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Association Of IL-4 Gene Polymorphism with Serum Ige And Eosinophil Levels in Asthma Patients

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Abstract

Asthma represents a chronic airway inflammatory disease with a Th2-cell polarization as the major design of immune response, and interleukin-4 (IL-4) is pivotal in IgE production and eosinophilia. Polymorphisms in the IL-4 gene can alter an individual's susceptibility to asthma and its associated immunological markers. The purpose of this study was to determine if there was a relationship between the genotypic distribution in 2 IL-4 gene polymorphic sites and the asthma IgE level and the peripheral eosinophil count. A cross-sectional case-control study was carried out at Al-Sadr Medical City, Najaf, Iraq from March to December 2025, that included 98 asthmatic patients who were diagnosed by the Global Initiative for Asthma (GINA) guidelines and 52 healthy controls age- and sex-matched. Demographic and clinical information was obtained with the help of structured questionnaires. Serum total IgE were quantified by ELISA, eosinophils were determined with an automated hematology analyzer and the IL-4 gene polymorphism was investigated using PCR-RFLP. Serum IgE levels (310.6 ± 118.4 IU/mL vs. 142.3 ± 64.7 IU/mL, P < 0.002) and eosinophil counts (468.2 ±152.6 vs.286·9 _. 104.s cellsip1L, :P<0T03,) were significantly higher in asthmatics than in control subjects; The IL-4 T allele, and TC and TT genotypes were significantly higher in asthmatic patients than in control individuals. In addition, the T allele and TT+TC genotype were significantly correlated with higher levels of IgE and eosinophilia in asthmatics. In summary, our results demonstrate that the IL-4 gene polymorphism is associated with asthmatic susceptibility and important immunological mechanisms of asthma such as total IgE production and eosinophilic inflammation. These findings reinforce the contribution of genetic variation at IL-4 to the immunopathogenesis of asthma, and propose that IL-4 might be

useful as a genetic and immunological marker for both asthma susceptibility and phenotype stratification.

Keywords: IgE, Eosinophils, Il-4, Asthma, Gene Polymorphism

Introduction

Asthma is a chronic inflammatory disease of the air passages that presents with different airflow obstruction, bronchial hyper-responsiveness and episodes of wheezing, dyspnea and cough. Although knowledge and treatment of asthma has progressed in recent years, the disease is still a global health issue, that have impact over 300 million people worldwide with significant morbidity, healthcare use and impaired quality of life. This disease is very heterogeneous, resulting from the interaction of complex environmental and genetic factors together with an immunological dysfunction (Bateman et al., 2024).

One characteristic of allergic asthma is TH2 biased immune response which confers chronic airway inflammation due to increased by cytokines IL-13, IL-4 and IL-5. Of those, IL-4 is a master in asthma, as it induces differentiation of Th2 cells and class switch of B cell to IgE and promotes eosinophil recruitment into the airways Salient Features (Paul & Zhu, 2010). Serum levels of IgE and peripheral blood eosinophilia are well-known biomarkers of allergic inflammation and disease severity in asthma, which have the potential to serve as relevant surrogates for both phenotyping the diseases and defining new therapeutic targets (Tiotiu, 2018).

The IL-4 gene, which is situated on chromosome 5q31–33 in a cytokine cluster, is extremely polymorphic. A number of single nucleotide polymorphisms (SNPs) of IL-4 gene have been linked to modified cytokine production and asthma susceptibility. Two of the well-studied variants are the −590C/T (rs2243250) promoter polymorphism and the intron 3 VNTR. It was suggested that these genetic variations might affect the IL-4 transcriptional activity and further alter immune responses of allergic inflammation (Shirkani et al., 2019).

Recent findings have indicated that genetic polymorphisms of the IL-4 gene are correlated with heightened levels of IgE in serum and eosinophil counts for patients with asthma. For example, the -590C/T polymorphism T allele carriers were found to have increased IL-4 production resulting in augmented IgE synthesis and eosinophilic inflammation (Cui et al., 2003). This genetic susceptibility could account, at least in part, for the heterogeneity of asthmatic symptomatology and therapy responsiveness between individuals. Characterization of such relationships is critical especially in the age of personalized medicine, where genetic markers may inform targeted therapeutic interventions (Meyers et al., 2014).

Recent studies have also suggested that IL-4 polymorphisms may have clinical implications in asthma. A meta-analysis by Liu et al. (2022) found an association of IL-4 −590C/T polymorphism with asthma risk in Asian and Middle Eastern populations. Moreover, elevated eosinophil counts in association with IL-4 gene polymorphisms have been correlated with elevated exacerbation frequency and deteriorated asthma control (Papi et al., 2018). These results suggest a necessity to study IL-4 genetic variability in various populations since ethnicity and geography may impact on the allele frequency as well as disease associations.

Although IL-4 gene polymorphisms have become progressively more studied, results are conflicting as to a possible association between these and serum IgE and eosinophils. Some studies have shown significant associations, while others did not find such an association possibly owing to the variations in sample size, asthma phenotypes, environmental exposures and methodological methodologies applied (Chiang et al., 2022). In addition, IL-4 polymorphisms have not been analyzed concomitantly with immunological markers in clinical well-defined asthma patients in some previous studies.

As such, it is of good scientific and clinical relevance to study the relationship between IL-4 gene polymorphisms and serum IgE and eosinophil levels. Such analyses may yield further insights into the immunogenetic processes leading to asthma and could potentially identify subgroups of patients at high risk for severe or inadequately controlled disease. In addition, understanding these relationships may provide insights for a genotype-based risk stratification and help to enhance the effectiveness of biologics aimed at the Th2 inflammatory pathway (Tavakkol Afshari et al., 2007).

In this context, the current study is designed to investigate whether IL-4 gene polymorphism contributes in serum IgE and eosinophil levels in asthmatic patients. By combining genomics and immunology, this study aims to provide new insights in the pathogenesis of asthma and contribute to the development of tailored therapies for asthma.

Methods

Patients and data collection

This cross-sectional case–control study was performed at Al-Sadr Medical City, Najaf, Iraq, from March 2025 to December 2025 to determine the correlation between IL-4 gene polymorphism and levels of serum IgE and eosinophils in asthmatic patients.

A total of 98 asthmatic patients and 52 apparently healthy control subjects were enrolled in the study. Diagnosis of asthma was made by consultant pulmonologists as per GINA guidelines i.e., on the basis of clinical history, physical examination and spirometry. Patients were consecutively selected from the outpatient of respiratory and internal medicine clinics in Al-Sadr Medical City. The level of asthma severity was categorized as severe, moderate or mild, relying on symptom frequency and treatment need according to the Global Strategy for Asthma Management (GINA), 16) and lung function parameters.

Healthy age- and sex-matched participants without any personal history of asthma, chronic respiratory condition, allergic disease or recent acute illness were recruited as the control group. Controls were hospital colleagues and people who came to the hospital for health screening.

For instance, individuals with chronic systemic diseases including diabetes mellitus, autoimmune diseases, cardiovascular disease, malignancies or chronic inflammatory conditions were excluded. Patients with known genetic diseases, current infections, or long-term immune suppression were also excluded. Patients with use of systemic corticosteroids within 4 weeks were excluded to prevent the immunological bias.

Data regarding demographics and clinical data such as age, sex, BMI, disease duration, family history of asthma and smoking status were collected with a structured questionnaire and confirmed by medical files. BMI was calculated as divided by the square of height (kg/m²) and categorized according to WHO criteria.

Sample Collection and Laboratory Analysis

5 mL of venous blood was obtained from each participant in the morning after overnight fasting under sterile conditions. The blood samples were aliquot such that some of the blood collected was stored in ethylenediaminetetraacetic acid tubes for genomic DNA extraction and eosinophil count, whereas other portion without anticoagulant added was stored for serum separation. Serum was isolated by centrifugation at 3000 rpm for 10 min and kept in –20°C prior to analysis.

Serum total IgE levels were measured with a commercial ELISA kit based on the manufacturer's instructions. The samples were measured twice (as duplicates) and absorbance was read at 450 nm in a microplate reader. Standard calibration curves were used to determine concentrations. The intra- and inter-assay coefficient of variations were kept <10%.

In the peripheral blood, eosinophils were quantified in most cases using an automated hematology analyzer and were reported as absolute counts (cells/µL).

Genotyping of IL-4 Gene Polymorphism

Peripheral blood leukocytes were processed and genomic DNA was isolated using a standard commercial DNA extraction kit based on the manufacturer's instructions. Polymorphisms in IL-4 gene were assayed by the "polymerase chain reaction–restriction fragment length polymorphism" (PCR-RFLP). IL-4 genotyping PCR amplification was carried out with primers specific for the IL-4 polymorphic region. Following digestion of the PCR products with a suitable restriction enzyme, the digestion reactions were electrophoresed on 1.6% agarose gels. Genotypes were observed under UV light and images of the gel were taken through a gel doc system.

Ethical Considerations

The research protocol was also done and reviewed by the Institutional Review Board of Al-Sadr Medical City, Najaf. Informed consent was taken from each individual at the time of enrollment. The research followed the principles embodied in the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The normal distribution of continuous variables was verified by the Kolmogorov–Smirnov test. Normally distributed variables were described by mean ± standard deviation (SD) and non-normally variables by median and IQR. Differences between asthma and control were analysed by independent samples t-test or Mann–Whitney U test where relevant. One-way ANOVA test was used to compare IgE levels and eosinophil counts in IL-4 genotypes. Chi-square was used to test the differences in genotype and allele frequencies. Results A p value < 0.05 was accepted as statistically significant.

The Results

General demographic background of both patients and control groups is presented in Table 1. There were no significant variations in age distribution, sex ratio or place of residence between patients with asthma and healthy controls (P > 0.05 for all comparisons). Such demographic comparability would suggest that the two groups were well balanced with respect to the potential confounding effect of these variables on IL-4 gene polymorphism, serum IgE level and eosinophils count. As a result, any differences that were noted based on immunologic or genetic markers are more likely due to disease status rather than intrinsic demographic heterogeneity.

Table 1. General characteristics of both patients and control groups

Items		Patients (N= 98)		Control (N= 52)		(P value)
		Freq.	%	Freq.	%	
Age/Years	15-24	14	14.3	6	11.5	0.362 (NS)
	25-34	22	22.4	14	26.9	
	35-44	26	26.5	15	28.8	
	45-54	20	20.4	10	19.2	
	> 55	16	16.3	7	13.5	
Gender	Male	56	57.1	32	61.5	0.312 (NS)
	Female	42	42.9	20	38.5	
Residence	Urban	60	61.2	34	65.4	0.287 (NS)
	Rural	38	38.8	18	34.6	

NS: Non-significant at P value >0.05

The percentage of asthmatic patients based on the severity of asthma is illustrated in Figure 1. The majority of patients were reported to have moderate asthma (41%), while severe asthma reported (31%) and finally mild disease (28%).

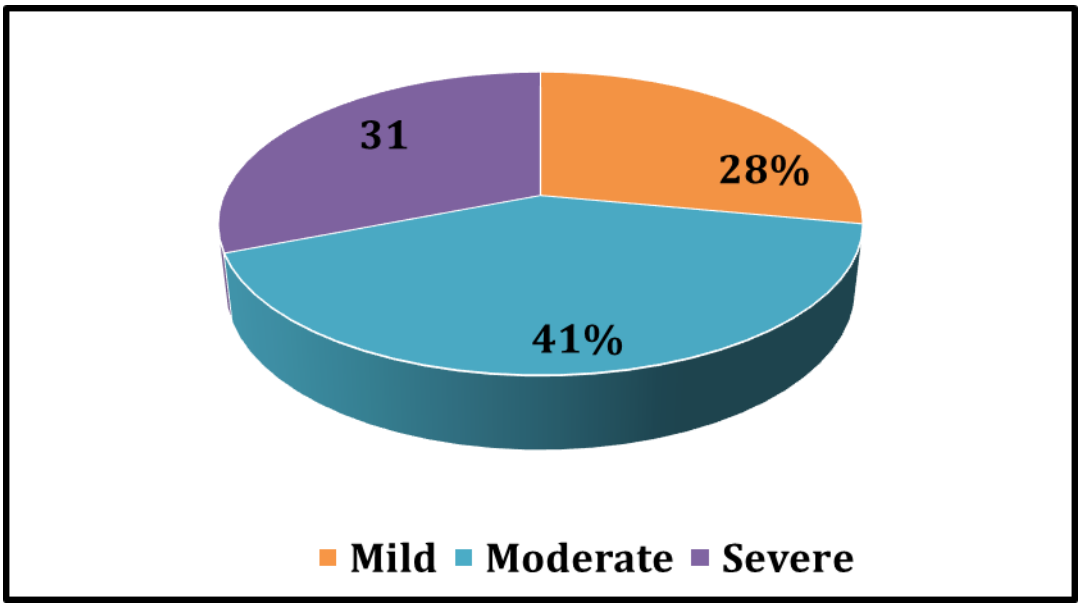

Figure 1. Distribution of patients based on the severity of asthma

One hundred and twenty-two patients with asthma showed statistically a significantly higher serum IgE levels than in the control group (310.6 ± 118.4 IU/mL vs 142.3 ± 64.7, P < 0.002) as shown in Table 2. Furthermore, the average peripheral blood eosinophil level was significantly higher in asthmatic patients (468.2 ± 152.6 cells/µL) when compared with controls (286.9 ± 104.3 cells/µL, P < 0.03).

Table 2. Comparison of levels of IE and eosinophil count between asthmatic patients and control

	Patients (N= 98)		Control (N= 52)		(P value)
	Mean	SD	Mean	SD	
IgE (IU/mL)	310.6	118.4	142.3	64.7	< 0.002 **
Eosinophil count (cells/µL)	468.2	152.6	286.9	104.3	< 0.03 *

*** Significant at P value <0.05; ** High Significant at P value <0.01**

The distribution of IL-4 alleles and genotypes among asthmatics and controls is shown in Table 3. Although the C allele was predominant in both groups, there were no significant differences in the distribution of the genotypes between patients (60.2%) and controls (69.2%, P = 0.072). In the present study, the frequency of T allele was found to be statistically higher in the asthma subjects (39.8%) than controls (30.8%, P = 0.015), indicating that T allele might be associated with asthma predisposition are interesting observations in this report. With respect to the genotype distribution, the CC genotype occurred more frequently in controls (46.2%) than in patients (34.7%), although this was not statistically significant (P = 0.083). The TC genotype, which is the heterozygous genotype, though was higher in asthmatics 51.0%) than non-asthmatics (42.3%, P = 0.041). Also, the frequency of TT genotype was significantly higher among patients (14.3%) compared with controls (11.5%, P = 0.023). These findings suggest that the IL-4 T allele

and T-containing genotypes (TC and TT) could be associated with higher susceptibility to asthma primarily due to enhanced IgE production and eosinophilic inflammation induced by IL-4.

Table 3. Comparison of IL-4 alleles and genotypes polymorphism among asthmatic patients and control

Polymorphism		Patients (N= 98)		Control (N= 52)		(P value)
		Freq.	%	Freq.	%	
Alleles	C	118	60.2	72	118	0.072
	T	78	39.8	32	78	0.015
Genotypes	CC	34	34.7	24	34	0.083
	TC	50	51	22	50	0.041
	TT	14	14.3	6	14	0.023

Distribution of IL-4 alleles and genotypes in the asthmatic patients by serum IgE levels is shown in Table 4. The frequency of C allele tended to be higher in the patients with normal IgE (65.0%) than those with elevated IgE (55.2%), but a statistically significant difference was not detected (P = 0.062). On the other hand, the frequency of T allele was significantly higher in cases with high IgE (44.8%) than in patients who had normal IgE (35.0%, P = 0.025). With regard to genotype distribution, the CC genotype was more frequent in the normal IgE group (45.0%) than in the elevated IgE group (27.6%), although the variation was not statistically significant (P = 0.066). In contrast, the heterozygous TC genotype frequency was significantly increased in patients with high IgE levels (58.6%) compared with those who had normal IgE (40.0% P = 0.032). Further, the TT genotype was also significantly associated with high IgE levels (P = 0.014) despite being less frequent overall. Together, these findings indicate that the IL-4 T allele and T-containing genotypes are linked with elevated IgE level in asthmatic patients, providing support for the concept of genetic variability in the IL-4 regulation of Th2 immunity Th2 reaction and IgE-related allergic inflammation.

Table 4. Comparison of IL-4 alleles and genotypes polymorphism among asthmatic patients with normal and elevated IgE

Polymorphism		Normal IgE (N= 40)		Elevated IgE (N= 58)		(P value)
		Freq.	%	Freq.	%	
Alleles	C	52	65	64	52	0.062
	T	28	35	52	28	0.025
Genotypes	CC	18	45	16	18	0.066
	TC	16	40	34	16	0.032
	TT	6	15	8	6	0.014

The distribution of the IL-4 alleles and genotypes among asthmatic patients, stratified by peripheral blood eosinophils levels is presented in table 5. In patients with normal or elevated eosinophil counts, the distribution of C allele was 64.4 and 51.9%, respectively (P = 0.052). The T allele, however, was significantly associated with higher eosinophil level group (48.1%) than lower eosinophil group (35.6%, P = 0.015). Regarding genotypes, the distribution ratio of CC genotype was higher in patients without eosinophilia (48.9%), compared to those with eosinophilia (33.3%), although this variation was not statistically significant (P = 0.096). In Comparison, the TC genotype was strikingly higher in patients with eosinophilic counts greater than normal (51.9%) versus less or equal to normal (35.6%, P = 0.042). The TT genotype was also associated with high level of eosinophils (P = 0.034). Together, these data suggest the myopic allele and T-containing genotypes may be a functionally relevant marker for increased eosinophilic inflammation in asthmatics, suggesting an additional role of IL-4 genetic variation in disease immunopathogenesis.

Table 5. Comparison of IL-4 alleles and genotypes polymorphism among asthmatic patients with normal and elevated eosinophils

Polymorphism		Normal Eosinophils (N= 45)		Elevated Eosinophils (N= 54)		(P value)
		Freq.	%	Freq.	%	
Alleles	C	58	64.4	56	51.9	0.052
	T	32	35.6	52	48.1	0.015
Genotypes	CC	22	48.9	18	33.3	0.096
	TC	16	35.6	28	51.9	0.042
	TT	7	15.5	8	14.8	0.034

Discussion

This article studied the association between IL-4 gene polymorphism, and serum IgE levels and eosinophil count in patients with bronchial asthma in comparison to normal controls. Its results support a role for genetic variation within IL-4 in susceptibility to asthma and its immunological phenotype, in particular through increased IgE production and eosinophilic inflammation.

There were no significant variations in the sex, age and residence between patients' group and control group according to demographic analysis. This age and sex comparability improve the robustness of immunological and genetic associations observed, by controlling for confounders. Analogous matching strategies have been given importance in Genome-Wide Association Studies (GWAS) to rule out that divergence of allele/genotype frequencies can be attributed to status rather than population (Ober & Yao, 2011).

An important result was the statistically higher serum levels of IgE and counts of eosinophil in asthmatic individuals compared to non-asthmatic controls. A high level of IgE (310.6 ± 118.4 IU/mL vs. 142.3 ± 64.7 IU/mL, P < 0.01) and eosinophila (468.2 ± 152.6 vs.286.9 ±104.3 cells/µL P <0.05) is one of the typical phenotypes of a Th2 type asthma which support that characterizing the pivotal role of type do cytokines in targeting allergic airway inflammation. These data are in agreement with the earlier findings that elevated IgE synthesis and eosinophil recruitment are strongly associated with disease severity and airway hyperresponsiveness (Fahy, 2015; Papi et al., 2018).

There was a significantly increased proportion of IL-4 T allele among asthmatics compared to the controls. The C allele showed no significant variation in distribution between cases and control in this population. Furthermore, TC and TT genotypes were significantly overrepresented in patients, while the CC genotype was more frequent among controls. These results indicate that the T allele might be a susceptibility allele for asthma, possibly enhancing IL-4 expression or function. IL-4 is a critical cytokine

in B-cell class switching to IgE, development of naïve T cells into Th2 cells as well as augmentation of allergic inflammation (Junttila, 2018).

The significant relationship of IL-4 polymorphism with asthma found in this study is consistent with a number of previous studies. For example, a study by Liu et al. (2018) found that the IL-4 gene polymorphisms were correlated with asthma susceptibility in a variety of populations. Conversely, studies performed in Middle Eastern and Asian individuals have identified an increased prevalence of T-containing genotypes in asthmatic populations further consolidating the biological importance of this polymorphism with respect to allergic disease development (Al-Hachamy & Al-Saadi, 2015; Imani et al., 2020). However, such SUV39H1 associations have been proven to be inconsistent among distinct studies, potentially due to ethnicity difference, sample size and environment (Ober & Yao, 2011).

Adaptation of asthmatics by serum IgE levels also demonstrated functional significance of IL-4 polymorphism. Patients with increased IgE levels had significantly higher T allele and TC and TT genotype frequencies than those with normal IgE levels. This observation is consistent with the mechanistic function of IL-4 as a regulator of IgE production. IL-4 is a T cell derived cytokine that in B lymphocytes induces immunoglobulin class switching, consequently a SNV or cluster of related SNVs which potentiate IL-4 signaling may result in exaggerated IgE responses and potentially increase sensitization and severity of disease (Junttila 2018; Fahy 2015).

When the patients were also stratified according to eosinophil count, T allele and T-containing genotypes remained associated with elevated eosinophils. This relationship highlights the involvement of IL-4 in eosinophil mobilization and viability, either directly or partly also by induction of other eosinophil attracting cytokines like IL-5. It has been shown that genetic variants in Th2 cytokines may affect eosinophilic inflammation and clinical presentations of asthma, especially the eosinophilic phenotype (Papi et al., 2018; Hinks et al., 2016).

The results of our study as a whole demonstrate that IL-4 polymorphism not only is associated with human asthma susceptibility, but it also relates to the immunological markers of disease activity: IgE production and eosinophil levels. These findings are compatible with the hypothesis that asthma is a genetically regulated inflammatory disease, where cytokine gene polymorphism not only influences susceptibility to the disease but also its immunopathological expression (Matucci et al., 2018).

Limitations of this study Despite the many strengths, limitations remain. It is noteworthy, however, that the sample size may have implications for generalizability of these findings. Furthermore, we did not consider gene–environment interactions and other cytokine polymorphisms. Larger cohorts, functional assays and several genetic markers are needed in future studies to further define the role of IL-4 polymorphism in asthma development.

Conclusion

The study has shown that IL-4 T allele and TT/CT genotypes were associated with asthma, increased IgE levels and eosinophilic inflammation. These results support the potential role of IL-4–mediated pathways in asthma and indicate that genetic variants are associated with differences in the amount of immune response conferred by IL-4 and disease phenotype.

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