (Amersham Biosciences).

Table 2
Allele and genotype frequencies of SNP IVS1−7 A → G*.

Nucleotide change IVS1−7 A → G	PD patients (N = 48) 15 (31.3%)	Controls (N = 61) 24 (39.4%)	p-Value#
Exon **2**			
Allele A	81	98	0.6
Allele G	15	24	
AA	33	37	0.34
GG	15	24	

* Nucleotide and protein changes are in accordance with the nomenclature guidelines available from the Human Genome Variation Society (HGVS). The A of the translation initiation codon ATG is designated base.
# Chi-square test.

Statistical analysis for continuous variables and comparisons between subgroups were performed by ANOVA test with Newmann–Kealls pos hoc test; for categorical variables, comparisons between groups were performed using the Chi-square test. Significant values of p were set at <0.05. Parametric data is presented as mean ± standard deviation (SD). The statistical analyses were performed using software Prism 3.0.

After excluding mutations either in *PARK2* or *LRRK2* genes in our initial group of sixty patients, forty-eight remained for the genetic analysis. We did not find *PINK1* mutations. Table 1 summarizes our finding of SNPs in patients and controls.

Fifteen patients (31.3%) and twenty-four controls (39.4%) presented PINK1 SNP IVS1−7 A → G. This polymorphism was in Hardy–Weinberg equilibrium in both groups. We did not find a difference either for allele or genotype frequencies between cases and controls Table 2.

We observed exposition to environmental factors in 26 patients (54.2%) and in 30 controls (49.2%), p = 0.6. Among those who were exposed to environmental factors, the majority were exposed to rural living or well-water drinking during their first and second decades of life. Exposure to other agents (pesticides, herbicides, or organic solvents) and smoking occurred mainly during the second and third decades of life. There was not a significant difference

Table 3
Exposure to environmental factors.

	EOPD patients (N = 48)	Controls (N = 61)	p-Value*
	Mean exposure period and range in years	*Mean exposure period and range in years*	
Smoking	13 out of 48 (27.1%) *14 (5–25)*	14 out of 61 (22.9%) *14.3 (5–27)*	0.8
Rural living	10 out of 48 (20.8%) *13 (2–30)*	8 out of 61(13.1%) *8.6 (2–17)*	0.4
Well-water drinking	19 out of 48 (39.6%) *14.5 (3–39)*	14 out of 61 (22.9%) *11.8 (2–18)*	0.06
Other agents	6 out of 48 (12.5%) *12.6 (4–30)*	2 out of 61(3.3%) *10 (5–15)*	0.06

* Chi-square test with Yates' correction.

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