Transcription Factor PITX3 Gene in Parkinson's Disease

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Abstract

PITX3 is a transcription factor important for the differentiation and survival of midbrain dopaminergic neurons during the development. Single nucleotide polymorphisms (SNP) in the gene may be associated with Parkinson's Disease (PD). To verify their findings and to determine the nature of the association in a subset of our PD patients we have analyzed two *PITX3* SNPs (rs2281983 and rs4919621) in PD patients and age-matched health controls. Our data show that the substitutions of C/T in SNP1 and A/T in SNP2 are significantly higher in PD, and this finding is even more robust in young onset and familial PD as compared with age-matched healthy controls. Our findings indicate that *PITX3* may play a role in the pathogenesis of PD.

Material and Methods

Patients: 265 North American Caucasian PD patients and 210 healthy controls from the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC), Baylor College of Medicine (BCM). All research subjects signed an informed consent, approved by BCM institutional Review Board for Human Research. PD samples were subcategorized into EOPD, LOPD, familial PD and sporadic PD.

Data Table 1.

Allele	Controls	Total PD	EOPD	LOPD	fPD	sPD
N (allele)	420	530	162	368	196	334
Gender M/F	101/109	143/122	41/40	102/82	53/45	90/77
Age	57.92±13.87	59.18±12.62	44.91±9.08	64.86±14.17	54.74±15.92	62.24±12.80

PCR: Genomic DNA was extracted from peripheral blood using standard protocols. PCR products of PITX3 were amplified with the following primers:

rs2281983	Forward	5'-CGGGTCTGGAGAGCATACC-3'
	Reverse	5'-GACGGTTCGCTGAAAAAGAA-3'
rs4919621	Forward	5'-CTGATCCTTCCAAACCCTGA-3'
	Reverse	5'-AGATGAGGGGGCCTTTTAGA-3'

Statistics: Pearson's $\chi 2$ tests were applied to test for significance in differences of gene frequencies. A value ($p < 0.05$, two-tailed) was considered to be significant.

Results

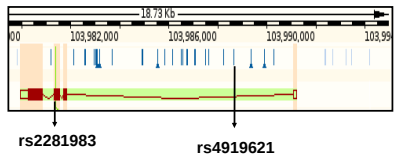

Figure 1. The gene loci of SNP1 rs2281983 and SNP2 rs4919621

Allele	Controls	Total PD	EOPD	LOPD	fPD	sPD
rs2281983						
T	248 (0.590)	271 (0.511)	78 (0.481)	193 (0.524)	89 (0.454)	182 (0.545)
C	172 (0.410)	259 (0.489)	84 (0.519)	175 (0.476)	107 (0.546)	152 (0.455)
Empirical-P		0.035	0.038	0.131	0.005	0.291
Adjusted OR* (95%CI)	Reference	1.34 (1.03-1.74)	2.05 (1.33-3.16)	1.24 (0.92-1.68)	1.72 (1.22-2.43)	1.18 (0.88-1.59)

	p-Value[a]	p-Value[b]	p-Value[c]	p-Value[d]	p-Value[e]
C allele:	0.015	0.018	0.063	0.002	0.209

Data Table 2. Gender: male vs female (M/F); Age: Mean±SD; Significant ($P < 0.05$)

P-Value a : All PD when compared to controls
P-Value b : EOPD when compared to controls
P-Value c : LOPD when compared to controls
P-Value d : fPD when compared to controls
P-Value e : sPD when compared to controls
*: adjusted by sex and age

Allele	Controls	Total PD	EOPD	LOPD	fPD	sPD
rs4919621						
T	268 (0.638)	294 (0.555)	87 (0.537)	207 (0.562)	103 (0.525)	191 (0.572)
A	152 (0.360)	236 (0.445)	75 (0.463)	161 (0.438)	93 (0.475)	143 (0.428)
Empirical-P		0.022	0.018	0.057	0.017	0.078
Adjusted OR (95%CI)	Reference	1.47 (1.07-1.92)	2.17 (1.41-3.36)	1.21 (0.89-1.64)	1.78 (1.07-2.58)	1.20 (0.96-1.53)

	p-Value[a]	p-Value[b]	p-Value[c]	p-Value[d]	p-Value[e]
A allele:	0.009	0.025	0.030	0.008	0.064

Data Table 3. Gender: male vs female (M/F) Age: Mean±SD; Significant ($P < 0.05$)

P-Value a : All PD when compared to controls
P-Value b : EOPD when compared to controls
P-Value c : LOPD when compared to controls
P-Value d : fPD when compared to controls
P-Value e : sPD when compared to controls
*: adjusted by sex and age

Conclusions

1. The frequency of substitutions of C/T in SNP1 rs2281983 and A/T in SNP2 rs4919621 is significantly higher in PD, and it is particularly high in EOPD and fPD as compared with age-matched healthy controls.
2. Our results support the hypothesis that *PITX3* is critical not only in the develop-ment and maintenance of the dopaminergic system, but also in the pathogenesis of PD.

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