Original Article

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

Akter K[1], Riad RZ[2], Ali T[3], Banu LA[4], Anjum S[5]

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 (TaqI) 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 the vitamin D receptor gene (TaqI) of all subjects was assessed byPCR-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 the TaqI VDR SNP was 0% (TT), 0% (Tt), 100% (tt) and 0% (TT), 0% (Tt), 100% (tt) COPD patients and healthy subjects, respectively. There was no association between TaqI VDR SNP with COPD.* ***Conclusion:*** *The present study reveals that TaqI of VDR SNP is not associated with COPD.*

Keywords: Vitamin D receptor gene, Single nucleotide polymorphism, TaqI

Received: May 25, 2022; **Accepted:** June 30, 2022

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease 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. It is a complex disease associated with the multifactorial background of long-term exposure to noxious gases and particles, combined withvarious host factors, including genetics, airway hyper-responsiveness and poor lung growth during child hood[1]. 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 (SERPINA1). In addition, Single nucleotide polymorphism (SNP) of matrix metalloproteinase 9 (MMP9), the promoter region of tumour necrosis factor-alpha (TNFα) gene and SERPINA3 were also associated with 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 by the researchers[10-14]. This immunomodulatory characteristic has been found in several studies that it acts via vitamin D receptor (VDR), which alters genomic signaling system[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, that makes itself a natural target of modulation in disease pathogenesis, including a variety of the 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 the development of the helper T- cell [9], such as in 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 470 single nucleotide polymorphisms (SNPs), a number of which modulate the uptake of $1,25(OH)_2 D_3$[29]. Among them, the common SNPs found on the research are the ApaI[30], BsmI[31], TaqI[32] and FokI[33].

[1]Dr. Khalada Akter, Assistant Professor, Department of Physiology, Eastern Medical College, Cumilla, Bangladesh.
[2]Dr. Md. Riadul Zannat Riad, Assistant Professor, Department of Anatomy, Eastern Medical College, Cumilla, Bangladesh.
[3]Dr. Taskina Ali, Professor, Department of Physiology, BSMMU, Dhaka, Bangladesh.
[4]Dr. Laila Anjuman Banu, Professor, Genetics & Molecular Biology, BSMMU, Dhaka, Bangladesh.
[5]Dr. Salma Anjum, Assistant Professor, Dept. of Physiology, Shaheed Tajuddin Ahmad Medical College, Gazipur, Bangladesh.

Address of correspondence: Dr. Khalada Akter, Assistant Professor, Department of Physiology, Eastern Medical College, Cumilla, Bangladesh. Mobile: +8801795745687, Email: khaledajmc11@gmail.com

These SNPs 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 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 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 (TaqI) with COPD.

Materials & 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, 5 ml 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).

TaqI polymorphism: PCR amplification of the VDR gene was done in 25 µl reaction mixtures containing primers for TaqI polymorphism45. The PCR amplification conditions were initial denaturation at 95°C for 5 minutes, followed by 35 cycles at 94oC for 30 sec, 52°C for 1 min, 72°C for 1 min and final extension at 72°C for 5 minutes. The primers for TaqI polymorphism were 5′-CTAGGTCTGGATCCTAAATGCA-3′ and 5′-TTAGGTTGGACAGGAGAGAGAA-3′ 45.

The PCR product (628 bp) was digested with a 1.0-unit TaqI 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 I). TaqI VDR SNP resulted in fragments of 628 bp, 433 bp and 201 bp. Thus, for TaqI, tt resulted in two fragments of 433 bp and 201 bp.

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.

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

Location	Locus	Alleles	PCR primer	PCR product (bp)	Restriction enzyme	RFLP products (bp)
Exon 9	rs731236	T/C	F: CTAGGTCTGGATCCTAAATGCA R: TTAGGTTGGACAGGAGAGAGAA **Initial denaturation:* 95 °C for 5 min; *35 cycles:* 94 °C for 30 s, 52 °C for 1 min, and 72 °C for 1 min; and *final extension*: 72 °C for 5 min	628	TaqI	628 433 201

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

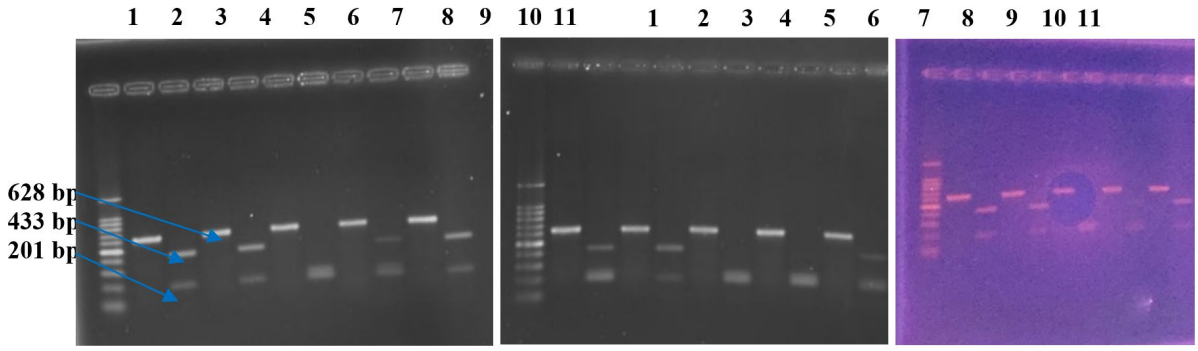

Figure-1: Restriction fragment length polymorphism digestion of TaqI in 1% agarose gel stained with ethidium bromide with 100 bp ladder in the first Lane, in lanes 2, 4, 6, 8, 10 shows PCR products; in lanes 3, 5, 7, 9, 11 shows digested products in gel picture. TaqI digestion – tt/433, 201 (minor homozygous).

Results

The baseline characteristics of all our study subjects are presented in Table II. The distribution of TaqI VDR genotype and allele frequency is shown in Table III. Frequency distribution of the TaqI VDR SNP was 0% (TT), 0% (Tt), 100% (tt) and 0% (TT), 0% (Tt), 100% (tt) COPD patients and healthy subjects, respectively. There was no statistical association between TaqI VDR SNP with COPD.

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-II: 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***

Table-III: Genotype and allele distribution of TaqI 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	%		
TaqI						
TT	0	0	0	0	-	-
Tt	0	0	0	0	-	-
tt	15	100	15	100	-	-
T	0	0	0	0	-	-
t	30	100	30	100	-	-

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

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. Among the four common VDR SNPs, TaqI is located in exon 9[10,47-49] codon 352 near the 3′ UTR. However, it has been reported that exon VII to IX involves the binding of VDR to vitamin D[47]. In addition, it has also been observed that variations in the 3′ UTR sequence often affect mRNA stability and the efficiency of protein translation[32] and altered protein levels[13,50-51]. The TaqI polymorphism in which a T nucleotide has

been substituted with a C. Since VDR is a transcriptional regulating factor for a large number of target genes, its altered expression can influence various aspects of cellular function[52]. Therefore, this TaqI polymorphism may affect the activity of VDR and subsequent downstream effects of vitamin D, including its immune-modulatory role[53]. Moreover, it has been observed that the vitamin D-VDR signalling 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], NF-kB binds to specific DNA sequences in different gene promoters to regulate the transcription of a wide range of genes, including those involved in immune and inflammatory responses[57-59].

These genes produce pro-inflammatory cytokines IL-1and TNF-α[55] along with chemokines IL-6, IL-8, IL-12[57-58]. TaqI VDR SNP is associated with gastric carcinoma, colorectal carcinoma, Crohn's disease, metabolic syndrome, obesity, breast cancer and new onset diabetes at transplant[52,60]. From the perspective of respiratory ailments, it was found that TaqI VDR SNP was associated with tuberculosis in Asian populations[61]. Very recently it has been found that this VDR SNP is associated with COVID-19[62]. However, in our study, neither the genotype nor the allele of TaqI VDR single nucleotide polymorphism was associated with COPD. Similarly, in India, as well as in Greece, China, Chile and American study, there was found no association between asthma and TaqI VDR SNP[6-66]. It may be explained as respiratory diseases showing similarity of genetic involvement.

Limitation & Recommendation:

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.

Conclusion

The results of the present study elucidate that TaqI VDR SNP is not associated with COPD.

Acknowledgement

The authors acknowledge Prof. Dr. Manzare Shamim, Professor of the Department of Anatomy, BSMMU, for permitting to do the laboratory work in his department (Genetic Lab).

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD. (GOLD) 2019. Available at: http://www.goldcopd.org. [Accessed on January 03, 2022].
2. Foreman MG, Campos M, Celedón JC. Genes and chronic obstructive pulmonary disease. Med Clin North Am. 2012; 96 (4): 699-11.
3. Kim WJ, Do Lee S. Candidate genes for COPD: current evidence and research. Int J of Chron Obstruct Pulmon Dis. 2015; 10: 2249-55.
4. Reid PT, Innes JA. Respiratory medicine. In: Colledge NR, Walker BR and Ralston SH, editors. Davidson's principles and practice of medicine, 23rded. Churchill Livingstone. Elsevier. 2018; p: 573-77.
5. Lomas DA, Silverman EK. The genetics of chronic obstructive pulmonary disease. Respir Res. 2001; 2 (1): 20.
6. Seifart C, Plagens A. Genetics of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2007; 2 (4): 541.
7. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol. 2008; 8 (3): 183-92.
8. Lane N, Robins RA, Corne J, Fairclough L. Regulation in chronic obstructive pulmonary disease: the role of regulatory T-cells and Th17 cells. Clin Sci (Lond). 2010; 119 (2): 75-86.
9. Poon AH, Laprise C, Lemire M, Montpetit A, Sinnett D, et al. Association of vitamin D receptor genetic variants with susceptibility to asthma and atopy. Am J Respir Crit Care Med. 2004; 170 (9): 967-73.
10. Uitterlinden AG, Fang Y, van Meurs JB, Pols HA, van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. Gene. 2004; 338 (2): 143-56.
11. Milenkovic J, Markovic D, Velickov A, Djordjevic, BStojnev S. Vitamin D Immunomodulatory Effect. Acta Medica Medianae. 2012; 51 (4): 58-64.
12. Heulens N, Korf H, Janssens W. Innate immune modulation in chronic obstructive pulmonary disease (COPD): moving closer toward vitamin D therapy. J Pharmacol Exp Ther. 2015; 353 (2): 360-68.
13. Neela VS, Suryadevara NC, Shinde VG, Pydi SS, Jain S, et al. Association of Taq I, Fok I and Apa I polymorphisms in Vitamin D Receptor (VDR) gene with leprosy. Hum Immunol. 2015; 76 (6): 402-5.
14. Ahmed AE, Sakhr HM, Hassan MH, El-Amir MI, Ameen HH. Vitamin D receptor rs7975232, rs731236 and rs1544410 single nucleotide polymorphisms, and 25- hydroxyvitamin D levels in Egyptian children with type 1 diabetes mellitus:

effect of vitamin D co-therapy. Diabetes Metab Syndr Obes. 2019; 12: 703-6.
15. Kliewer SA, Umesono K, Mangelsdorf DJ, Evans RM. Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D3 signalling. Nature. 1992; 355 (6359): 446-49.
16. Jurutka PW, Whitfield GK, Hsieh JC, Thompson PD, Haussler CA, et al. Molecular nature of the vitamin D receptor and its role in regulation of gene expression. Rev Endocr Metab Disord. 2001; 2 (2): 203-16.
17. Amano Y, Komiyama K, Makishima M. Vitamin D and periodontal disease. J Oral Sci. 2009; 51 (1): 11-20.
18. Mahmoud AA, Ali AH. Vitamin D receptor gene polymorphism and 25 hydroxy vitamin D levels in Egyptian patients with pulmonary tuberculosis. Egypt J Chest Dis Tuberc. 2014; 63 (3): 651-55.
19. Lee SW, Chuang TY, Huang HH, Liu CW, Kao YH, et al. VDR and VDBP genes polymorphisms associated with susceptibility to tuberculosis in a Han Taiwanese population. J MicrobiolImmunol Infect. 2016; 49 (5): 783-87.
20. Lang PO, Aspinall R. Vitamin D status and the host resistance to infections: what it is currently (not) understood. Clin Ther. 2017; 39 (5): 930-45.
21. Krishnan AV, Swami S, Feldman D. The potential therapeutic benefits of vitamin D in the treatment of estrogen receptor positive breast cancer. Steroids. 2012; 77 (11): 1107-12.
22. Huang Y, Li X, Wang M, Ning H, Lima A, et al. Lipoprotein lipase links vitamin D, insulin resistance, and type 2 diabetes: a cross-sectional epidemiological study. Cardiovasc Diabetol. 2013; 12 (1): 17.
23. Schuch NJ, Garcia VC, Vívolo SR, Martini LA. Relationship between Vitamin D Receptor gene polymorphisms and the components of metabolic syndrome. Nutr J. 2013; 12 (1): 96.
24. Vu D, Sakharkar P, Tellez-Corrales E, Shah T, Hutchinson I, et al. Association of vitamin D binding protein polymorphism with long-term kidney allograft survival in Hispanic kidney transplant recipients. Mol Biol Rep. 2013; 40 (2): 933-39.
25. Swelam MM, El-Barbary RA, Saudi WM, Fathi MS, Soliman DA et al. Associations among two vitamin D receptor (VDR) gene polymorphisms (ApaI and TaqI) in acne vulgaris: A pilot susceptibility study. J Cosmet Dermatol. 2019; 18 (4): 1113-20.
26. Simmons JD, Mullighan C, Welsh KI, Jewell DP. Vitamin D receptor gene polymorphism: association with Crohn's disease susceptibility. Gut. 2000; 47 (2): 211-14.
27. Wilkinson RJ, Llewelyn M, Toossi Z, Patel P, Pasvol G, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. Lancet. 2000; 355 (9204): 618-21.
28. Dabirnia R, Mahmazi S, TaromchiA, Nikzad M, Saburi E. The relationship between vitamin D receptor (VDR) polymorphism and the occurrence of osteoporosis in menopausal Iranian women. Clin Cases Miner Bone Metab. 2016; 13 (3): 190.
29. Ilhan M, Toptas-Hekimoglu B, Yaylim I, Turgut S, Turan S, et al. Investigation of the vitamin D receptor polymorphisms in acromegaly patients. Biomed Res Int. 2015; 625981: 1-7.
30. Faraco JH, Morrison NA, Baker A, Shine J, Frossard PM. ApaI dimorphism at the human vitamin D receptor gene locus. Nucleic Acids Res. 1989; 17 (5): 2150.
31. Morrison NA, Yeoman R, Kelly PJ, Eisman JA. Contribution of trans-acting factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. Proc Nat Acad Sci USA. 1992; 89 (15): 6665-69.
32. Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, et al. Prediction of bone density from vitamin D receptor alleles. Nature. 1994; 367 (6460): 284-87.
33. Arai H, Miyamoto KI, Taketani Y, Yamamoto H, Iemori Y, et al. A vitamin D receptor gene polymorphism in the translation initiation codon: effect on protein activity and relation to bone mineral density in Japanese women. J Bone Miner Res. 1997; 12 (6): 915-21.
34. Palomba S, Orio F, Russo T, Falbo A, Tolino A, et al. BsmI vitamin D receptor genotypes influence the efficacy of antiresorptive treatments in postmenopausal osteoporotic women. A1- year multicenter, randomized, and controlled trial. Osteoporosis Int. 2005; 16 (8): 943-52.
35. Swapna N, Vamsi UM, Usha G, Padma T. Risk conferred by FokI polymorphism of vitamin D receptor (VDR) gene for essential hypertension. Indian J Hum Genet. 2011; 17 (3): 201-6.
36. Yousaf N, Afzal S, Hayat T, Shah J, Ahmad N, et al. Association of vitamin D receptor gene polymorphisms with prostate cancer risk in the Pakistani population. Asian Pac J Cancer Prev. 2014; 15 (22): 10009-13.
37. Colombini A, Brayda-Bruno M, Lombardi G, Croiset SJ, Ceriani C, Buligan C et al. BsmI, ApaI and TaqI polymorphisms in the vitamin D receptor

gene (VDR) and association with lumbar spine pathologies: an Italian case- control study. PLOS ONE. 2016; 11 (5): e0155004.
38. Yucel FE, Kamıslı O, Acar C, Sozen M, Tecellioğlu M, et al. Analysis of vitamin D receptor polymorphisms in patients with familial multiple sclerosis. Med Arch. 2018; 72 (1): 58-61.
39. Nabih ES, Kamel TB. Association between vitamin D receptor gene FokI polymorphism and atopic childhood bronchial asthma. Egypt J Chest Dis Tuberc. 2014; 63(3): 547-52.
40. Zhao DD, Yu DD, Ren QQ, Dong B, Zhao F, et al. Association of vitamin D receptor gene polymorphisms with susceptibility to childhood asthma: A meta- analysis. Pediatr Pulmonol. 2017; 52 (4): 423-29.
41. Rashedi J, Asgharzadeh M, Moaddab SR, Sahebi L, Khalili M, et al. Vitamin D receptor gene polymorphism and vitamin D plasma concentration: Correlation with susceptibility to tuberculosis. Adv Pharm Bull. 2014; 4 (Suppl 2): 607-11.
42. Acen EL, Worodria W, Mulamba P, Kambugu A, Erume J. The frequency distribution of vitamin D Receptor fokI gene polymorphism among Ugandan pulmonary TB patients. F1000Res. 2016; 5: 1-10.
43. Kim SW, Lee JM, Ha JH, Kang HH, Rhee CK et al. Association between vitamin D receptor polymorphisms and osteoporosis in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2015; 10:1809-17.
44. Hopkinson NS, Li KW, Kehoe A, Humphries SE, Roughton M, et al. Vitamin D receptor genotypes influence quadriceps strength in chronic obstructive pulmonary disease. Am J Clin Nutr. 2008; 87 (2): 385-90.
45. Papadopoulou A, Kouis P, Middleton N, Kolokotroni O, Karpathios T et al. Association of vitamin D receptor gene polymorphisms and vitamin D levels with asthma and atopy in Cypriot adolescents: a case–control study. Multidisciplinary respiratory medicine. 2015; 10 (1): 26.
46. Taymans SE, Pack S, Pak E, Orban Z, Barsony J, et al. The human vitamin D receptor gene (VDR) is localized to region 12cen-q12 by fluorescent in situ hybridization and radiation hybrid mapping: genetic and physical VDR map. J Bone Miner Res. 1999; 14 (7): 1163-66.
47. Moemen Y, Khalil F, Khalil A. FokI polymorphism in vitamin D receptor gene and its association with hepatocellular carcinoma in Egyptian patients with chronic liver disease. Meta Gene. 2019; 19: 104-10.
48. Bhanushali AA, Lajpal N, Kulkarni SS, Chavan SS, Bagadi SS et al. Frequency of fokI and taqI polymorphism of vitamin D receptor gene in Indian population and its association with 25-hydroxyvitamin D levels. Indian J Hum Genet. 2009; 15 (3): 108-13.
49. Saadi A, Gao G, Li H, Wei C, Gong Y, et al. Association study between vitamin D receptor gene polymorphisms and asthma in the Chinese Han population: a case-control study. BMC Med Genet. 2009; 10 (1): 71.
50. Videman T, Leppävuori J, Kaprio J, Battie MC, Gibbons LE et al. Intragenic polymorphisms of the vitamin D receptor gene associated with intervertebral disc degeneration. Spine (Phila Pa 1976). 1998; 23 (23): 2477- 85.
51. Cheung KM, Chan D, Karppinen J, Chen Y, Jim JJ et al. Association of the Taq I allele in vitamin D receptor with degenerative disc disease and disc bulge in a Chinese population. Spine (Phila Pa 1976). 2006; 31 (10): 1143-48.
52. Hoseinkhani Z, Rastegari-Pouyani M, Tajemiri F, Yari K, Mansouri K. Association of vitamin D receptor polymorphisms (FokI (Rs2228570), ApaI (Rs7975232), BsmI (Rs1544410), and TaqI (Rs731236)) with gastric cancer in a Kurdish population from west of Iran. Rep Biochem Mol Biol. 2021; 9 (4): 435.
53. Mohammadi A, Jafari M, Khanbabaei H, Nasiri-Kalmarzi R, Khademi F, et al. Vitamin D receptor ApaI (rs7975232), BsmI (rs1544410), Fok1 (rs2228570) and TaqI (rs731236) gene polymorphisms and susceptibility to pulmonary tuberculosis in an Iranian population: A systematic review and meta-analysis. J Microbiol Immunol Infect. 2019.
54. Yanagisawa J, Yanagi Y, Masuhiro Y, Suzawa M, Watanabe M, et al. Convergence of transforming growth factor-β and vitamin D signaling pathways on SMAD transcriptional coactivators. Science. 1999; 283 (5406): 1317-21.
55. Lu X, Farmer P, Rubin J, Nanes MS. Integration of the NfκB p65 subunit into the vitamin D receptor transcriptional complex: Identification of p65 domains that inhibit 1, 25-dihydroxyvitamin D3-stimulated transcription. J Cell Biochem. 2004; 92 (4): 833-48.
56. Baltimore D. Discovering NF-κB. Cold Spring Harb Perspect Biol. 2009; 1 (1): a000026.
57. Bonizzi G, Karin M. The two NF-κB activation pathways and their role in innate and adaptive immunity. Trends Immunol. 2004; 25 (6): 280-88.
58. Nakanishi C, Toi M. Nuclear factor-κB inhibitors as sensitizers to anticancer drugs. Nat Rev Cancer. 2005; 5 (4): 297-309.

59. Sun J, Kong J, Duan Y, Szeto FL, Liao A, et al. Increased NF-κB activity in fibroblasts lacking the vitamin D receptor. Am J Physiol Endocrinol Metab. 2006; 291 (2): E315-E322.
60. Sakharkar P, Deb S, Vu D (2017). Vitamin D Receptor (VDR) gene polymorphism: Implications on non-bone diseases. J. Basic Clin. Pharm. 2017; 8: S06-10.
61. Singh A, Gaughan JP, Kashyap VK. SLC11A1 and VDR gene variants and susceptibility to tuberculosis and disease progression in East India. The International journal of tuberculosis and lung disease. 2011; 15 (11): 1468-75.
62. KARCIOĞLU L. Correlation of the variations in prevalence of coronavirus disease 2019 and vitamin D receptor genepolymorphisms in cohorts from 26 countries. Anatolian Clinic the Journal of Medical Sciences. 2020; 27 (1): 60-70.
63. Awasthi N, Awasthi S, Pandey S, Gupta S. Association of vitamin D receptor gene polymorphisms in North Indian children with asthma: a case-control study. Int J Mol Epidemiol Genet. 2021; 12 (2): 24.
64. Iordanidou M, Paraskakis E, Giannakopoulou E, Tavridou A, Gentile G, et al. Vitamin D receptor ApaI a allele is associated with better childhood asthma control and improvement in ability for daily activities. Omics: a journal of integrative biology. 2014; 18 (11): 673-81.
65. Hou C, Zhu X, Chang X. Correlation of vitamin D receptor with bronchial asthma in children. Experimental and therapeutic medicine. 2018; 15 (3): 2773-6.
66. Einisman H, Reyes ML, Angulo J, Cerda J, López-Lastra M, et al. Vitamin D levels and vitamin D receptor gene polymorphisms in asthmatic children: a case–control study. Pediatric Allergy and Immunology. 2015; 26(6): 545-50.

Citation of this article
Akter K, Riad RZ, Ali T, Banu LA, Anjum S. Association of Vitamin D Receptor Gene Single Nucleotide Polymorphism (TaqI) with COPD. Eastern Med Coll J. 2022; 7 (2): 21-27.