Novel Nurr1 point mutations identified in ethnic Chinese patients with Parkinson's disease

Weidong Le, MD, PhD[4*], Ming Ming, PhD1, Liu HM, MS[1], Pingyi Xu, MD, PhD[2] and Hao Deng, PhD[3]

[1]Neurology, Ruijing Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;
[2]Neurology, 1[st] Hospital, Sun Yat-san University, Guangzhou, China
[3]Center for Experimental Center, 3[rd] Xiangyan Hospital, Center South University, China
[4]Neurology, Baylor College of Medicine, USA

Abstract

NR4A2 (also known as Nurr1) is a nuclear transcription factor important for the differentiation and survival of midbrain dopaminergic neurons. Recently it has been reported several mutations in this gene associated with Parkinson's disease (PD) in Caucasian population, suggesting that Nurr1 may play a role in the cause and pathogenesis of PD. The genetic study in ethnic Chinese is still lacking. To address this issue, we performed a mutation screen of Nurr1 in 679 PD patients and 689 control subjects in Chinese population, and identified a new single nucleotide polymorphism (SNP) -35 A-G located in exon2 and two novel heterozygous mutations (711C-A, -21 C-G) located in exon3 and in exon2, respectively. The case-control study results suggest that the 711C-A and 21 point mutations are specific for PD while -35 A-G variant in exon2 may protect the carrier from the risk of PD. We identified novel mutations of Nurr1 in ethnic Chinese population for the first time. The results from this study further support the notion that Nurr1 might be associated with PD.

Objective

To identify whether there is any mutations in NR4A2 gene associated with Parkinson's disease in ethnic Chinese population.

Background

NR4A2 (Nurr1) encodes a transcription factor regulating the expression of genes including tyrosine hydroxylase and is requiredfor the differentiation/maintenance of nigral dopaminergic neurons. The human Nurr1 gene maps to chromosome 2q22-23 and is about 8.3 kb long and consists of eight exons. Several mutations have been identified in exon1, exon3, and intron6 in PD patients and these observations suggest that Nurr1 Recently it has been reported several mutations in this gene including that were identified in exon1, exon3, and intron6 in PD patients associated with Parkinson's disease (PD) in Caucasian population, suggesting that NR4A2 may play be a potential candidate gene for PD susceptibility. The genetic study in ethnic Chinese is still lacking..

Materials and Methods

Patients and Controls: In this study, 689 patients with sporadic and familial PD were included. All the ethnic Chinese patients signed an informed consent, which was approved by our three collaborator's Institutional Review Board for Human Research. Among the research subjects, 656 patients are sporadic PD and 33 patients have at least one relative with PD. The age ranged from 21 to 91 years with a mean of 64.0 ± 10.6 years and the onset of disease ranged from 15 to 78 years with a mean of 61.7 ± 11.8 years. A total of 431 PD patients were men, whereas 268 patients were women. 689 healthy controls with the age, sex, and origins similar to the PD patients were also collected.

Mutational analysis: We designed primers amplifying the whole exon regions of Nurr1 (Bio-Rad iCycler Optical Module). The PCR product was then purified by a purification kit (Sangon, Shanghai, China) and then sequenced using an ABI 3730 automated DNA sequence (Applied Biosystem, Foster city City, CA).

Statistics: The software SPSS 13.0 was used for statistical analysis. Data were analyzed by means of the Pearson's chi-square test. Relative risk for the variants was calculated by the odds ratio (OR) for the disease. Data were expressed as mean±SEM. Statistical significance was considered at the P < 0.05 level.

Results

Table 1. The demographic information of the Chinese population screened in the Nurr1 gene mutational analysis

Samples	Total number	Mean age ± st. dev. (range, yr)	Mean age of onset ±st. dev. (range, yr)	Gender		Faminlial History		Age at onset (yr)	
				Male	Female	Familial PD	Sporadic PD	young onset PD (< 50 yr)	late onset PD (≥50 yr)
PD	689	64.0 ± 10.6 (21-91)	61.7 ± 11.8 (15-78)	431	268	33	656	197	492
Control	672	62.7.6±11.8 (25-92)	ND	365	314	ND	ND	ND	ND

PD: Parkinson's disease; ND: None Done

Table 2. Clinical data of PD patients and control individuals

Study ID	PD/Con	Gender	Age (yr)	Diseases duration (yr)	Family history of PD	Resting tremor	Rigidity	Bradykinesia	Postural instability	Asymmetric onset	Hyperreflexia	Diurnal fluctuations	Cognitive decline	Dyskinesia	Response to levodopa
M253	PD	M	61	1	None	+	+	+	+	+	+	+	-	-	Good
M1021	PD	M	72	1	Yes	+	+	+	+	+	+	+	+	+	Good
P27	PD	M	63	2	None	+	+	+	+	+	+	+	-	-	Good
P54	PD	M	71	1	None	+	+	+	+	+	+	+	-	-	Good
C13	Con	M	70												
C52	Con	M	70												
C77	Con	M	65												
C78	Con	M	53												
C79	Con	M	59												

F: Female; M: Male; Con: Control;

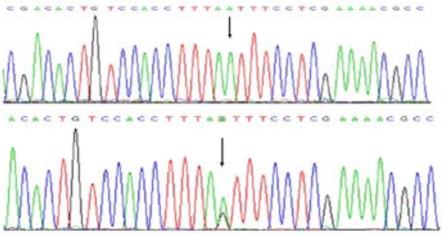

Figure 1. lAnalysis of the 711C-A mutation in exon3 in patients with PD. The panel above showed the DNA sequence of control. The other panel showed the DNA sequence of PD patients carrying the 711C-A mutation. Arrows showed the position of the mutation.

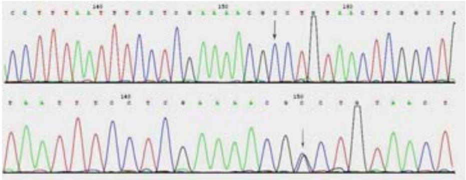

Figure 2. Analysis of the -21 C-G mutation in exon2 in patients with PD. The panel above showed the DNA sequence of control. The other panel showed the DNA sequence of PD patients carrying the -21 C-G mutation. Arrows showed the position of the mutation.

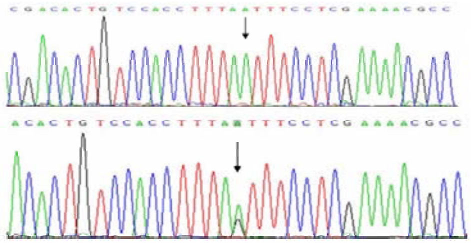

Figure 3. Analysis of the -35 A-G SNP in exon2. The panel above showed the DNA sequence of control. The other panel showed the DNA sequence of PD patient and control subjects carrying the -35 A-G mutation. Arrows showed the position of the mutation.

Table 3. Association of Nurr1 mutation/SNP with Parkinson's disease

Genotype	Location	Carriers No./total No.		Chi-square analysis			
		PD	Control	Chi-square	p-Value	OR	95%CI
711 C-A	Exon3	2 /689	0/679	1.954	0.162	1.003	0.999-1.007
-21 C-G	Exon2	1 /689	0 /679	0.976	0.323	1.001	0.999-1.004
-35 A-G	Exon2	1 /689	5 679	2.78	0.095	0.194	0.023-1.664

No. :Number; OR:Odd Ratio

Conclusions

Our data support the notion that Nurr1 mutations are a rare cause of PD in Asian cohort as well as in Caucasian PD patient, and some other kind of Nurr1 mutation likely displayed protective effect. Indentifying the new mutation and greater understanding of the novel mutation will shed light to the study of pathogenesis of PD, and help us to develop new strategies against neurodegenerative diseases.

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