Original Article

Association of Vitamin D Receptor Gene Single Nucleotide Polymorphism (ApaI) with Chronic Obstructive Pulmonary Disease

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Abstract

Background: *Association of Vitamin D receptor gene single nucleotide polymorphism and its association with various diseases have been previously researched, but its association with chronic obstructive pulmonary disease (COPD) has not been investigated yet. To evaluate the association between vitamin D receptor gene polymorphism (ApaI) and COPD.* ***Materials and Methods:*** *This study was conducted in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2019 to February 2020. For research, pulmonologists diagnosed 15 (fifteen) 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 genetic assessment of (ApaI) was assessed by PCR-RFLPs. Data were stated as mean ± SD and percentage. The Independent sample 't' test and chi-square test were done for statistical analysis. In the interpretation of the results, ≤ 0.05 level of probability (p) was accepted as significant.* ***Results:*** *The frequency distribution of the ApaI VDR SNP was 20% (AA), 80% (Aa), 0% (aa) and 46.67% (AA), 40% (Aa), 13.33% (aa) COPD patients and healthy subjects, respectively. Furthermore, the AA (OR 0.28, 95% Cl 0.05-1.44, p = 0.12) and aa (p=0.14) were not associated with COPD. However, the heterozygous SNP of ApaI, Aa (OR 6, 95% CI 1.17-30.72, p = 0.02) was significantly associated with COPD.* ***Conclusion:*** *This study showed that ApaI of VDR SNP is associated with COPD.*

Keywords: Vitamin D receptor gene, Single nucleotide polymorphism, ApaI, COPD.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health challenge, but it is preventable and treatable, characterized by persistent respiratory symptoms and airflow limitation due to airway and or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and a significant cause of chronic morbidity and mortality throughout the world. COPD is a complex condition linked to multiple factors, including prolonged exposure to harmful gases and particles, as well as various host factors such as genetics, airway hyper-responsiveness, and impaired lung development during childhood[1].

It has been confirmed that several genes are associated with COPD, with alpha1-antitrypsin (AAT) deficiency being one of the most common genetic causes. This enzyme deficiency arises from the Taq-1 polymorphism of AAT, the Z-isoform of AAT, and mutations in the SERPINA1 gene, which belongs to the serpin family A. In addition, Single nucleotide polymorphism (SNP) of matrix metalloproteinase 9 (MMP9), matrix metalloproteinase 12 (MMP12), glutathione S-transferase, the promoter region of tumour necrosis factor-alpha (TNFα) gene and SERPINA3 were also associated with COPD[1-6].

COPD is a chronic inflammatory respiratory ailment, thereby it is suspected that immunomodulation would be one of its major causative factor[7-9]. Now a days the immunomodulatory role of vitamin D has been explored[10-14]. It acts via vitamin D receptor (VDR), which regulates gene expression in various types of cells including immune cells and alters genomic signalling[12,15-19]. So, the main regulator of vitamin D signaling is the VDR[20], besides immune cells it also presents in numerous tissues, including kidney, heart, muscle, breast, colon, prostate, and brain, making itself a natural target of modulation in disease pathogenesis, including a variety of

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cancers[21], metabolic syndrome[22,23], renal transplant[24] and dermal disorders[25]. Furthermore, variations in the VDR gene have been linked to immune-mediated disorders, which are marked by an imbalance in the development of helper T-cells[9], such as Crohn's disease[26] and tuberculosis[27].

The VDR gene is located on chromosome 12 at 12q13.11 with a total length of 5.6 kb which contains 11 exons[28]. The VDR gene has more than 470 single nucleotide polymorphisms (SNPs), some of which influence the absorption of 1,25(OH)2 D3[29]. Common SNPs associated with this gene are ApaI[30], BsmI[31], TaqI[32] and FokI[33]. These SNPs have been linked to the effectiveness 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 sclerosis (with TaqI)[38]. Additionally, regarding respiratory conditions, both FokI and ApaI VDR SNPs have been linked to asthma[11,39,40], and FokI VDR SNP was found to be associated with tuberculosis[41,42]. Furthermore, ApaI has been linked to osteoporosis[43], while FokI and BsmI have been associated with skeletal muscle strength in patients with COPD[44]. As far as we are aware, various diseases have been linked to VDR polymorphisms. However, to the best of our knowledge, no studies have explored the association between VDR SNPs and COPD. Thus, the aim of this study was to investigate the relationship between a common VDR SNP (ApaI) and COPD.

Materials and Methods

This cross-sectional study was carried out in the Department of Physiology at Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2019 to February 2020, after getting approval from the Institutional Review Board (IRB) of BSMMU. For the research purpose, fifteen male patients with aged 40 to 80 years (the study group) were diagnosed with COPD by a pulmonologist due to 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 the comparison, 15 apparently healthy males, matched in terms of age, BMI and smoking status, were selected from personal contacts to select as the comparison group. Ethical and data collection permission from the NIDCH and informed consent from all the participants was taken after detailing the study procedure. With all aseptic precautions, 5 ml of venous blood was drawn from the ante-cubital vein.

DNA extraction: DNA was extracted using the ReliaPrep™ Blood gDNA isolation kit (Promega, Wisconsin, USA) and assessed for purity and concentration through spectrophotometry, measuring absorbance at 260 nm and 280 nm.

ApaI polymorphism: PCR amplification of VDR gene was done in 25 µl reaction mixtures containing primers for ApaI polymorphism. The PCR amplification conditions included an initial denaturation at 95°C for 5 minutes, followed by 35 cycles of 94°C for 30 seconds, 52°C for 1 minute, and 72°C for 1 minute, with a final extension at 72°C for 5 minutes and 5′-CTAGGTCTGGATCCTAAATGCA-3′ and 5′-TTAGGTTGGACAGGAGAGAGAA-3′ were the primers for ApaI polymorphism[45]. ApaI restriction enzyme (1.0-unit) (New England Biolabs Inc, USA) is used for PCR product with 628bp digestion in a heat block at 25°C for 20 minutes. The restriction enzyme digestion products were analyzed using 1% agarose gels, and the bands were visualized under UV light after staining with ethidium bromide (Figure 1, Table I). The ApaI VDR SNP was produced in fragments of 628 bp, 477 bp, and 151 bp. Thus, for ApaI, AA resulted in one fragment of 628 bp, aa in two fragments of 477 and 151 bp, and Aa exhibited all three fragments (628 bp, 477 bp, 151 bp).

Statistical analysis: The data were stated as mean ± SD and frequency distribution in percentage. The data were statistically analyzed by IBM-SPSS version 22.0 by using Student's 't' test and $\chi 2$ test. Allele frequencies of VDR gene polymorphisms were calculated based on Hardy-Weinberg equilibrium. A p-value of less than 0.05 was judged as statistically significant.

Results

In this study among the 30 male participants 15 was the patients of COPD and 15 was healthy subjects. There was significant difference of FEV1/FVC (%), FEV1 (% of predicted value), FEV1 and FEV1/FVC between COPD patients and healthy subjects. Then genetic study was done on 15 COPD patients. Table I showed the Primer sequence and PCR conditions for genotyping of ApaI VDR. Table II shows the distribution of ApaI VDR genotypes and allele frequencies. Frequency distribution of the ApaI VDR SNP was 20% (AA), 80% (Aa), 0% (aa) and 46.67% (AA), 40% (Aa), 13.33% (aa) COPD patients and healthy subjects, respectively. The AA SNP (OR 0.28, p=0.12) and aa SNP (p=0.14) were not associated with COPD. However, the heterozygous SNP of ApaI, Aa (OR 6, p=0.02) was significantly associated with COPD.

Table-I: Primer sequence and PCR conditions for genotyping of ApaI VDR

Location	Locus	Alleles	PCR Primer	PCR Product (bp)	Restriction Enzyme	RFLP Products (bp)
Intron 8	rs7975232	G/T	F:CTAGGTCTGGATCCTAAATGCA R:TTAGGTTGGACAGGAGAGAGAA *Initial denaturation: 95°C for 5 mins; 35 cycl: 94°C for 30s, 52°C for 1 min and 72°C for 1 min and final extension: 72°C for 5 mins	628	ApaI	628 477 151

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

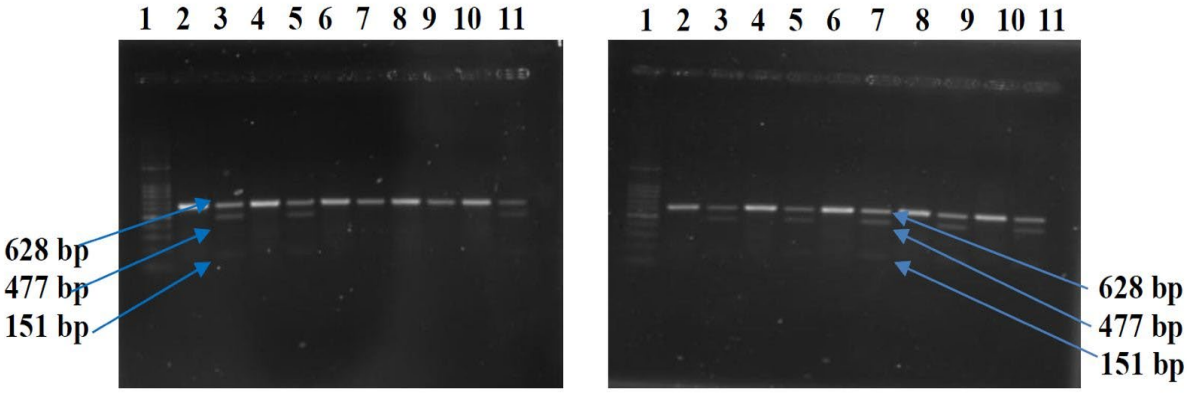

Figure-1: 100 bp ladder in the first Lane, in lanes 2, 4, 6, 8, 10 shows PCR products: in lanes 3, 5, 7, 9, 11 shows digested products in gel picture (Restriction fragment length polymorphism digestion of ApaI in 1% agarose gel stained with ethidium bromide). ApaI digestion - AA/628 (major homozygous), Aa/628, 477, 151 (heterozygous), aa/477, 151 (minor homozygous).

Table-II: Genotype and allele distribution of ApaI VDR SNP in study subjects (n=30)

SNP	COPD patients (n=15) mean±SD (range)		Healthy Subjects (n=15) mean±SD (range)		OR (95%CI)	χ^2 value (p value)
	No	%	No	%		
ApaI						
AA	3	20	7	46.67	0.28 (0.05-1.44)	χ2=2.40, p= 0.12
Aa	12	80	6	40	6 (1.17-30.72)	χ2=5.00, p=0.02*
Aa	0	0	2	13.33	0	
A	18	60	20	66.66	1.33 (0.46-3.82)	χ2=0.28, p= 0.59
a	12	40	10	33.34	0.75 (0.26-2.15)	χ2=0.28, p= 0.59

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

Discussion

Chromosome 12q13.11 contains VDR gene and its exon II to IX encode the VDR protein[28,46]. ApaI is in intron 8 between exon VIII and IX[10,47-49] near the 3′ UTR. It has been reported that exon VII to IX involves the binding of VDR to vitamin D[47], and 3′ UTR of VDR gene involved in regulation of gene expression. However, it has been observed that, variations in the 3′ UTR sequence often affect mRNA stability and the efficiency of protein translation[32] and altered protein levels[13,40,50,51]. That's why, ApaI polymorphism can affect the activity of VDR and subsequent downstream effects of vitamin D[52] including its immune modulatory role[50,51]. It was also found that 3′UTR is associated with tuberculosis in Asian populations[53]. In addition, it has been noted that vitamin D-VDR signaling pathway is related to some regulatory proteins, such as, Smad3[54], β-catenin[55], NF- kB[55] and cyclin D3[56]. Among them, as a transcription factor[56,57], NF-kB binds to specific DNA sequence in different gene promoters, to regulate transcription of a wide range of genes, including those involved in immune and inflammatory responses[58-61]. These genes produce pro-inflammatory cytokines IL-1 and TNF-α[55] along with chemokines IL-6, IL-8, IL-

12[58,59]. It is well known that all these NF-kB dependent cytokines and chemokines are involved in COPD pathogenesis[62]. Association of VDR ApaI SNP with cancers, type 1 diabetes, multiple sclerosis, and several autoimmune diseases has previously been reported[63-66]. ApaI is also associated with inflammation and oxidative stress. From the perspective of respiratory ailments, it was found that ApaI VDR SNP was associated with asthma in Asian[11,40] also with shortness of breath and asthma in COVID-19 patients. And surprisingly it was found that there is increasing risk of severity found in COVID-19 patients with "Aa" genotype. The findings of our study regarding association of VDR ApaI SNP with COPD revealed that ApaI "Aa" genotype is associated with our COPD population. It has been reported that VDR is directly involved in suppression of NF-kB activation[60,61]. Therefore, VDR dependent NF-kB inhibition might explain the significant association of ApaI (Aa) genotype of VDR SNP with our COPD population.

The limitations of our research were intake of vitamin D and environmental exposure to ultraviolet radiation of our study population could not be assessed and as a genetic association study, the results were based on a small number of samples.

Conclusion

This study elucidates that heterozygous (Aa) genotype of ApaI VDR SNP is associated with COPD. While the relationship between vitamin D receptor genetic variants and COPD pathogenesis is complex, our results indicate that the ApaI polymorphism may influence the susceptibility to COPD, potentially through mechanisms involving inflammation and immune regulation. However, further research involving larger, more diverse populations including information of vitamin D intake and environmental exposure to ultraviolet radiation in COPD patients to confirm this association.

Conflict of Interest

The authors declared that they have no conflicts of interest.

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