Embase (Elsevier)

ORIGINAL ARTICLE

Association of VDR *Fok*I and *Apa*I Genetic Polymorphisms with Parkinson's Disease Risk in South Western Iranian Population

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Article Information

Received: 29 Aug 2015
Accepted: 06 Nov 2015
Plagiarism software: Turnitin

Keywords:
Parkinson's disease,
Vitamin D receptor (VDR),
Single nucleotide polymorphisms (SNP),
Polymorphism,
Iranian population

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ABSTRACT

Background: Parkinson's disease comes second comparing to Alzheimer's disease being responsible for nerve destructing diseases; it is a complex and multifactorial disease. Gene associated studies help to identify the genetic factors that introduce the Single Nucleotide Polymorphisms in different genes as genetic risk factors for non-Mendelian Parkinson's disease in diverse populations. We intended to study the association of VDR (Vitamin D Receptor) gene polymorphisms with Parkinson's disease in south western Iranian population.

Results: In the present study 150 patients with Parkinson's disease and 160 Healthy controls from an Iranian population were genotyped for two polymorphic sites. The prevalence of VDR polymorphisms in two restriction fragment length polymorphism sites including *Fok*I and *Apa*I were analyzed in patients and controls. Our data demonstrated no significant association between VDR *Fok*I polymorphism and PD, whereas the *Apa*I polymorphism showed a significant association with PD in Iranian patient. Also no association between the age at onset, the male-female ratio and the VDR polymorphism in the PD group was detected.

Conclusions: In conclusion these results determined that VDR *Apa*I (TG and GG) genotype might affect development of PD in our study population. There was no association between *Fok*I polymorphism and the risk of PD. Our results were analogous only with American/Hungarian Caucasian race.

INTRODUCTION

Parkinson disease (PD) is the second common neurodegenerative disorder characterized by Bradykinesia, Rigidity and Resting Tremor. Neuropathological features of PD include presence of Lewy bodies and lack of dopaminergic cells in the substantia nigra pars compacta. The prevalence in the general population is about 0.2 percent and at the population over 65 years is 1 to 2 percent.[1] Development of PD - a complex and multifactorial disease –is the result of the interaction between genes and environment.[2] Possible effect of vitamin D and its receptor gene variants have recently gained interest in Parkinson research. Vitamin D is a hormone that active form (1, 25-dihydrooxyvitamin D3) binds to vitamin D receptor (VDRs) which has a key role in calcium and phosphate homeostasis.[3,4] The gene encoding the VDR located on the 12q13 chromosome is consisted of 11 exons and the length of introns and exons altogether is approximately 75 kb in. The noncoding 5′-end of the gene includes exons 1A, 1B, and 1C. VDR receptor structural protein is encoded by eight additional exons (exons 2–9).[5] Despite existence of many polymorphisms in the VDR gene, their effect on VDR protein function and signaling is unknown.[6] To place the associations observed with VDR gene polymorphisms in biological perspective, it is necessary to take into account the functional sequence variant's analysis found in the phase of alleles across the entire VDR gene, and to define heliotype patterns. Various studies suggested that the effects of VDR gene polymorphisms are associated with an increased risk of neural diseases such as PD.[7,8] The low level of vitamin D in PD has been reported and demonstrated by numerous research,[9,10] however only limited data are available about the association between VDR polymorphisms and

Access this article online	
Website: www.actamedicainternational.com	Quick Response code
DOI: 10.5530ami.2016.1.24	

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Parkinson disease. The *Fok*I polymorphism (rs2228570) is one of the VDR gene polymorphisms, which is located in exon 2 and results in an alternative transcription initiation site, leading to different translation initiation region due to thymine (T) to cytosine (C) substitution, altering the activity of VDR protein.[11-13] Study of VDR 3′-regulatory region is one of the initial efforts to identify functional sequence variations because this is close to the anonymous markers used so far in associated studies, Including the *Bsm*I, *Apa*I and *Taq*I polymorphism located near the 3′ end of the gene.[12,14,15] In 2012, a report by Suzuki et al was demonstrated that *Fok*I CC genotype was associated with PD in a Japanese population.[16] Furthermore, in 2005, Kim et al found the *Bsm*I bb polymorphism of VDR gene and PD association in a Korean population.[8] A report by Butler et al was described an association of VDR polymorphisms with the risk of PD in a Caucasian population.[17] The study in a Chinese population revealed the association between *Fok*I C allele and increased risk of PD.[18] The aim of this study was to investigate the association between polymorphisms in the VDR *Fok*I and *Apa*I and the risk of Parkinson's disease in south western Iranian population.

MATERIAL AND METHOD

Subjects

150 idiopathic PD cases were recruited from the Imam Reza hospital of Shiraz. Diagnosis of the patients evaluated by a movement disorders specialist, when the subject has features of PD. Age of patients according to the medical records were classified as early-onset (diagnosed ≤ 60 yr) or late-onset (diagnosed > 60 yr) PD (Table 1). Also the age option, the sex of all participants in PD group and control group were selected in such a way that there was no statistically significant correlation between the two groups (Table 2). 160 Healthy individuals as control group were enrolled being selected from Imam Reza hospital of Shiraz with no past mental or psychiatric disorder. Also the written informed consents were received from all study participants.

DNA Isolation and PCR Experiments

Peripheral blood was poured into tubes containing EDTA from each PD patients and healthy individuals. The genomic DNA was extracted using the salting out method and stored at -20°C. The *Fok*I and *Apa*I polymorphic sites were considered. Uniqueness of the primer pairs for the target sequences were aligned using the BLAST (two) online software. FokI C/T polymorphism (rs10735810) was amplified by the following primers: Forward 5′-AGCTGG CCCTGGCACTGACTCTGC TCT-3′ and reverse 5′-ATGGAAACACCTTGCTTCTTC TCCCTC-3′. The condition for Polymerase Chain Reaction (PCR) was optimized with the following cycling parameters: 95°C for 5 min, followed by 30 cycles of 95°C for 30 sec, 60°C for 30 sec, 72°C for 30 sec and finally 72°C for 7 min. Amplification of the ApaI G/T polymorphic site (rs7976091) was performed with these primers: forward primer sequence 5′-CAACCAAGACTACA AGTACCGCGTCAGTAGA-3′ and reverse primer sequence 5′CACTTCGAGCACAA GGGGCGTTAGC-3′. PCR condition was as it follows: 95°C for 10 min, 95°C for 30 sec, 59°C for 30 sec, 72°C for 2 min for 35 cycles, and finally 72°C for 7 min.

Table 1: General demographic information and parameters of patients and control groups

Parameters	PD group (n=150)	Control group (n=160)	OR (95% CI)	p value
The mean age	65.3	62.6		
Age at onset ≤60 (%)	81 (54)	90 (56.7)	OR=1.11, 95% CI (0/52-2/37)	0/77
Age at onset >60 (%)	69 (46)	70 (43.3)		
Gender n (%)				
Male	66 (44)	77 (48.3)	OR=1.191, 95% CI (0/56-2/53)	0/65
Female	84 (56)	63 (51.7)		

Table 2: Genotype and allele frequencies of PD cases, and controls

SNP	PD group n=150 (%)	Control group n=160 (%)	p value
*FokI genotype			
TT	0 (0)	0 (0)	0/85
CT	27 (18)	26 (16/25)	
CC	123 (82)	134 (83/75)	
*FokI alleles			
T	27 (18)	26 (16/25)	0/85
C	123 (82)	134 (83/75)	
#ApaI genotype			
TT	36 (24)	128 (80)	0/0001
TG	84 (56)	26 (16/25)	
GG	30 (20)	6 (3/75))	
#ApaI alleles			
G	114 (76)	32 (20)	0/0001
T	36 (24)	128 (80)	

Genotyping and Polymorphism Analysis

The VDR gene polymorphisms were determined by PCR-RFLP techniques. The size of the PCR products was determined by electrophoresis on a 1% agarose gel. Then a reaction product was digested with the *Fok*I restriction enzyme (thermo scientific) at 37°C for 3 hours. The digested products were separated by 1/5% agarose gel electrophoresis. Three genotypes as CC (265bp), TT (169 and 96 bp) or CT (265, 169 and 96 bp) were defined. The *Apa*I primer PCR product's size was determined by 1% agarose gel electrophoresis and then incubated with *Apa*I restriction enzyme (thermo scientific) at 37°C for 24 hours and fragments analyzed by electrophoresis in 1/5% agarose gel. The presence of restriction site led to bands of 1700

and 300 bp (GG) whereas the absence of the restriction site yielded one fragment at 2000 bp (TT). Three bands under UV light (2000, 1700 and 300 bp) reflected the TG heterozygotes.

Statistical Analysis

The statistical software SPSS (ver. 19.0) was used for statistical analysis and the difference in genotype frequencies were assessed using the $\chi 2$ test and Fisher exact test. Associated analysis between the genotypes and the Parkinson disease were estimated via the odds ratio (OR), with a 95% confidence interval (CI). A P-value of less than 0.05 was assumed statistically significant. *Fok*I and *Apa*I SNPs frequencies were matched with the Hardy-Weinberg equilibrium in both PDs and healthy controls.

RESULTS

Subject Characteristics

The 150 Parkinson patients and 160 healthy controls were analyzed. Table 1 shows the General demographic information and parameters of patients and control groups. The gender distribution frequency between patients and controls was not statistically significant at the 5% level (P=0.65), OR=1/191, %95 CI (0/56-2/53). Also the age distribution frequency did not show significant difference at the 5% level (P=0.77), OR=1/11, %95 CI (0/52-2/37). Genotype and allele frequencies of PD cases and controls are shown in Table 2. The risk of PD associated with VDR genotypes are shown in Table 3.

VDR *ApaI* and *FokI* Polymorphism

Following digestion of PCR products in all samples, the distribution of *Apa*I restriction site genotypes and *Fok*1 restriction site genotypes in the patient groups and the control group are given in Table 2. There was a significant difference in the distribution of VDR *Apa*I genotypes in PD patients (P<0.0001). VDR *Apa*I TG genotype was significantly increased in PD patients (56%) compared to controls (16.7%), and carriers of *Apa*I (TG+GG) genotype had an increased risk for PD cases (P<0.0001) OR=7.7, 95% CI (3.2-18.38) (Table 3). The G allele showed a significant association with PD patients. The VDR *Fok*I genotype frequencies for PD patients, and control cases did not show a significantly difference ((P=0.85, p > 0.05) (Table 3).

Table 3: The risk of PD associated with VDR genotypes

SNP	PD group n=150 (%)	Control group n=160 (%)	OR (95% CI)	p value
*Fok-I genotype				
TT	0 (0)	0 (0)	OR=7.7, 95% CI (3.2-18.38)	0/85
TT+CT	27 (18)	26 (16.25)		
CC	123 (82)	134 (83.75)		
CC+CT	150 (100)	160 (100)		
#Apa-I genotype				
TT	36 (24)	128 (80)	OR=7.7, 95% CI (3.2-18.38)	0/0001
TG+GG	114 (76)	32 (20)		
TT+TG	120 (80)	154 (69.71)		
TG	84 (56)	27 (16.78)		
GG	30 (20)	5 (3.12)		

DISCUSSION

Although extensive research has been done about Parkinson's disease, the etiology of molecular and genetic processes that lead to neuronal damage will rarely be available.[19-21] Few monogenic forms of PD (about 10 percent) have been known, but multiple genetic defects as well as environmental factors seem to be responsible in most patients with Parkinson's disease.[22,23] Associated studies are one of the best approaches to identify genetic risk factors for complex diseases such as PD (21). In general, vitamin D level and genetic variants in VDR gene have significant effect on PD disease and neurodegenerative research, the studies show.[9,10,24] Association of higher serum vitamin D level with reduced risk for PD was demonstrated; the study in Finland showed.[10] Negative correlation between the serum vitamin D level and PD proved relation between VDR gene polymorphism and Vitamin D related diseases.[5,25] Currently more than 25 different polymorphisms were identified in the VDR locus. In Previous VDR polymorphism studies, four restriction fragment length polymorphisms (RFLPs) were mainly being focused on: *Taq*I (rs731236), *Apa*I (rs7975232), *Bsm*I (rs1544410) and *Fok*I (rs10735810).[26-30] The polymorphisms are mostly near the 3′-end, the 5′-end of the gene and in or near the promoter sequence. Most efforts were aimed to identify the sequence variations in the 3′-regulatory region and 5′ region of VDR Gene.[18,31] Thus, 3′-UTR region variations may affect the mRNA stability and/or protein translation efficacy, whereas 5′- region variations may affect expression patterns and levels. These combinations of genotypic difference may affect the VDR protein levels and/or function, depending on the cell type, developmental stage and activation status.[13,16,32] The haplotypes in intron 8 and exon 9 are closely linked with alleles of the *Bsm*I, *Apa*I and *Taq*I polymorphisms.[15,30] The RFLPs analysis showed these allele polymorphisms extend to the 3′-untranslated region (UTR) which is a 3.2 kb sequence adjacent to exon 9.[30,33] More than 10 different sequence variations in the 3′-UTR have been analyzed including a poly (A) repeat polymorphism. The LD analysis of the 3′-UTR of the VDR gene in different racial populations indicates different LD among populations.[33] It is possible mentioned explanations for allele polymorphisms such as *Bsm*I, *Apa*I and *Taq*I included differences in translation (rather than mRNA stability) of the different mRNA 3′-UTR variants. Certain parts of the UTR, so-called destabilizing elements, interfere with the determination of VDR–mRNA stability.[14] The RFLP is the most frequently used method for associated studies of the VDR gene with Parkinson

disease. Different VDR polymorphism studies have been demonstrated in PD in Japanese, Korean, Chinese and Caucasian populations.[8,16-18]

The distribution of *Fok*1 polymorphisms in the PD group was similar to the control group, whereas the *Apa*1 polymorphisms showed a signification association between the VDR gene polymorphisms and Parkinson's disease. The significance of the VDR gene in *Apa*1 polymorphism indicates a possible role for the VDR gene in the development of parkinsonian symptoms.

However, care should be taken when interpreting the results of this study because the distribution of the VDR genotype shows ethnic variations. Our results demonstrated that there is no association between the *Fok*1 C allele and PD; the frequency of the C allele did not show any significant difference in Iranian PD patients when compared to controls (P=0.85). *Fok*I (rs10735810) was studied in Han population and the results indicated increased frequency of C allele in PD group and late-onset PD group than in controls.[31] Also a Hungarian study found an connection between PD and the *Fok*I C allele.[7], Suzuki examined PD severity, the *Fok*I CC genotype for VDR polymorphism was associated with a milder form of PD.[16,34] In a Chinese study it was described that *Fok*I C allele associates with an increased risk of both PD and early-onset PD.[18] Han et al. (2012) proposed *Fok*I C allele might be a risk factor for sporadic PD development (16). In regard to polymorphisms, the *Fok*I CC genotype is associated with PD risk in multiple studies.[16,35-37] interestingly only one report was similar to our outcome from among American Caucasians which showed no association between *Fok*I polymorphism and PD patients.[17]

Also our studies showed the *Apa*I polymorphisms had a signification association with PD, this polymorphism may associated in the development of PD in these patients (in Iranian patients), whereas In Japan and Korean population, *Apa*I polymorphisms did not show any significant association.[8,31] In a Faroe Island population no association was seen with the polymorphisms assessed, *Apa*I, *Bsm*I, and *Taq*I, but there was an association between vitamin D levels and *Apa*l/AC genotype.[34] No relation was seen with *Bsm*I, *Apa*I, or *Taq*I in the Hungarian population.[7], but *Apa*I is associated with PD in the Hungarian and American population, which belongs to the Caucasian race.[17,18] Our data determined that VDR *Apa*I (TG and GG) genotype might affect development of PD, but neither did we find statistically significant difference between *Fok*1 VDR polymorphisms with PD cases in Iranian PD partitions, nor detect an association between the age at onset, the male-female ratio and the VDR polymorphisms in the PD group. So the *Fok*1 and *Apa*I polymorphisms in Iranian PD patients were analogous only with American Caucasian race and Hungarian/American Caucasian race. The differences between the results of the various authors must be interpreted with regard to the facts that the study populations and sample sizes differed, with the additional possibility of certain ethnic variations. Furthermore, generalizing these results might be limited because this study population is small. Since the evidence for an association between PD and the VDR gene polymorphisms is just based on *Apa*I and *Fok*I RFLP, the distribution of other polymorphisms in the VDR gene, such as *Bsm*I and *Taq*I will need to be analyzed to confirm these results. In addition, the role of a VDR gene polymorphism should be further examined in other populations in order to confirm another susceptible gene for PD and to determine more adequate strategies for treating PD. As far as we are aware, this is the first report on the potential correlation between *Fok*I and *Apa*I VDR polymorphism and PD from an Iranian population.

CONCLUSION

There was association between *Apa*I (TG and GG) genotype and the PD risk. There was no association between *Fok*I polymorphism and the PD risk. Our results were analogous only with American/Hungarian Caucasian race. First report on the *Fok*I and *Apa*I VDR polymorphism and Iranian PD patients.

ACKNOWLEDGEMENTS

This work was supported by 93.7234.1 grants, Maragheh University, Iran.

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How to cite this article: Mohammadzadeh R, Pazhouhesh R. Association of VDR *FokI* and *ApaI* genetic polymorphisms with Parkinson's disease risk in south western Iranian population. Acta Medica International. 2016;3(1):111-115.

Source of Support: 93.7234.1 Grants, Maragheh University, Iran, **Conflict of Interest:** None declared.