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VDR (Apa 1) Gene Polymorphism in Asthma in Karachi Population

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Abstract

***Background*:** Asthma, a chronic allergic respiratory disease, is influenced by complex gene environment interactions. Variations in the vitamin D receptor (VDR) gene have been linked to asthma susceptibility and severity. This study aimed to determine the distribution of VDR (ApaI) gene polymorphisms among asthmatic patients in Karachi.

***Methodology*:** A total of 146 asthmatic patients were recruited from the outpatient unit of Ziauddin Hospital, Karachi, after obtaining informed consent. Genomic DNA was extracted from blood samples and subjected to polymerase chain reaction followed by restriction fragment length polymorphism (RFLP) analysis to identify ApaI genotypes (AA, Aa, aa). Data were analyzed using SPSS Version 24. Quantitative variables were expressed as mean ± SD, and qualitative variables as frequencies and percentages. Associations between genotypes and demographic factors (age group, gender) were evaluated using the Chi-square or Fisher's exact test, with $p \leq 0.05$ considered statistically significant.

***Results*:** Participants ranged in age from 10 to 77 years, with a mean of 42.79 ± 15.62 years. The majority of patients were within the 21–40 (39.7%) and 41–60 (39.0%) age groups. Males comprised 58.9% and females 41.1% of the study population. The most frequent genotype was aa (45.2%), followed by AA (34.2%) and Aa (20.6%). No statistically significant association was found between VDR (ApaI) genotypes and demographic characteristics.

***Conclusion*:** The aa genotype of the VDR (ApaI) polymorphism was predominant among asthmatic patients in Karachi. However, no significant association was observed between VDR genotypes and demographic variables.

Keywords: Asthma, vitamin D3, polymorphism, genetic association, Pakistani population.

1. INTRODUCTION

Asthma is a chronic, non-communicable respiratory disease characterized by variable airflow limitation, airway inflammation, and recurrent episodes of wheezing, coughing, and breathlessness. It affects individuals of all ages and remains a major global public health concern due to its increasing prevalence and substantial socioeconomic burden [1, 2]. International estimates highlight that asthma contributes significantly to morbidity and is predicted to remain a leading cause of disease-related disability worldwide [2, 3].

In Asia, Pakistan faces a high burden of asthma, with prevalence rising over recent decades [4-6]. Environmental exposures such as air pollution, tobacco smoke, urbanization, and increased allergen load have been identified as contributors to disease occurrence and exacerbation in the region [5, 3]. Local reports and epidemiological data further indicate regional variability in prevalence and clinical presentation across Pakistan [6-8].

Genetic and ethnic factors importantly influence asthma susceptibility and phenotypic heterogeneity. Studies have

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demonstrated that ancestry and population structure affect the distribution and impact of asthma-related genetic variants, and population-specific investigations are essential to identify relevant risk alleles [9-11]. For example, polymorphisms in ADAM33 have been associated with childhood and adult asthma in Saudi and Pakistani cohorts, illustrating the role of gene variants in regional asthma risk [7, 8, 10].

Vitamin D and its receptor have garnered attention for immunomodulatory roles beyond calcium homeostasis. Vitamin D status and VDR gene variants may influence immune responses implicated in asthma pathogenesis [12]. The VDR gene encodes the vitamin D receptor and contains polymorphic sites that have been studied across disease contexts; alterations at these loci (e.g., ApaI, TaqI, FokI) can affect receptor function and downstream immune regulation [13-15]. Meta-analyses and mechanistic reviews support the potential relevance of VDR polymorphisms to immune-mediated diseases and cancer, reinforcing a plausible link to asthma susceptibility [14, 15].

Given the genetic diversity in Pakistan and the limited local data on VDR variants and asthma, region-specific studies are needed to clarify these associations. Therefore, this study aims to investigate the association of the VDR (ApaI) gene variant with asthma in the Karachi population.

2. METHODOLOGY

A total 146 patients were selected from Ziauddin Hospital OPD, after an informed consent. Before that approval from Ethics Review Committee was taken. After obtaining an informed written consent, 5 ml of whole blood was collected in ethylene diamine tetra acetic acid (EDTA) from subjects of both the groups.

DNA was isolated using a kit by Fermentas, named as Gene Jet Genomic kit. All guidelines from the manufacturer were followed for DNA isolation. The extracted DNA samples were stored in aliquots at 4°C until further analysis using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) techniques. For the PCR procedure, a total reaction volume of 25 µL was prepared. This mixture included 4.5 µL of DNA template, 2 µL each of forward and reverse primers.

Forward: AGCTGGCCCTGGCACTGACTCTGCTCT

Reverse: ATGGAAACACCTTGCTTCTTCTCCCTC

A volume of 12.5 µL of Master Mix was used, comprising PCR buffer, $MgCl_2$, dNTPs, and Taq DNA polymerase. To complete the total reaction volume, 4 µL of nuclease-free water was included. After assembling the reaction mix, the amplification begun by placing the PCR tubes into a thermal cycler.

The thermocycling protocol for the ApaI region included denaturing for 4 min at 95°C, followed by 35 cycles involving three steps: denaturing for 30 seconds at 95°C, annealing for 60 seconds at 63°C, and extension for 2 minutes at 68°C. A final extension was carried out for 5 minutes at 72°C.

Following PCR, each product was digested using 3.0 units of the ApaI restriction enzyme (Fast Digest, Fermentas) at 65°C for a duration of one hour.

For RFLP electrophoresis 5 µl of PCR product along with Apa1 was run on 2% agarose gel containing ethidium bromide. After 2 hours it was studied under the UV light using 100 bp DNA ladder for comparison.

The RFLP electrophoresis of Apa1 digestion showed its three genotypes homozygote AA, and aa genotype Aa as heterozygote with 740, 530 & 210 bp fragments respectively.

Statistical analysis was performed using SPSS software, version 24. Quantitative variables, such as age, were presented as mean ± standard deviation, while categorical variables including age groups, gender, and genotypes were summarized using frequencies and percentages. Comparisons between clinical and laboratory parameters of individuals with type 2 diabetes mellitus (T2DM) and healthy controls were conducted using either the unpaired Student's t-test or the Chi-square test, depending on the type of data. Associations between genotypes and variables such as age group and gender were assessed using the Chi-square test or Fisher's exact test, where appropriate. A p-value of 0.05 or less was considered to indicate statistical significance.

3. RESULTS

The data of 146 patients was analyzed having mean age of 42.79±15.624 years (Min: 10 years and Max: 77 years). Most of the patients were found between 21 - 40 years age-group i.e., 58 (39.73%) and 41 - 60 years age-group i.e., 57 (39.04%). Males were found 86 (58.9%) and females were 60 (41.1%). The highest frequency was found for genotype 3 i.e., 66 (45.21%), followed by genotype 1 i.e., 50 (34.25%), and genotype 2 i.e., 30 (20.55%) (Table **1**).

The proportion of males were high in each age-group as compared to females. Most of the males 37 (63.8%) were between 21 to 40 years of age, while most of the females 28 (49.1%) were fall between 41 to 60 years of age (Fig. **1**).

Table 1: Demographic characteristics of study participants.

Gender	Frequency	Percentage
Male	86	58.90%
Female	60	41.10%
Age Categories		
≤ 20 Years	11	7.53%
21 to 40 Years	58	39.73%
41 to 60 Years	57	39.04%
> 60 Years	20	13.70%
Vitamin D Receptor Genotypes		
Genotype 1 (AA)	50	34.25%
Genotype 2 (Aa)	30	20.55%
Genotype 3 (aa)	66	45.21%

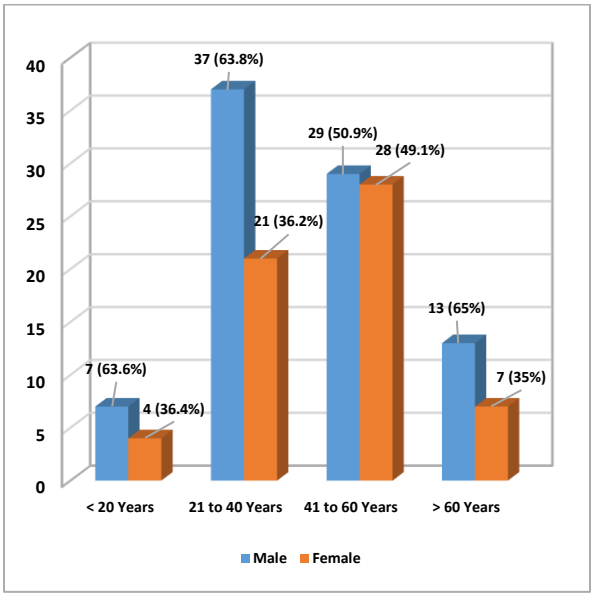

Figure 1: Frequency distribution of age-groups between gender.

Vitamin D receptor genotypes were compared with gender, but no statistically significant association was observed (p-value = 0.710). In both genders, the highest proportion was found for genotype 3 i.e. 41 (47.7%) and 25 (41.7%) in males and females respectively (Table **2**, Fig. **2**).

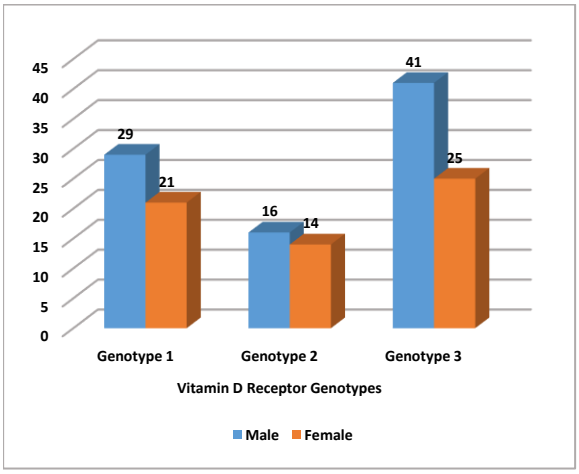

Figure 2: Frequency distribution of genotypes between gender.

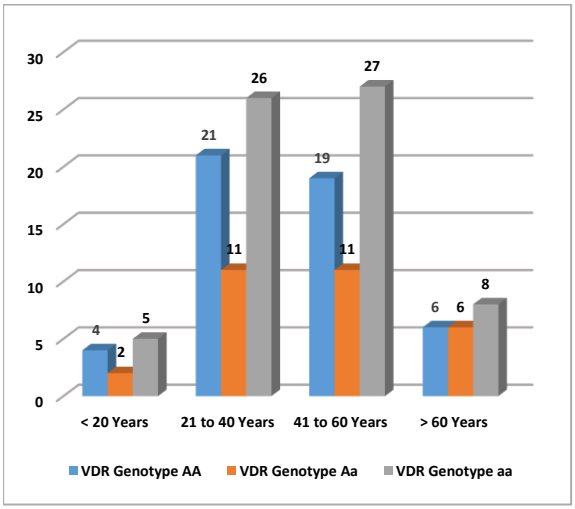

Figure 3: Frequency distribution of genotypes between age-groups.

Table 2: Association of vitamin D receptor genotypes with gender.

Gender	Vitamin D Receptor Genotypes			Total	P-value
	Genotype 1 (AA)	Genotype 2 (Aa)	Genotype 3 (aa)		
Male	29 (33.7%)	16 (18.6%)	41 (47.7%)	86 (100%)	0.710
Female	21 (35%)	14 (23.3%)	25 (41.7%)	60 (100%)	
Total	**50 (34.2%)**	**30 (20.5%)**	**66 (45.2%)**	146 (100%)	

Chi-square test applied

Table 3: Association of vitamin D receptor genotypes with age-groups.

Age Groups (Years)	Vitamin D Receptor Genotype			Total	P-value
	AA	Aa	aa		
≤ 20	4 (36.4%)	2 (18.2%)	5 (45.5%)	11 (100%)	0.968
21 to 40	21 (36.2%)	11 (19%)	26 (44.8%)	58 (100%)	
41 to 60	19 (33.3%)	11 (19.3%)	27 (47.4%)	57 (100%)	
> 60	6 (30%)	6 (30%)	8 (40%)	20 (100%)	
Total	**50 (34.2%)**	**30 (20.5%)**	**66 (45.2%)**	**146 (100%)**	

Chi-square test applied

There was no statistically significant association was observed on comparison of vitamin D receptor genotypes with age-groups (p-value = 0.968). In each age-group, the genotype 3 was found in higher proportion, followed by genotype 1 and genotype 2, as shown in Table **3** and Fig. (**3**).

4. DISCUSSION

This study examined the distribution of the vitamin D receptor (VDR) ApaI polymorphism in asthmatic patients in Karachi. The Gly/Gly genotype was the most common (45.2%), followed by Arg/Arg (34.2%) and Arg/Gly (20.5%). No significant associations were found between these genotypes and demographic characteristics such as age or gender. These results add to existing discussions about whether VDR polymorphisms, particularly ApaI, meaningfully contribute to asthma risk or clinical variation.

The high frequency of the Gly/Gly genotype in our sample differs from several studies that suggest the Arg/Arg (AA) genotype may offer some protection against asthma. A meta-analysis by Tizaoui *et al*. found that the AA genotype was associated with reduced asthma susceptibility in several populations, especially in Asians. However, this updated analysis showed significant links for TaqI, BsmI, and FokI, but not for ApaI, highlighting inconsistency across populations [16]. More recent meta-analytic findings also report no significant association between ApaI and childhood asthma [17]. Population-specific differences were similarly noted in a Chinese case–control study assessing vitamin D pathway genes [18]. These variations may reflect genetic diversity and environmental exposures unique to each population.

Supporting this, Tunisian research found significant associations for several VDR polymorphisms (FokI, BsmI, TaqI) but again emphasized ethnic variability in genetic effects [19]. Family-based West African studies showed increased transmission of the ApaI A allele among tuberculosis cases, pointing to ancestry-specific influences [20]. Another recent meta-analysis also highlighted inconsistent ApaI associations globally [21]. Large North American family-based analyses further showed sex-specific transmission patterns for ApaI, suggesting even more complexity in genotype distribution [22]. In addition, research from Chinese Han cohorts, although focused on urolithiasis, reported significant population-level variability in ApaI allele frequencies, reinforcing broader ethnic differences in VDR genetics [23].

Previous studies have also shown that linkage disequilibrium patterns and allele frequencies of VDR polymorphisms differ across ethnic groups, which may explain why associations appear in some populations but not others. Similar effects were reported in Egyptian children, where rs2228570 variants were linked with asthma risk [24]. In contrast, Chinese Han studies found that VDR SNPs such as FokI and BsmI were not associated with asthma, again highlighting ethnic variation [25]. A major challenge is the limited ethnic diversity in asthma genetics research, which affects the generalizability of findings to South Asian populations [26]. Functional studies also suggest that VDR pathway variants, including ApaI, modify vitamin D activity and atopic responses in ways that differ among populations [25]. Because global genetic studies are still dominated by European ancestry, South Asian genetic data remain underrepresented [28].

The high frequency of the Gly/Gly (aa) genotype in our cohort is notable, especially since similar patterns have been observed elsewhere. A Greek study reported that this genotype was more common in children with well-controlled asthma, suggesting it may be linked to better disease control [29]. If this trend also applies to Pakistani

populations, the prevalence of this genotype may reflect more stable symptoms, although asthma severity was not assessed here. Egyptian studies similarly found that VDR polymorphisms influence asthma features, supporting the idea that ApaI-related effects vary by population [24]. Comparable allele-frequency trends in Chinese Han populations, where the ApaI "a" allele has been associated with disease patterns beyond asthma, suggest broader functional relevance [23].

Family-based European studies found no strong evidence of ApaI transmission to asthmatic children but did note a tendency toward protective transmission in unaffected siblings again hinting at possible protective effects for certain ApaI genotypes [30]. Sex-specific associations in North American studies also show that ApaI may influence asthma risk differently across demographic subgroups [22]. Meta-analytic evidence further confirms the inconsistent nature of ApaI associations, which aligns with the non-significant associations seen in our study [21].

The heterozygous Arg/Gly (Aa) genotype was the least frequent in our sample. Turkish studies have suggested that heterozygosity may increase atopy risk, although results remain inconsistent. Tunisian findings linked several VDR SNPs to asthma but not specifically ApaI with disease severity or atopy [19]. Chinese Han populations similarly showed no major differences in allele frequencies between asthmatics and controls [25]. Most broader analyses also conclude that ApaI is generally not strongly linked with asthma susceptibility [17]. In contrast, studies from North India found that the AC heterozygous genotype increased asthma risk, suggesting that heterozygote effects may appear in specific populations [31].

Asthma is influenced by more than 100 genetic loci, reflecting its highly complex nature. African American studies have linked VDR variants such as rs2228570 with exacerbation rates and IgE levels [32]. Family studies in Quebec populations identified multiple VDR variants associated with asthma and atopy, suggesting intricate inheritance patterns [33]. Genome-wide studies further show that asthma develops through interactions among many small-effect genes and environmental factors [34]. The absence of consistent transmission disequilibrium for VDR polymorphisms in larger families also illustrates asthma's polygenic basis [30].

Human migration, genetic admixture, and ethnic diversity contribute to significant differences in asthma-related genetic variants globally. European ancestry still dominates global genomic datasets, leaving South Asian populations underrepresented [26, 28]. Pharmacogenetic studies further show that genetic differences influence treatment responses to bronchodilators and corticosteroids [35]. The contrasting findings from North India where ApaI shows significant associations highlight how local genetic backgrounds shape the relationships between VDR variants and asthma [31].

Vitamin D plays a central role in immune regulation, including inflammatory control and regulatory T-cell activity. VDR polymorphisms can alter how vitamin D mediates these functions, influencing atopy and airway inflammation [27]. Clinical studies also show that VDR variants can affect lung function and allergic sensitization [32]. Vitamin D deficiency, which is widespread in South Asia, is associated with increased inflammation and airway changes [36]. Evidence also shows that vitamin D deficiency is more common among adults with asthma [37], and VDR variants may influence susceptibility to infections such as tuberculosis in Chinese Han individuals [38]. Research from Gujarati Asian populations also highlights strong gene–nutrient interactions, where disease risk rises when VDR variants coexist with vitamin D deficiency [39].

This study has a few limitations that should be kept in mind when interpreting the results. The work was conducted only on individuals with asthma, so direct comparison of genotype frequencies with healthy individuals was not possible. The analysis focused solely on the ApaI variant of the VDR gene, although other polymorphisms such as FokI, TaqI, and BsmI have also been linked with asthma in previous studies. Clinical details including asthma severity, treatment history, and vitamin D levels were not recorded, and these factors may influence the relationship between VDR variants and asthma. The sample size was modest, which may limit the ability to detect smaller genetic effects. Even with these considerations, the study provides useful information on ApaI genotype patterns among asthmatic individuals in Karachi and supports the need for more extensive research in this area.

5. CONCLUSION

In summary, the Gly/Gly genotype was the most frequent ApaI variant among asthmatic individuals in Karachi. No significant associations were observed between genotypes and demographic factors. These findings highlight the importance of population-specific research on VDR polymorphisms and emphasize the need for larger, more comprehensive studies exploring the genetic and environmental factors shaping asthma risk in South Asia.

Future research should include larger samples with appropriate healthy controls and evaluate multiple VDR polymorphisms. Genome-wide approaches that consider gene-gene and gene-environment interactions, including nutrition, UV exposure, and pollutants, are essential. Incorporating pharmacogenetic analysis may support precision-medicine strategies in South Asian populations. Improving South Asian representation in genomic datasets will also be crucial for better understanding VDR-related asthma risk.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for this study was obtained from the Institutional Ethics Review Committee of Ziauddin University prior to participant recruitment. Written informed consent was obtained from all participants before sample collection. The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki, as outlined in its 2013 revision.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

SB: Conceptualization, study design, supervision, and manuscript drafting.

HA: Laboratory analysis, data interpretation, and literature review.

FA: Data collection, statistical analysis, and result validation.

All authors read and approved the final manuscript.

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