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ORIGINAL ARTICLE

Vitamin D receptor gene variants in Parkinson's disease patients

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Abstract *Background:* Vitamin D plays an important role in neurodegenerative disorders as a crucial neuro-immunomodulator. Accumulating data provide evidences that vitamin D receptor (VDR) gene is a candidate gene for susceptibility to Parkinson's disease (PD).

Aim: To find out whether the risk of the development of sporadic PD might be influenced by VDR gene polymorphisms in an Iranian population or not.

Subjects and methods: A genetic study was conducted to investigate the relationship between VDR gene polymorphisms and the severity of PD. Fifty-nine PD patients and 53 matched-healthy controls were genotyped using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) analysis. For this purpose, four single nucleotide polymorphisms (SNPs) in VDR gene including *Fok*I T > C (rs 10735810), *Bsm*I A > G (rs 1544410), *Apa*I A > C (rs 7975232), and *Taq*I C > T (rs 731236) have been evaluated.

Results: Our genotyping studies revealed that holding *Apa*I a allele and *Fok*I f allele could significantly increase the risk of developing Parkinson's disease 1.85 and 2.46 times, respectively ($p = 0.023$ and 0.008). Moreover, Aa heterozygous of *ApaI* also shows a significantly elevated risk of developing PD when compared to AA homozygous (OR = 7.44, $p = 0.005$). For *Bsm*I and *Taq*I polymorphisms, no significant difference in genotype or allele distribution was found between PD patients and the controls. Moreover, in this study, no significant association was found between different genotypes and Hoehn & Yahr staging and Unified Parkinson Disease Rating Stage (UPDRS) rating scale.

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Conclusion: This study demonstrates a possible association between the VDR *Fok*I and *Apa*I polymorphism and PD, indicating that VDR polymorphisms may change genetic susceptibility to sporadic PD in the Iranian population.

1. Introduction

Parkinson's Disease (PD) is known as the most common neurodegenerative movement disorder in elderly people [1]. Recently, vitamin D3 has been suggested as an environmentally modifiable factor, effective in the pathogenesis of PD [2]. A significantly lower 25-hydroxyvitamin (25OH) D levels were observed both in Caucasian [3] and Japanese patients with more severe PD [4,2]. On the other hand, expression of vitamin D receptor (VDR) is tremendously high in neurons of the substantia nigra, where dopaminergic neurons are selectively lost in PD [5]. In previous studies, besides the neuroprotective effects of vitamin D3 on cells of the nervous system [6], there were some epidemiological evidences confirming the potential value of vitamin D in PD prevention [7,2].

However, multiple genetic studies have revealed an association between the risk of PD with polymorphism in the VDR gene [2,8,9], although the results are conflicting [10]. Based on genome-wide association studies, the correlations between VDR polymorphisms and both risk and age at the onset of PD have been investigated in a Caucasian population [2,9]. Moreover, overexpression of the *BsmI* A > G (rs 1544410) polymorphism was reported among Korean PD patients [8]. Recent studies have shown a significant correlation between VDR *FokI* T > C (rs 10735810) genotype and PD in the Japanese and Chinese Han populations [2,11]. In contrast to these results, Petersen et al. found no difference in genotype (*ApaI* A > C (rs 7975232), *BsmI*, *TaqI* C > T (rs 731236)) frequencies between PD cases and controls in the VDR polymorphisms in Faroe Island [12].

Previous data have shown that genetic variation in VDR gene could induce serious defects of receptor activation by altering the affinity of the receptor to vitamin D [13]. However, there has been no report on the severity of PD and vitamin D gene variants in the Iranian population. Hence, a genetic study was conducted to investigate the relationship between VDR gene polymorphisms and both risk and severity of PD.

2. Subjects and methods

2.1. Patient selection for genetic analysis

The case–control study of the Iranian PD patients was conducted during September to November 2011, as it has been previously described [14,15]. The people gave an informed consent and agreed to participate in the current study. The ethics committee of the Isfahan University of Medical Sciences approved the protocol for this study. It was according to Declaration of Helsinki.

All PD cases were examined clinically by the same experienced neurologist according to the United Kingdom Parkinson's Disease Brain Bank criteria [16]. Then, the Hoehn and Yahr scale (H&Y) was used for clinical staging according to four stages of 1–1.5, 2–2.5, 3, and 4–5 [17] as well as the motor part of the Unified Parkinson's Disease Rating Scale III (UPDRS III) [18]. Exclusion criteria included having a history of taking vitamin D or being diagnosed to have familial background or early onset of PD (< 40 years old) and lack of voluntary participation for DNA extraction. Finally, 59 PD patients and 53 age-sex matched controls were chosen for genetic analysis.

After receiving consent from patients and controls, a blood sample was taken and DNA was isolated using a standard salting out procedure. The presence of the VDR *Fok*I T > C (rs 10735810), *Bsm*I A > G (rs 1544410), *Apa*I A > C (rs 7975232), and *Taq*I C > T (rs 731236) SNPs were identified by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) according to the manufacturer's instructions. The primer information including their annealing temperature, PCR product length before and after the digestion and the exact position of amplification is listed in Table 1.

DNA fragments were separated in 2% agarose gels and visualized by Gel Red staining. The presence of the *Fok*I T > C (rs 2228570), *Bsm*I G > A (rs 1544410), *Apa*I C > A (rs 7975232), and *Taq*I T > C (rs 731236) polymorphisms was also confirmed by repeated PCR–RFLP analysis. Allelic nomenclature of dominant (FBAT) alleles is based on endonuclease success over its restriction sites *Fok*I, *Bsm*I, *Apa*I and *Taq*I. In view of that, recessive (fbat) alleles were used when the above restriction endonucleases fail to cut their corresponding DNA molecules.

2.2. Statistical analysis

Statistical analysis was carried out using online SISA software available at: http://www.quantitativeskills.com/sisa/index.htm. p-values less than 0.05 were considered statistically significant and odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to judge the correlations between specific factors and the risk of developing PD.

3. Results

Allelic comparison of four polymorphic sites of VDR illustrated that *Apa-I* (*a*) and *Fok-I* (f) recessive alleles were very significantly related to the risk of developing PD (Table 2). As indicated in Table 2 and 51% of PD patients carry *a* allele, while only 36% of control individuals hold that allele. The same results were also recorded for *Fok-I* as 28.8% of Parkinson's disease patients carry *f* allele and only 14.1% of healthy individuals carry the same allele. As depicted in Table 2, holding *a* allele and *f* allele could significantly increase the risk of developing PD by 1.85 and 2.46, respectively (p value = 0.023 and 0.008).

Based on the significant allelic relationship, further analysis on genotypes was encouraged. As expected from allelic

Table 1 Characterizations, conditions and primers of vitamin D receptor (VDR) gene polymorphisms.

SNP	dbSNP#	Position	Alleles	Primer (5′–3′)	PCR Product (bp)	Annealing temp.(°C)	Restriction fragment length (bp)
*Fok*I	rs2228570/ rs10735810	Exon 2	C/T	F: GCACTGACTCTGGCTCTGAC	341	72.5	C(F) = 341
			(F/f)	R: ACCCTCCTGCTCCTGTGGCT			T(f) = 282 + 59
*Bsm*I	rs1544410	Intron 8	A/G	F: GGAGACACAGATAAGGAAATAC	248	60	A(B) = 248
			(B/b)	R: CCGCAAGAAACCTCAAATAACA			G(b) = 175 + 73
*Apa*I	rs7975232	Intron 9	A/C	F: AGCAGAGCAGAGTTCCAAGC	701	58	A(A) = 701
			(A/a)	R: GTGAGGAGGGCTGCTGAGTA			C(a) = 246 + 455
*Taq*I	rs731236	Exon 9	T/C	F: AGCAGAGCAGAGTTCCAAGC	701	58	T(T) = 701
			(T/t)	R: GTGAGGAGGGCTGCTGAGTA			C(t) = 523 + 178

frequencies, being *aa* homozygote elevates the risk of developing PD nine times as compared to *AA* homozygous (OR = 9.15, $p = 0.004$). On the other hand, *Aa* heterozygous also shows a significant elevated risk of developing Parkinson's disease, when compared to *AA* homozygous (OR = 7.44, $p = 0.005$). Parallel to *Apa-I*, *Fok-I* homozygous *ff* and heterozygous *Ff* genotypes also demonstrate a non-significant relationship, as being *ff* and *Ff* could increase the risk of developing PD 3.84 and 1.50 times, respectively (Table 2).

Further analysis has been conducted based on VDR gene polymorphisms and Vitamin D serum levels to explore the possible relationships between different genotypes and serum levels of vitamin D in patients and control (Table 3). As illustrated in Table 3, none of our singular VDR gene polymorphic sites showed any kind of relationship with vitamin D serum levels. Likewise, no significant relationship was found between different genotypes and H&Y staging or UPDRS rating when evaluating the correlation of VDR gene polymorphisms and the severity of PD (Table 4).

4. Discussion

In a population based case–control comprehensive study, the severity of PD and vitamin D gene variants including FokI, BsmI, TaqI, and ApaI has been accomplished in the Iranian population. Our preliminary data had shown that FokI genetic variation in VDR gene may increase the risk of PD development in the local population in our country [19].

In our recent study, some positive results in polymorphisms of vitamin D-related genes were obtained. Among the four kinds of VDR SNPs, the FokI/*f* allele and ApaI/*aa* genotypes showed a strong association with risk of PD. It must be also mentioned that there are some positive results that could correlate the polymorphisms of VDR genes to PD development [9,11,8,2,20]. The only study assessing the ApaI genotypes in relation to PD [2] confirmed our finding. The ApaI polymorphism was associated with the early-onset of PD in the American Caucasian population [9]. According to our results, holding *f* allele in FokI genotype might increase the risk of PD development up to 2.5-fold. In concordance to our finding, FokI *FF* genotype was accompanied by milder forms of PD in Japan [2]. Unlike these findings, in Hungarian and Chinese populations, the frequency of *F* allele was significantly higher in PD patients [5]. As indicated before, *FokI* polymorphism as a 5'UTR polymorphic site can cause different translation initiation in the subsequent VDR gene [21]. Subsequently, the length of protein would be three amino acids shorter in *F* allele and it may induce changes in VDR function. According to Arai et al. [22], if the VDR gene contains *F* allele, it results in better intestinal calcium absorption compared to *f*-VDR. Based on the relation between serum hormone levels and PD [7], it has supposed that *f* allele may predict lower serum vitamin D levels and consequently higher risk for PD [11]. This is in complete accordance with the findings of the present study.

Consistent with our findings, no association between BsmI polymorphism and PD was found by Suzuki et al. and Han et al. [2,11]. In contrast, one report has been shown an association between BsmI polymorphism and PD development [8]. Lastly, the TaqI polymorphism was not correlated with PD in our study, which confirms the findings of previous studies [2,10,9]. A Meta-analysis also confirms this proposition, detecting no association between ApaI, BsmI, and TaqI polymorphisms and PD susceptibility in its all four genetic models [10]. In addition, according to four genetic models in East Asian subgroup, a significant correlation was observed between ApaI polymorphism and PD susceptibility [10]. Whereas, BsmI, ApaI and TaqI polymorphisms are located in the 3′ region of the VDR gene and consequently no alteration in the amino acid sequence of the encoded protein has been assumed. Therefore, these polymorphisms may not alter the structure or the function of the VDR protein [23].

The differences in the results, found by various authors, could be clarified with regard to the study populations, sample sizes, and ethnic variations. On the other hand, the data diversity in the Caucasian population suggests that this population is not homogeneous.

In our previous study, we have compared biochemical levels which are related to bone metabolism, between PD patients and age-matched healthy controls [15]. As the first study in the Middle East population, no significant difference in 25OHD was found between PD patients and control group [15]. Low vitamin D level is probably a common problem in Iranian population. Also, in our previous study, a high prevalence of 25OHD insufficiency (72.8%) and deficiency (38.4%) was reported among Iranian parkinsonism [14]. Although a correlation was found between PD risk and ApaI in this study, no association was found between ApaI and 25(OH) D levels. In a study performed in Faroese island, subjects with

Table 2 Association between Vitamin D receptor polymorphisms and risk of developing Parkinson's disease.

SNP		PD patients (%)	Control (%)	Odd ratio (95% CI)	Pearson (*p*-value)	Overall Pearson (*p*-value)
ApaI	AA	14 (23.7)	2 (3.8)	1		7.21 (0.027)
	Aa	32 (54.3)	34 (64.2)	7.44 (1.57–35.33)	6.37 (0.012)	
	aa	13 (22)	17 (32)	9.15 (1.76–47.58)	6.93 (0.008)	
	a	60 (51)	38 (36)	1.85 (1.08–3.17)	5.10 (0.023)	
	A	58 (49)	68 (64)			
BsmI	BB	24 (40.7)	17 (32.1)	1		0.891(0.640)
	Bb	27 (45.8)	28 (52.8)	1.46 (0.65–3.31)	0.84 (0.360)	
	bb	8 (13.5)	8 (15.1)	1.41 (0.44–4.51)	0.34 (0.560)	
	b	75 (63.6)	62 (58.5)	1.24 (0.72–2.12)	0.60 (0.440)	
	B	43 (36.4)	44 (41.5)			
FokI	FF	6 (10.2)	2 (3.8)	1		6.27(0.043)
	Ff	22 (37.3)	11 (20.8)	1.50 (0.26–8.69)	0.21 (0.651)	
	ff	31 (52.5)	40 (75.5)	3.87 (0.73–20.51)	2.53 (0.112)	
	f	34 (28.8)	15 (14.1)	2.46 (1.25–4.83)	7.03 (0.008)	
	F	84 (71.2)	91 (85.9)			
TaqI	tt	28 (47.5)	23 (43.4)	1		0.26(0.878)
	Tt	25 (42.4)	26 (49.1)	1.22 (0.56–2.66)	0.24 (0.622)	
	TT	6 (10.1)	4 (7.5)	1.01 (0.27–3.76)	0.00 (0.983)	
	T	81 (68.6)	72 (67.9)	1.03 (0.59–1.82)	0.01 (1)	
	t	37 (31.4)	34 (32.1)			

PD: Parkinson's disease; CI: confidence interval.

Table 3 Association of Vitamin D receptor polymorphisms with the vitamin D3 serum concentration between Parkinson's disease patients and controls.

SNP	Genotype	VitD3 PD (Mean ± SD)	VitD3 Controls (Mean ± SD)	Odd Ratio (95% CI)	Pearson (*p*-value)
ApaI	AA	30.71 ± 13.64	32.50 ± 23.33	1	
	Aa	34.33 ± 16.98	30.44 ± 12.79	0.84 (0.42–1.68)	0.25 (0.62)
	aa	28.10 ± 10.04	26.50 ± 14.22	0.89 (0.43–1.84)	0.10 (0.76)
BsmI	BB	32.29 ± 15.31	27.88 ± 10.69	1	
	Bb	36.09 ± 16.81	28.85 ± 12.71	1.12 (0.57–2.23)	0.11 (0.74)
	bb	30.94 ± 10.56	35.00 ± 22.68	0.99 (0.48–2.08)	0 (1)
FokI	FF	29.22 ± 13.73	26.50 ± 13.43	1	
	Ff	34.10 ± 15.15	27.73 ± 10.78	0.90 (0.43–1.85)	0.09 (0.77)
	ff	31.27 ± 15.56	29.86 ± 14.37	1.05 (0.51–2.18)	0.02 (1)
TaqI	tt	33.81 ± 15.96	32.14 ± 16.23	1	
	Tt	30.99 ± 15.17	26.61 ± 10.78	0.90 (0.45–1.83)	0.08 (0.78)
	TT	30.10 ± 1.30	28.80 ± 10.00	1.00 (0.50–2.03)	0 (1)

PD: Parkinson's disease; CI: confidence interval.

heterozygous genotype in ApaI showed significantly higher 25 (OH)D values compared to the two homozygous genotypes [12]. Suzuki et al. did not find any association between ApaI or the other VDR genotypes and vitamin D levels among the Japanese patients [2]. However, as the genotype distribution varies among different ethnicities, it is not unexpected that our results are more concordant with Susuki's findings in an Asian population. According to the previous documents that have considered ApaI as a silent polymorphism, larger studies in different ethnic populations are required to assess the precise implication.

In the previous report, we obtained no association between the 25OHD levels and HY stages, UPDRS III even after multivariate adjustment for possible confounders in Iran [14]. In accordance to our previous study, we found no significant relationship between different genotypes and HY staging or UPDRS rating. To conclude, none of our singular VDR gene polymorphic sites showed any kind of relationship with Vitamin D serum levels.

Prior to this study, only one paper has been published to include both VDR polymorphisms and circulating 25(OH) D levels [2]. However, focusing on the severity of PD, Suzuki et al. found that higher levels of 25(OH) D were significantly associated with lower HY stages and lower UPDRS scores [2]. The reason for this inconsistency may be attributed to the smaller number of patients with advanced PD in our study. The mean HY stage was 1.8 in the current study, which is lower than the same value in Suzuki's study (2.4) [2]. Also, this

Table 4 Association of Vitamin D receptor polymorphisms sites and severity of Parkinson's disease according to H&Y scale and UPDRS.

SNP	Genotype	HY stages		*p*-Value	UPDRS	
		OR	95%CI		Coefficient	*p*-Value
ApaI	AA	1			Reference	
	Aa	0.77	−1.45 to 0.93	0.67	0.022	0.84
	aa	0.50	−2.10 to 0.71	0.33	−0.121	0.26
BsmI	BB	1				
	Bb	0.50	−2.16 to 0.78	0.358	−0.183	0.18
	bb	0.53	−2.12 to 0.86	0.406	−0.082	0.55
FokI	FF	1				
	Ff	1.39	−0.68 to 1.34	0.52	0.26	0.196
	ff	1.08	−1.53 to 1.69	0.92	0.16	0.430
TaqI	tt	1				
	Tt	0.45	−2.47 to 0.87	0.348	−0.11	0.48
	TT	0.43	−2.50 to 0.81	0.317	−0.12	0.47

Hoehn &Yahr: H&Y; UPDRS: Unified Parkinson's Disease Rating Stage; CI: confidence interval.

study reported no interaction between FokI and ApaI VDR gene on the severity of PD [2], similar to the findings of the current research.

This study, carried out for the first time in central Iranian subpopulation, revealed the role of VDR gene polymorphisms in increasing the risk of developing PD. In conclusion, *Aa* homozygosity for the *Apa*I genotype and *FokI f* allele are genetic risk factors for PD.

Also, some limitations of this study need to be enounced: First, the study population was small; hence, we could not generalize the obtained results to the overall population. Second, selection of healthy controls was significant, because choosing fully matched controls with cases is very important. Nevertheless, the exact association between VDR gene polymorphisms and risk of PD cannot be opined and more research is required for better clarification.

Conflict of interest

None declared.

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