Investigating the Role of GSDMB rs7216389 Polymorphism in Childhood Asthma

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ABSTRACT

Objective

This study investigates the GASDERMIN B (GSDMB) gene variant rs7216389, exploring the clinical and genetic factors associated with pediatric asthma. It underscores the increasing prevalence of childhood asthma, its distinct characteristics compared to adult-onset asthma, and its significant healthcare burden and mortality, particularly during exacerbations.

Methods

A case-control study was conducted over 18 months at CMH Lahore and Children's Hospital, involving 100 participants (50 asthmatics, 50 controls) aged 3-18. Blood samples were analyzed for genetic factors, and statistical analysis was performed using SPSS (v25.0) with significance set at $p<0.05$. Ethical approval and informed consent were obtained.

Results

The study identifies the GASDERMIN B variant rs7216389 as a potential genetic marker for asthma, highlighting its association with asthma severity in children. The research emphasizes the challenges of translating genetic findings into clinical practice while recognizing the therapeutic potential of targeting these genetic markers. Additionally, it sheds light on the healthcare costs and unique clinical features of pediatric asthma, contextualizing its overall impact.

Conclusion

This article provides a comprehensive overview of asthma pathogenesis, stressing the importance of genetic markers like rs7216389 in the GSDMB gene. It calls for further research to explore the complex interactions between genetic, environmental, and immune factors in childhood asthma, with the goal of developing targeted therapeutic interventions.

Keywords: *Childhood asthma, Asthma pathogenesis, GASDERMIN B, GSDMB, rs7216389 variant, genetic polymorphism*

Abbreviations: GASDERMIN B (GSDMB), CMH (Combined Military Hospital), UHS (University Health Sciences), World Health Organization (WHO), Global Initiative for Asthma (GINA), Forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC), chronic obstructive pulmonary disease

(COPD), primary healthcare (PHC), genome-wide association studies (GWAS), single-nucleotide polymorphism (SNP), Institutional Review Board (IRB), Ethylenediaminetetraacetic acid (EDTA), Peak Expiratory Flow Rate (PEFR)

INTRODUCTION

Asthma is the most prevalent chronic condition in children and one of the most common disorders affecting them globally [1]. Recent data from the World Health Organization (WHO) highlights the increasing worldwide prevalence of asthma [2]. Research shows that acute treatments, emergency room visits, and hospitalizations account for 87% of asthma-related costs [3]. The Global Initiative for Asthma (GINA) defines exacerbations as periods when a patient's condition worsens and requires a change in treatment [4]. Symptoms such as shortness of breath, coughing, wheezing, chest tightness, and a reduction in the FEV1/FVC ratio typically worsen during these episodes [5]. Asthma pathogenesis involves airway inflammation, edema, wheezing, exercise-induced bronchial hyperresponsiveness, and elevated IgE levels in response to inhaled allergens [6]. Despite extensive research, asthma remains one of the most challenging conditions to treat worldwide, with many unresolved issues regarding its molecular causes and available therapies. Key features of asthma include wheezing, airway constriction, hyperresponsiveness, and elevated IgE levels in response to airborne allergens [6]. Asthma's features and outcomes vary based on age and gender. In children, asthma is often atopic, linked to increased bronchial reactivity, a decreased FEV1/FVC ratio, elevated IgE levels, and allergen exposure [6]. In contrast, adult-onset asthma, which is less commonly associated with allergens, tends to affect women more frequently [4]. Adult asthma is often more difficult to treat and may show resistance to standard therapies [7]. Major risk factors for asthma include tobacco use, exposure to indoor and outdoor air pollution, and occupational irritants [8]. While chronic obstructive pulmonary disease (COPD) affects 251 million people globally, asthma impacts 339 million individuals and causes over 1,000 deaths per day [9]. By 2030, it is estimated that COPD and related diseases will result in 4.5 million deaths annually worldwide, with 90% of these deaths occurring in low- and middle-income countries [10]. In Pakistan, asthma affects around 7.5 million adults and 15 million children, accounting for 2.1% and 4.3% of the population, respectively [11,12]. In primary healthcare facilities, one-fourth of patients suffer from either COPD or asthma [11]. Genome-wide association studies (GWAS) have identified over 150 genetic markers linked to asthma, offering insights into its underlying causes in both adults and children [13]. Research has explored the connection between childhood asthma and the rs7216389 polymorphism of the ORMDL3 gene located at 17q21, which appears to present a significant risk for asthma, particularly in children and adolescents [14,15]. Childhood-onset asthma is primarily influenced by T-cells and the airway epithelium, with studies indicating gene and tissue specificity differences between asthma in children and adults [16]. The 17q12-q21 chromosomal region, first identified four years ago, is the most significant region associated with childhood asthma, spanning a 6-mb area [16]. Similar to GWAS findings, research on the genetic association between 17q12-q21 and asthma has predominantly focused on European populations, though Asian populations also exhibit a significant genetic contribution [17]. SNPs in the 17q12-q21 region are consistently linked to

asthma in cross-population studies involving African Americans, Asian Americans, and multiethnic groups [18,19]. However, the complexity of connections between these regions makes it challenging to pinpoint the exact genetic changes contributing to elevated asthma risk in children [5].

This article examines the clinical and genetic factors contributing to pediatric asthma, with a focus on the rs7216389 polymorphism in the GSDMB gene. It aims to explore the role of the GSDMB gene in inflammatory and immune responses and to understand how it impacts asthma differently in adults and children. Additionally, the article investigates the gene regulatory mechanisms and biological effects of rs7216389 on pediatric asthma development, along with the prevalence of GSDMB in various cell types. By providing insights that may inform future research and treatment strategies, this analysis aims to
clarify the influence of GSDMB genetic variants on asthma susceptibility.

RESEARCH METHODS

In accordance with clinical practice guidelines, this case-control study was conducted at CMH Lahore Medical and Dental College and Children's Hospital. Sampling was carried out after obtaining informed consent and necessary administrative approvals. PCR and DNA sequencing were performed at the University of Health Sciences. The study spanned 18 months, from March 3, 2023, to May 21, 2024, following IRB approval (Case #.536/ERC/CMH/LMC) dated February 14, 2023, from the Office of Research, Innovation, and Commercialisation (ORIC), CMH Lahore Medical College and Institute of Dentistry. The sample size was calculated using the finite population correlation formula with a 95% confidence interval and 5% absolute precision, resulting in 100 participants, with 50 asthmatic individuals (case group) and 50 non-asthmatic controls (control group). Probability purposive sampling was employed. Participants aged 3 to 18 with a current or prior diagnosis of asthma, as defined by the Global Initiative for Asthma (GINA) 2019 guidelines, were included. The study adhered to the Declaration of Helsinki.

Asthmatic participants were selected based on symptoms such as wheezing, coughing, and dyspnea, risk factors including a family history or exercise-induced symptoms, and radiographic evidence excluding other lung conditions. Non-asthmatic controls, aged 3 to 18, had no history of coughing, wheezing, dyspnea, allergies, or asthma. Individuals with acute lung infections (e.g., pneumonia) or congenital conditions (e.g., chronic lung disease, cystic fibrosis, congenital lobar emphysema, or COPD) were excluded, while non-asthmatics with any asthma-like symptoms were also excluded. Informed consent was obtained from the guardians of children with asthma prior to data collection. Blood samples (2 mL) were drawn using 3 cc syringes from each participant and placed in vacutainer tubes containing EDTA anticoagulant at 4°C. These samples were then sent to the Department of Human Genetics and Molecular Biology at the University of Health Sciences, Lahore, for analysis.

Statistical analysis was performed using SPSS Statistics 25.0 (IBM Corp., 2017). Quantitative variables were reported as means and standard deviations (SD), while qualitative variables were presented as percentages. A p-value of <0.05 was considered statistically significant. Frequencies

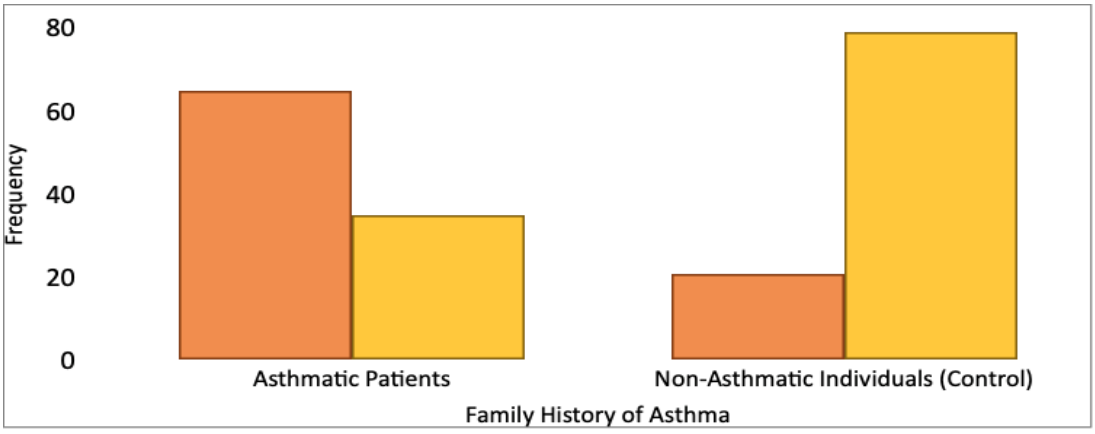
and percentages were calculated for categorical variables, and means and standard deviations were reported for quantitative variables. The Chi-square test was used to evaluate associations between categorical variables.

RESULTS

Family History

Figure 1 elucidates the prevalence of a family history of asthma in the patient and control groups. Patients with asthma responded as follows: 65% recalled having a family history of asthma, while 35% recalled no such history. Of the 100 participants in the non-asthmatic control group, 21% have a family history of asthma, while 79% do not.

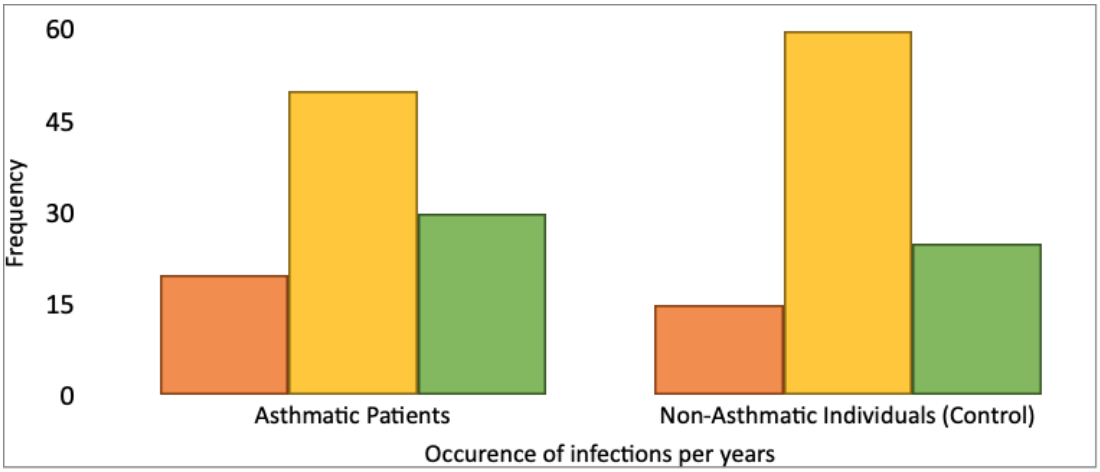
Figure 1: Family History Based distribution among both groups



Childhood Respiratory Infections

Figure 2 shows the number of children experiencing respiratory infections annually in asthmatic patients and non-asthmatic individuals (controls). Among asthmatic patients, 20% of people often get infected (more than three times a year), 50% of people occasionally (1-2 times a year), and 30% of people rarely (less than once a year). Out of the 90% non-asthmatic control group, 15% of patients complain of frequent infections, 60% of patients have occasional infections, and 25% have rare diseases.

Figure 2: Occurrence of childhood respiratory infections each year among both groups



Comparison of SNP Profiles in Asthmatic and Non-Asthmatic Individuals

The Chi-Square test results (Table 1) reveal a significant relationship between asthma status and SNP. variants. The p-value of <0.001 indicates a significant variation in the frequency of SNP variants (C/C, T/C, T/T) between asthmatic and non-asthmatic individuals.

Table 1: Comparison of SNP Profiles in Asthmatic and Non-Asthmatic Individuals

Chi-Square Tests			
	Value	Df	Asymptotic Significance (2- Sided)
Pearson Chi-Square	200.000[a]	3	0.000
Likelihood Ratio	277.259	3	0.000
Linear-by- Linear Association	81.557	1	0.000
N of Valid Cases	200		

Impact of Pet Exposure on Asthma vs. Non-Asthma Cases

The Chi-Square test results presented in Table 2 demonstrate an association between asthma severity and exposure to pets. Both Chi-Square tests show a significant relationship ($p<0.001$) between these variables. However, the Linear-by-Linear Association value of 2.970 ($p=0.085$) suggests that the linear relationship between the frequency of pet exposure and asthma status is not statistically significant.

Table 2: Impact of Pet Exposure on Asthma vs. Non-Asthma Cases

Chi-Square Tests			
	Value	df	Asymptotic Significance (2- sided)
Pearson Chi-Square	62.216[a]	3	0.000
Likelihood Ratio	86.167	3	0.000
Linear-by- Linear Association	2.970	1	0.085
N of Valid Cases	200		

Comparison of Spirometry Results (FEV1) in Asthmatic and Non-Asthmatic Groups

The Chi-Square tests in Table 3 indicate a highly significant correlation between asthma status and spirometry results, specifically FEV1 (Forced Expiratory Volume in 1 second). The Pearson Chi-Square result ($p<0.001$) demonstrates a significant association between asthma status and FEV1 scores. The Linear-by-Linear Association value of 145.237 ($p<0.001$) confirms a direct proportionality between changes in FEV1 scores and asthma status.

Table 3: Comparison of Spirometry Results (FEV1) in Asthmatic and Non-Asthmatic Groups

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi- Square	200.000[a]	4	0.000
Likelihood Ratio	277.259	4	0.000
Linear-by- Linear Association	145.237	1	0.000
N of Valid Cases	200		

Analysis of Peak Expiratory Flow Rate (PEFR) in Asthmatic vs. Non-Asthmatic Groups

The Chi-Square tests in Table 4 establish a connection between asthma status and Peak Expiratory Flow Rate (PEFR). Both the Pearson Chi-Square ($p<0.001$) and the Likelihood Ratio ($p<0.001$) indicate a strong association between asthma status and PEFR measurements. These results provide substantial evidence supporting the positive link between asthma status and PEFR, reflecting the impact of asthma on lung function and expiratory flow.

Table 4: Analysis of Peak Expiratory Flow Rate (PEFR) in Asthmatic and Non-Asthmatic Groups

Chi-Square Tests			
	Value	df	Asymptotic Significance (2- sided)
Pearson Chi-Square	113.609[a]	2	0.000
Likelihood Ratio	129.325	2	0.000
Linear-by- Linear Association	98.483	1	0.000
N of Valid Cases	200		

Association of Gender with Asthma Status in Asthmatic vs. Non-Asthmatic Groups

Table 5 shows a significant relationship between asthma status and gender. Pearson Chi-Square ($p=0.005$) and the Likelihood Ratio ($p=0.005$) confirm that gender is meaningfully associated with asthma status. The Linear-by-Linear Association ($p=0.005$) further supports a significant linear relationship, highlighting the importance of gender differences in understanding asthma status. Fisher's Exact Test results ($p=0.007$ for two-sided and $p=0.001$ for one-tailed) strengthen the evidence for this association, as shown in the 2x2 contingency table analysis.

Table 5: Association of Gender with Asthma Status in Asthmatic and Non-Asthmatic Groups.

Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2 sided)	Exact Sig. (1-sided)
Pearson Chi- Square	8.013[a]	1	0.005		
Continuity Correction[b]	7.232	1	0.007		
Likelihood Ratio	8.068	1	0.005		
Fisher's Exact Test				0.007	0.004
Linear-by- Linear Association	7.973	1	0.005		
N of Valid Cases	200				

DISCUSSION

This study aimed to investigate the presence of the rs7216389 polymorphism in the GSDMB gene in children with asthma. It contributes to the growing body of research on genetic and environmental factors that influence childhood asthma, a condition affecting millions globally, where susceptibility is shaped by a complex interplay of genetic and environmental factors [20,21]. Among the participants, 61% of those with asthma were female, while 62% of the non-

asthmatic control group were male. Table 5 demonstrates a strong association between gender and asthma status, with females more likely to have asthma. This gender disparity may be attributed to differences in gene expression, epigenetic changes, and environmental factors [22].

The study also shows that children with asthma have significantly lower mean FEV1 values and a higher percentage of patients in the Yellow and Red Zones of PEFR compared to non-asthmatic children.

Previous research has highlighted that airway inflammation and bronchial hyperresponsiveness (BHR) often impair pulmonary function in children with asthma [23, 24]. FEV1 is commonly used to assess

asthma severity and has a strong positive correlation with both the frequency of exacerbations and clinical symptoms. The study supports the high test-retest reliability of FEV1 in evaluating asthma morbidity [25]. Among the asthmatic participants, 67% had an FEV1 below the predicted value (PFEV1), compared to just 4% in the control group. This finding corroborates previous studies showing a higher prevalence of reduced pulmonary function in asthmatic individuals. These results reinforce the clinical significance of spirometry as a diagnostic and monitoring tool for asthma [26].

Environmental factors, such as pet exposure, were found to significantly influence asthma prevalence in the studied group. Pet ownership has been identified as both a protective and risk factor for asthma, with the effect depending on factors like genetic background and the age of exposure [27]. The data indicates that children with asthma had higher rates of occasional pet exposure, suggesting that sporadic exposure may increase sensitivity to asthma rather than providing desensitization, which aligns with findings from other studies [28, 29].

The GSDMB gene, located on chromosome 17q12-21, has been implicated in the immune response in asthma, influencing inflammation and epithelial cell function. Previous research suggests that GSDMB regulates the release of TSLP, IL-33, and IL-25, key molecules in asthma pathophysiology, promoting neutrophil and eosinophil infiltration in inflamed airways. This effect is more pronounced in individuals with the T/C or T/T genotype [30]. Studies in children have also shown that carriers of the rs7216389 polymorphism exhibit increased ORMDL3 gene expression in airway cells, which predisposes them to endoplasmic reticulum (ER) stress and disrupted calcium signaling, both of which are associated with asthma inflammation processes [31].

Genetic evidence indicates a significant association between the rs7216389 polymorphism and asthma susceptibility ($p<0.001$), supported by a Chi-Square value of 277.259. This SNP is a major risk factor for childhood asthma, with studies in other populations also linking it to the condition [32]. The T/C heterozygous genotype is most common in asthma patients (64%), suggesting that this genotype may increase susceptibility to asthma. This is further supported by the concept of gene-environment interactions, where certain genotypes may predispose individuals to environmental factors like allergens or smoke, contributing to asthma development [33].

Research has shown that individuals with the rs7216389 polymorphism may experience epigenetic changes, such as altered methylation patterns at the GSDMB locus, which can increase

the production of inflammatory genes in response to allergens or pollutants [34]. The frequency of the rs7216389 variant differs across populations, with European and Hispanic groups being more likely to carry the T allele, associated with a higher asthma risk, compared to African and East Asian populations [35]. Additionally, the rs7216389 SNP has been shown to influence the immune response in dendritic and airway epithelial cells, playing a crucial role in regulating responses to inhaled allergens [36]. The rs7216389 mutation may also affect the airway microbiome, with children carrying this variant showing a unique microbiome profile, including a higher frequency of harmful bacteria linked to more severe asthma [37].

The rs7216389 polymorphism is also associated with an earlier onset of asthma, suggesting that it may increase the risk of developing asthma symptoms at a younger age [24]. Furthermore, it may affect the response to asthma therapies, particularly corticosteroids. Studies indicate that children with the T/T genotype of rs7216389 may exhibit reduced sensitivity to corticosteroids due to increased production of pro-inflammatory cytokines [24].

These findings have important clinical implications, suggesting that genetic testing for rs7216389 and other asthma-related SNPs could become part of routine screening, especially for children with a family history of asthma [31]. From a pharmacogenomics perspective, these results may lead to more personalized asthma therapies, with treatment plans tailored to genetic factors, such as the rs7216389 variant, to improve outcomes, particularly for corticosteroid response. The ongoing advancement of technologies like next-generation sequencing (NGS) will further enhance our understanding of asthma genetics, allowing for more precise identification of risk factors and better patient stratification [32].

CONCLUSION

This study underscores the crucial interaction between genetic, demographic, and environmental factors in the development of childhood asthma. The rs7216389 SNP in the GSDMB gene emerges as a key genetic factor, potentially influenced by a dosage effect. Gender differences indicate a higher susceptibility among females, while variations in allergen exposure highlight the complex role of environmental influences in the disease's onset. Reduced lung function serves as a hallmark of asthma, stressing the need for early diagnosis and timely intervention.

These findings emphasize the importance of a comprehensive strategy for asthma prevention and treatment. Integrating genetic screening, environmental assessments, and personalized interventions presents a promising approach. This precision medicine model focuses on addressing each patient's unique genetic and environmental profile, aiming to enhance outcomes and foster individualized care in the management of childhood asthma.

Highlight Key Points

1. **Genetic Factor in Asthma:** The rs7216389 SNP in the GSDMB gene is strongly linked to childhood asthma, with T/C and T/T genotypes present in 64% and 36% of asthmatic children, suggesting a potential dosage effect that increases susceptibility.
2. Gender Differences in Susceptibility: Asthma prevalence exhibited a slight gender

difference, with 61% of females and 62% of males in the asthmatic group, indicating possible gender-related susceptibility factors.

3. **Environmental Influences:** Children with asthma reported lower levels of pet exposure compared to non-asthmatics, emphasizing the complex role of allergen exposure in asthma development.

4. **Lung Function Impairment:** Spirometry results showed that only 33% of asthmatic children had normal FEV1 values (>80%), compared to 96% in the control group, while PEFR results revealed significant airflow restrictions in 68% of asthmatics.

5. **Implications for Precision Medicine:** This study highlights the importance of incorporating genetic screening, environmental assessments, and personalized lifestyle modifications to improve individualized asthma prevention and management strategies.

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