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Original Article

Association of Vitamin-D Receptor Gene Single Nucleotide Polymorphism (FokI) with COPD

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Abstract

Background: *Vitamin D receptor gene (VDR) polymorphism and its association with various diseases have been previously investigated. But the association of vitamin D receptor gene polymorphism with COPD has not been investigated yet.* ***Objective:*** *To assess the association between vitamin D receptor gene polymorphism (FokI) and COPD.* ***Methods:*** *This cross sectional study was carried out in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from March 2019 to February 2020. For this study, 15 (fifteen) pulmonologists diagnosed COPD patients with age 40 to 80 years (post-bronchodilator FEV1/FVC<0.70 and FEV1<80% predicted) and 15 (fifteen) apparently healthy age-matched individuals (for comparison), were selected. The single nucleotide polymorphism of vitamin D receptor gene (FokI) of all subjects was assessed by PCR-RFLPs. Data were expressed as mean ± SD and percentage. Statistical analysis was done by independent sample 't' test and chi-square test. In the interpretation of the results, ≤0.05 level of probability (p) was accepted as significant.* ***Results:*** *The frequency distribution of FokI genotype was 13.33% (FF), 73.34% (Ff), 13.33% (ff) and 13.33% (FF), 80% (Ff), 6.66% (ff) COPD patients and healthy subjects, respectively. Associations of FokI [FF (OR 1,95% CI 0.12-8.21, p=1.00); Ff (OR 0.68,95% CI 0.12-3.78, p=0.66); ff (OR 2.15,95% CI 0.17-26.67, p=0.54)] VDRSNP with COPD was statistically non-significant. Conclusion: The present study reveals that the FokI of VDR SNP is not associated with COPD.*

Keywords: *Vitamin D receptor gene, Single nucleotide polymorphism, FokI.*

Introduction: Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. It is a complex disease associated with the multifactorial background of long-term exposure to noxious gases and particles, combined with a variety of host factors, including genetics, airway hyper-responsiveness and poor lung growth during childhood1. It has been found that different genes are associated with COPD. Among them, alpha1- antitrypsin (AAT) deficiency is one of the most common genetic causes of COPD. This enzyme deficiency occurs due to Taq-1 polymorphism of AAT, Z-isoform of AAT, and mutation of serpin family A member 1 (SERPINA 1). In addition, Single nucleotide polymorphism (SNP) of matrix metalloproteinase 9 (MMP9), the promoter region of tumour necrosis factor-alpha (TNFα) gene and SERPINA3werealsoassociatedwith COPD[2-6].

As COPD is a chronic inflammatory respiratory ailment, so, immunomodulation would be one of its major causative factor[7-9]. Recently the immunomodulatory role of vitamin D has been explored[10-14]. This immunomodulatory characteristic acts via vitamin D receptor (VDR), which alters genomic signaling[12,15-19]. So, the main regulator of vitamin D signaling is the VDR[20], which is present in numerous tissues, including kidney, heart, muscle, breast, colon, prostate, brain and immune cells,

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making itself a natural target of modulation in disease pathogenesis, including a variety of cancers[21], metabolic syndrome[22,23], renal transplant[24] and dermal disorders[25]. In addition, polymorphisms of the VDR gene have been found to be associated with immune-mediated diseases characterized by an imbalance in helper T- cell development[9], such as Crohn's disease[26] and tuberculosis[27].

VDR gene is located on 12q13.11 possessing 11 exons with a length of 5.6 kb[28]. This VDR gene has more than[3] 470 single nucleotide polymorphisms (SNPs), a number of which modulate the uptake of 1,25 (OH)2D[29]. Among them, the common SNPs are ApaI[30], BsmI[31], TaqI[32] and FokI[33].

These SNP s have been found to be associated with the efficacy of antiresorptive treatments in postmenopausal women (with BsmI)[34], essential hypertension (with FokI)[35], metabolic syndrome (with FokI)[23], prostate cancer (with ApaI)[36], Leprosy (with FokI and ApaI)[13], lumbar spine pathogenesis (with BsmI, ApaI and TaqI)[37] and multiple familial sclerosis (with TaqI)[38]. Moreover, in the perspective of respiratory ailments, both FokI and ApaI VDR SNPs were found to be associated with asthma[11,39,40] and FokI VDR SNP was found to be associated with tuberculosis[41,42]. In addition, ApaI was associated with osteoporosis[43] and FokI along with BsmI were associated with skeletal muscle strength in COPD patients[44]. To the best of our knowledge, different diseases were found to be associated with VDR polymorphism. However, as far as we searched, no study was available on the association of VDR SNP with COPD. Therefore this study aimed to investigate the association of one common VDR SNP (FokI) with COPD.

Materials and Methods Data collection

This cross-sectional study was conducted from March 2019 to February 2020 in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), after getting protocol approval from the Institutional Review Board (IRB) of BSMMU. For this study, 15 male (age 40 to 80 years) COPD patients (Study group) were diagnosed by a Pulmonologist with spirometric evidence of COPD (presence of a post-bronchodilator FEV1/FVC <0.70 and FEV1 <80% predicted) and enrolled by purposive sampling from Out-Patients Department (OPD) of the National Institute of the Diseases of Chest and Hospital (NIDCH). For comparison, 15 age, BMI and smoking status matched apparently healthy males (Comparison group) were selected by personal contacts. Written informed consent was taken from all the participants after detailing the study procedure. With all aseptic precautions, 5ml of venous blood was drawn from the ante-cubital vein.

DNA extraction

DNA extraction was done by ReliaPrep™ Blood gDNA isolation kit (Promega, Wisconsin, USA) and assayed for purity and concentration by spectrophotometry (absorbance at 260 nm and 280 nm).

FokI polymorphism

PCR amplification of the VDR gene was done in 25µl reaction mixtures containing primers for FokI polymorphism45. The PCR amplification conditions were initial denaturation at 94°C for 5 minutes followed by 35 cycles at 94oC for 30 sec, 58°C for 30 sec, 72°C for 1 min and final extension at 72°C for 7 minutes. The primers for FokI polymorphism were 5′- GATGCCAGCTGGCCCTGGCACTG-3′ and 5′-ATGGAAACACCTTGCTTCTTCTCCCTC-3′45. The PCR product (272 bp) was digested with 1.0 unit FokI restriction enzyme (New England Biolabs Inc, USA) in a heat block at 25°C for 20 minutes. The products of restriction enzyme cleavage were analyzed on 1% agarose gels and were visualized under UV light after staining with ethidium bromide (Figure 1, Table 1). FokI VDR SNP resulted in fragments of 272 bp, 198 bp and 74 bp. Thus for FokI, FF resulted in one fragment of 272 bp, ff in two fragments of 198 and 74 bp, and Ff exhibited all three fragments (272bp,198bp,74bp).

Table no. 1: Primer sequence and PCR conditions for genotyping of FokI VDR.

Location	Locus	Alleles	PCR primer	PCR product (bp)	Restriction enzyme	RFLP products (bp)
Exon2	rs2228570	C/T	F: GATGCCAGCTGGCCCTGGCACTG	272	FokI	272
			R: ATGGAAACACCTTGCTTCTTCTCCCTC			198
			* Initial denaturation: 94°C for 5 min; 35cycles: 94°C for 30s, 58°C for 30s, and 72°C for 1min; and final extension: 72°C for 7min			74

PCR- Polymerase chain reaction; RFLP-Restriction fragment length polymorphism; bp- Base pair.

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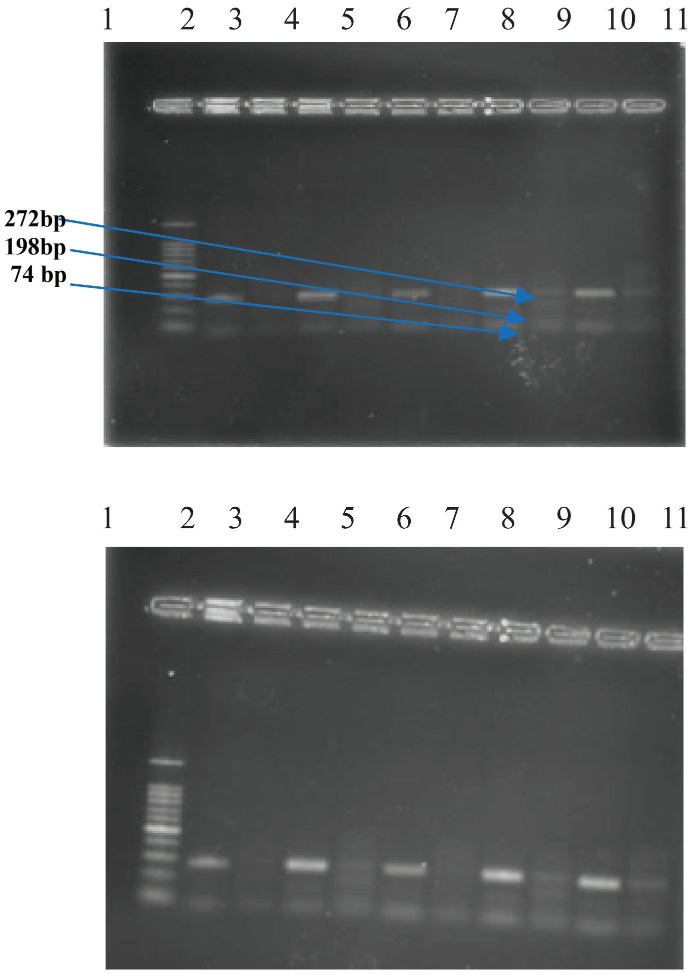

Figure 1: Restriction fragment length polymorphism digestion of FokI in 1% agarose gel stained with ethidium bromide with 100 bp ladder in the first Lane, in lanes 2, 4, 6, 8, 10 shows PCR products; in lanes 3, 5, 7, 9, 11 shows digested products in gel picture. FokI digestion – FF/272 (major homozygous), Ff/272, 198, 74 (heterozygous), ff/198,74 (minor homozygous).

Statistical analysis

The data were expressed as mean with standard deviation (mean ± SD) and frequency distribution in percentage. The data were statistically analyzed by SPSS statistical package, version 22.0 (IBM, SPSS Inc., Chicago, IL), using the Chi-square test. Allelic frequencies of VDR gene polymorphisms were determined by Hardy-Weinberg equilibrium. In the interpretation of the results, ≤0.05 level of probability (p) was accepted as significant.

Results

The baseline characteristics of all our study subjects are presented in Table 2. The distribution of FokI VDR genotype and allele frequency is shown in Table 3. The FokI genotype, frequency distribution was 13.33% (FF), 73.34% (Ff), 13.33% (ff) and 13.33% (FF), 80% (Ff), 6.66% (ff) COPD patients and healthy subjects, respectively. The associations of FokI FF (OR 1, 95% CI 0•12-8.21, p = 1.00); Ff (OR 0•68, 95% CI 0•12-3.78, p=0•66); ff (OR2.15, 95% CI0•17-26.67, p = 0•54)] VDR SNPs with COPD were statistically non-significant.

Table no. 2 : Baseline characteristics of COPD patients and healthy subjects (N=30)

Characteristics	COPD patients (n=15)	Healthy subjects (n=15)	p-value
Age (years)	60.46 ±6.31 (40-80)	56.00 ±7.80 (40-80)	0.096^{ns}
Body mass index (BMI) (kg/m^2)	22.76 ±4.26 (16.90-33.70)	21.96± 2.30 (18.80-25.91)	0.531^{ns}
Duration of smoking (pack year)	14.07 ±5.41 (4-30)	17.16 ±5.17 (4-30)	0.121^{ns}
FEV1/FVC(%)	57.60±10.61 (39-68)	80.60 ±6.38 (72-92)	0.000***
FEV1(% of predicted value)	44.88 ±10.98 (28.30-63.60)	83.26 ±10.51 (70-100)	0.000***

Data were expressed as mean ± SD; Figures in parentheses indicate ranges; Statistical analysis was done by Independent sample t-test; N = Total number of subjects; n = number of subjects in each group; Pack year = (number of cigarettes smoked per day/20) X no. of years smoked; FEV1 = Forced expiratory volume in the first second; FVC = Forced vital capacity; ns = non-significant; *** = statistically significant (p<0.001)

Table no 3: Genotype and allele distribution of FokI VDR SNP in study subjects (N = 30)

SNP	COPD patients (n = 15)		Healthy subjects (n = 15)		OR(95%CI)	χ^2 value (p value)
	no	%	no	%		
FokI						
FF	2	13.33	2	13.33	1 (0.12-8.21)	χ^2=0.00, p=1.00
Ff	11	73.34	12	80	0.68 (0.12-3.78)	χ^2=0.18, p=0.66
ff	2	13.33	1	6.66	2.15 (0.17-26.67)	χ^2=0.37, p=0.54
F	15	50	16	53.34	1.14 (0.41-3.14)	χ^2=0.06, p=0.79
f	15	50	14	46.66	0.87 (0.31-2.41)	χ^2=0.06, p=0.79

VDR = Vitamin D receptor; SNP = Single Nucleotide polymorphism; OR = odds ratio; CI = confidence interval

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Discussion

It is well known that the VDR gene is located on chromosome 12q13.11[28,46] encoding the VDR protein by exon II to IX. In addition, it has been reported that exon VII to IX involves the binding of VDR to vitamin D[47]. It has also been observed that variations in the 3′ UTR sequence often affect mRNA stability, the efficiency of protein translation and alter protein levels. Among the four common VDR SNPs, FokI is located in exon 2 at the 5' end of the VDR gene[10,13,32,47,48,49,50,51,52]. However, it is due to the nucleotide substitution of T to C within the first codon of exon 2 (ATG to ACG, giving rise to the allelic conversion of "f" to "F")[52]. Therefore, this FokI polymorphism may affect the activity of VDR and subsequent downstream effects of vitamin D[53], including its immunomodulatoryrole[50,51]. FokI VDR SNP was found to be associated with essential hypertension, metabolic syndrome, acromegaly, leprosy, hepatocellular carcinoma, multiple sclerosis, urolithiasis and skeletal muscle strength in COPD patients[13,22,23,29,35,44,47,54]. From the perspective of respiratory ailments, FokI VDR SNP was found to be associated with asthma and tuberculosis[39,41,42]. However, in our study, neither the genotype nor the allele of FokI VDR single nucleotide polymorphism was associated with COPD. Similarly, in a Turkish study regarding the global COVID condition, was found no association between FokI polymorphism of the VDR gene with COVID-1955. It may be explained as respiratory diseases showing the similarity of genetic involvement.

Conclusion

The results of the present study elucidate that FokI VDR SNP is not associated with COPD. There were a few limitations in our study. First, the intake of vitamin D and environmental exposure to ultraviolet radiation of our study population could not be assessed. Second, as a genetic association study, the results were based on a small number of samples. For further research, a similar type of study should be done, including information on vitamin D intake and environmental exposure to ultraviolet radiation in a large number of COPD patients.

Conflict of interest

There is no existence of a conflict of interest in this study.

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