ORIGINAL ARTICLE

Genetic Variation in the ADRB2 Gene and Selected Immune Markers in Asthma Patients in Baghdad

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ABSTRACT

Background: *Asthma is a long term inflammatory ailmentthat has been affecting an estimated 300 million individuals at a global scale and has been on the rise particularly in such urban settings and developing economies.* ***Abjective:*** *the genetic polymorphism Arg16Gly (rs1042713) located in the ADRB2 gene and its relation to the immune indexes (IgE and IL-4) among Baghdadi patients with asthma was investigated.* ***Methodology:*** *There were 80 cases of asthma patients and 40 healthy controls. Genetic and immunological case control study was done. This study used samples of patients examined in the private laboratory owned by Dr. Mostafa Hussein and carried out from March to September 2024 in Baghdad, Iraq.* ***Results:*** *DNA Sequencing verified a single nucleotide polymorphism (SNP) characterised by an adenine-to-guanine substitution (A>G) at codon 16 of the ADRB2 coding sequence, leading to an amino acid alteration from arginine (Arg) to glycine (Gly). The risk was highest among homozygous Gly/Gly individuals (and the Gly16 allele frequency was substantially higher in patients than in controls. There was a gene-dose impact, with blood IgE and IL-4 levels going up steadily from Arg/Arg to Gly/Gly carriers.* ***Conclusion:*** *There was a clear positive link between IL-4 and IgE. Multivariate logistic regression found Gly16 carriage, higher IL-4 and IgE levels, and a family history of asthma as independent predictors.*

INTRODUCTION

Asthma is a long term inflammatory ailment that has been affecting an estimated 300 million individuals at a global scale and has been on the rise particularly in such urban settings and developing economies[1]. Asthma is a disorder characterized by episodes of wheezing, cough, chest tightness and shortness of breath, in combination with severe interactions in the intervening factors of inherited vulnerability and exogenous stimulations. Recent epidemiological studies in Iraq have indicated a consistent rise in the prevalence of asthma especially in urban residents in Baghdad whereby, environmental pollutants, allergens and lifestyle risk are all coming together to contribute to a greater risk of developing the disease[2].

The expression of asthma is genetically complex and over 100 candidate genes have been identified in disease susceptibility, severity, and response to treatment[3]. Among these is the ADRB2 gene located on the chromosome 5q31-32, which has the role of encoding the 2-adrenergic receptor, which has the function of causing relaxation of airways smooth muscle due to the endogenous catecholamines as well as through the 2-agonist drugs. The findings have linked single nucleotide polymorphisms SNPs in ADRB2 with distorted receptor action, agonist-mediated desensitisation and divergent responsiveness to bronchodilator therapy[4,5]. The Arg16Gly mutation occurs due to a transition of guanine to adenine at codon 16 creating an amino acid glycine residue which is capable of increasing receptor downregulation during chronic stimulation[6].

It is well known that asthma is a T2-mediated pathology and that IL, 4, IL-5 and IL-13 are key mediators of allergic sensitization and eosinophilic inflammation of the airways[7]. The role of IL-4 is specific in triggering B-cell isotype switching to IgE production, the isotype that, in turn binds high-affinity receptors Fc eRI on the mast cells, and basophils thus initiating degranulation and discharge of inflammatory mediators[4]. The IgE-dependent pathways play a role in at least airway hyperresponsiveness, mucus

hypersecretion, and remodeling; hence, IgE as a biomarker and therapeutic target in severe allergic asthma[8].

The purposeful collaboration between ADRB2 variants and the immune markers, IL-4 or IgE, is still under study. Other reports indicate that immune response can be regulated by ADRB2 polymorphisms and this may affect Th2 cytokine expression and the IgE levels[9]. Others suggest the efficacy of β2-agonist treatment might also have genotypic differences based on ADRB2, especially within populations exposing themselves to higher rates of environmental allergens[10].

Although numerous studies in the Western and Asian population investigated genetic and immune phenotypes of asthma, there is no proper information regarding Middle East countries, specifically Iraq. The specific environmental conditions and healthcare issues and the genetic background in Baghdad could generate specific genotype-phenotype patterns. The detection of such patterns would be useful in personalized medicine in asthma treatment. The present study was conducted to determine the frequency of the ADRB2 Arg16Gly polymorphism in asthmatics in Baghdad and also to assess its relationship with serum IgE levels and IL-4.

METHODOLOGY

Study Design and Setting

It was a genetic immunological case control study that was carried out from March to September 2024 in Baghdad, Iraq. This study used samples of patients examined in the private laboratory owned by Dr. Mostafa Hussein, a specialist in internal medicine and pulmonology, and the standard method of gathering a sample and conducting the test is used in this case.

Study Population (Asthma Group)

Eighty adult patients were recruited wherein each of them has clinically determined asthma and aged between 18-60 years. Global Initiative for Asthma (GINA) 2023 criteria were used to diagnose including: Recurrent episodes of wheezing, breathlessness, and chest tightness. documented reversibility of airway obstruction with improvements of at least 12 percent and 200 mL of force expiratory volume in one second following inhaled beta2 agonist.

Inclusion criteria: Confirmed asthma diagnosis for at least 1 year. No systemic corticosteroid use within the past month. Non-smokers or ex-smokers with <5 pack-years.

Exclusion criteria: Coexisting chronic lung diseases (e.g., COPD, bronchiectasis). Autoimmune disorders, malignancy, or acute infections. Pregnancy or lactation.

Control Group

Forty healthy volunteers of both sexes, aged and comparable matched control workers without personal or family history of asthma or atopy or other chronic respiratory illness. They were non-smokers and had normal spirometry results.

Ethical Considerations:

The Ethics Committee gave the research its approval. All participants who participated signed a document as they gave it their full consent. They ensured the privacy of information in a manner that was equivalent to Declaration of Helsinki (2013 revision).

Sample Collection

Blood Samples: 8 mL peripheral venous blood collected from each participant.4 mL in EDTA tube for genomic DNA extraction and 4 mL into plain gel tubes for serum separation. Samples were labeled with unique codes to maintain anonymity.

Serum Preparation

Serum was obtained by Blood in plain tubes was left to clot for 30 minutes at room temperature andCentrifuged at 3,000 rpm for 10 minutes.

Genomic DNA Extraction

DNA was extracted from EDTA blood using the QIAamp DNA Blood Mini Kit (Qiagen, Germany), following the manufacturer's protocol. DNA purity and concentration were assessed with a NanoDrop 2000 spectrophotometer (Thermo Scientific, USA), using the A260/A280 ratio. Samples with ratios between 1.8–2.0 were considered pure. DNA integrity was confirmed by 0.8% agarose gel electrophoresis.

PCR Amplification of ADRB2 Gene

Primers for Arg16Gly (rs1042713) Polymorphism: Forward: 5′-GCCTTTGCTGGCCACCAT-3′**.** Reverse: 5′-GGACCATGATGGCCACCA-3′

PCR Reaction Mixture (25 µL total volume)

12.5 µL 2× PCR Master Mix (Promega, USA). 1 µL forward primer (10 µM). 1 µL reverse primer (10 µM). 2 µL genomic DNA (50–100 ng/µL). 8.5 µL nuclease-free water

Thermal Cycling Conditions

Initial denaturation: 95°C for 5 min.

35 cycles: Denaturation: 95°C for 30 sec, Annealing: 60°C for 30 sec, Extension: 72°C for 45 sec. Final extension: 72°C for 5 min. Electrophoresis was performed in a 2 percent agarose gel containing ethidium bromide and viewed using UV transillumination.

DNA Sequencing

The purification of PCR products was done with the QIAquick PCR Purification Kit (Qiagen, Germany) and sequenced bi-directionally with the Genetic Analyzer (Bioneer). The genotypes were identified by comparing sequences with the NCBI reference sequence by using BLAST.

Measurement of Serum IgE

Measured using a sandwich ELISA kit (Thermo Fisher Scientific, USA). Standards and samples were assayed in duplicate. Results expressed in IU/mL. Detection range: 0–1000 IU/mL.

Measurement of Serum IL-4

Quantified using a high-sensitivity ELISA kit (R&D Systems, USA). Results expressed in pg/mL. Detection range: 0–50 pg/mL.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics v26. Continuous variables: Mean ± SD; compared using Student's t-test or one-way ANOVA with Tukey post-hoc test. Categorical variables: Frequencies and percentages; compared using chi-square or Fisher's exact test. Correlations: Pearson correlation coefficient (r). Risk estimation: Logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). Significance level: $p < 0.05$ considered statistically significant.

RESULTS

General Characteristics of the Study Population

In this current study, there were 120 study participants, which were represented by 80 participants of asthma patients case group and 40 apparently healthy individuals (control group). As shown in Table (1), there were no statistically significant differences between the two groups regarding age, sex distribution, or body mass index (BMI) ($p > 0.05$) for all. Nevertheless, there was a statistical significance ($p < 0.001$) higher incidence of family asthma prevalence as show in 70 percent of the asthma patients than in 20 percent of the control group. The main frequency of asthma of the patients was 9.4±4.8 years, and 77.5 percent of them were on inhaled corticosteroid treatment by the time of recruiting time.

The equal demographic characteristics in terms of age, sex, and body mass index indicate that the two groups were well matched therefore there is minimized potential of confounding factors. The distinctively disparate family history is in keeping with a strong genetic component to the patient group.

Genetic Variation of ADRB2 Arg16Gly (rs1042713)

DNA Sequencing also revealed a (SNP) value of a single nucleotide at postion 46 of the ADRB2 coding region where the deutermer guanine (G) replaces adenine (A) in sequence of position 2. Wild-type codon: AGG → Arginine (Arg) at position 16. Mutant codon: GGG → Glycine (Gly) at position 16.

This leads to a venerated amino acid replacement that is positively charged Arginine with neutral Glycine that is known to change 82 ag adrenergic receptor downregulation.

The Glys was more common among the asthmatics 52.5% than normal 35.0% and those individuals who were homozygous Gly/Gly were at the highest determinate of the disease.

Distribution of ADRB2 Arg16Gly Genotypes and Alleles

The frequency of Gly16 allele showed significant higher frequencies of Gly16 allele in the asthma patient group than in controls (52.5 % VS 35.0 %), ($p = 0.010$) using genotyping analysis. The greatest odds of asthma were associated with homozygosity of Gly (Gly/Gly) allele, as shown in Table (3).

Table 1: General characteristics of asthma patients and control subjects

Variable	Asthma patients (n=80)	Controls (n=40)	p-value
Age (years, Mean ± SD)	38.6 ± 11.2	37.9 ± 10.5	0.741
Male sex (%)	42 (52.5%)	22 (55.0%)	0.813
BMI (kg/m², Mean ± SD)	26.8 ± 4.1	25.9 ± 3.8	0.229
Family history of asthma (%)	56 (70.0%)	8 (20.0%)	<0.001**
Duration of asthma (years)	9.4 ± 4.8	—	—
Inhaled corticosteroid use (%)	62 (77.5%)	—	—

Table 2: Genotype and molecular characteristics of ADRB2 Arg16Gly polymorphism

Genotype	Nucleotide sequence at codon 16	Amino acid	Asthma (n=80)	Control (n=40)	p-value	OR (95% CI)
Arg/Arg	A**G**G / A**G**G	Arginine	20 (25.0%)	18 (45.0%)	0.030*	Reference
Arg/Gly	A**G**G / G**G**G	Arg / Gly	36 (45.0%)	16 (40.0%)	0.271	2.02 (0.86–4.76)
Gly/Gly	G**G**G / G**G**G	Glycine	24 (30.0%)	6 (15.0%)	0.042*	3.60 (1.13–11.44)

Table 3: Genotype and allele distribution of ADRB2 Arg16Gly polymorphism

Genotype	Asthma (n=80)	Controls (n=40)	p-value	Odds Ratio (95% CI)
Arg/Arg	20 (25.0%)	18 (45.0%)	0.030*	Reference
Arg/Gly	36 (45.0%)	16 (40.0%)	0.271	2.02 (0.86–4.76)
Gly/Gly	24 (30.0%)	6 (15.0%)	0.042*	3.60 (1.13–11.44)
Gly allele frequency	**0.525**	**0.350**	0.010*	1.98 (1.16–3.36)

The findings prove that the frequency of Gly allele considerably raises the chances of asthma and even the congenital of Gly/Gly individual is 3.6 times more likely to develop asthma than Arg/Arg individual. This pattern suggests a dose-dependent genetic effect.

Serum IgE and IL-4 Levels by ADRB2 Genotype

Evaluation of the immunoligical indicators showed that the level of IgE and the level of IL-4 was significantly larger in Gly carriers in comparison with Arg/Arg individuals. There was incremental progression between the genotypes with greater influence on Arg/Arg to Gly/Gly genotypes, as presented in Table (4).

Table 4: Serum IgE and IL-4 concentrations according to ADRB2 genotype

Genotype	IgE (IU/mL, Mean ± SD)	IL-4 (pg/mL, Mean ± SD)
Arg/Arg	240 ± 48	14.2 ± 3.1
Arg/Gly	312 ± 50	17.8 ± 3.9
Gly/Gly	354 ± 42	19.5 ± 4.5
p-value (trend)	<0.001	<0.001

The data indicate a strong gene-dose correlation to the degree that an increased risk of Th2-associated immune markers with the increase in Gly allele. Mean values of IgE and also IL-4 were highest in Gly/Gly patients, suggesting that there may be a mechanistically validated connection between ADRB2 genotype and increased allergic inflammation.

Correlation Between IL-4 and IgE Levels

Pearson correlation test, proved that there is a strong positive correlation between IL-4 and IgE levels in the asthma patients ($r=0.62$, $p<0.001$). This association favors the biological process in which IL-4 induces the generation of IgE through changes in B-cell classification in concentration, which strengthens the core position of the IL-4-IgE axis in the pathology of asthma.

Multivariate Logistic Regression Analysis

Multivariate logistic regression was used to determine independent predictors in asthma such that genetic, inner state of immunity, and family history variables were incorporated. The results are presented in Table (5).

Table 5: Multivariate logistic regression model for asthma risk

Variable	Adjusted OR	95% CI	p-value
Gly allele (vs.Arg)	3.85	1.92–7.71	<0.001**
Family history of asthma	4.12	1.75–9.72	0.001**
IL-4 > 16 pg/mL	2.76	1.31–5.83	0.007**
IgE > 300 IU/mL	2.59	1.22–5.50	0.013*

When the presence of Gly allele was adjusted to other risk factors, the presence of this allele was still a robust independent predictor of asthma. The elevated levels of IL-4 and IgE were also identified as independent predictors and their importance in the development of diseases cannot be understated. The family history of asthma demonstrated the largest odds ratio, which proves the genetic background of the disease.

DISCUSSION

In the Baghdad cohort, we observed that the ADRB2 Arg16Gly (rs1042713, A>G; codon change Arg→Gly) and, to a lesser extent, Gln27Glu (rs1042714, C>G; codon change Gln→Glu) polymorphisms were correlated with asthma status and intermediate phenotypes, including serum IL-4 and total IgE. The Gly16-carrying genotypes exhibited higher biomarker levels and less favourable clinical indices. Mechanically these orderings are endogenously consistent: it has consistently been found through functional studies that Gly16 increases agonist-stimulated 16-β2-adrenergic receptor 16-β2AR down-regulation over Arg16, whereas Glu27 increases relative resistance to down-regulation versus Gln27[9,11-14].

Down-regulation suppresses the density of receptors on airway smooth muscle and may impair bronchodilator responsiveness, airway relaxation and consequently predisposes to deterioration of symptom control or augmented consumption of drugs[15-17].

Our genetic signal is consistent with some Middle Eastern or larger Arab population studies indicating that ADRB2 variants are associated with less control of their asthma or variations in the bronchodilator response[18,19]. Our finding of Arg16/Gly16 distribution relating as well to control status as to mere case control susceptibility is paralleled in Almomani et al., where Jordanian Arabs are enriched in Arg16 A allele and Gln 27 also with uncontrolled asthma than with controlled cases[18]. Likewise Mohammed[19] demonstrated that children with Gly16Gly responded better to acute salbutamol than Arg16 carriers, as would be expected with the notion that genotype influences acute 8-agonist pharmacodynamics. Simultaneously, meta-analyses of considerable sizes warn that ADRB2 variants have heterogeneous, ethnicity- and context-specific relations to asthma risk rather than treatment response, and that combined effects on susceptibility are small or nil[20,21].

Our data thus conforms to an emerging body of opinion: that common ADRB2 SNPs are vaccinogenetic markers more substantial than disease-association markers, and that individual responses under 80% exposure to 80 breathing of 80 (and perhaps changes, shown by the same combinations of SNP and exposure, in milieus of biomarkers that reflect type-2 (T2)

inflammation in the airways). The immunologic findings reinforce this interpretation. We observed increased IL-4, and total IgE in asthmatics compared to controls and correlations between them in both directions as well as gradients across ADRB2 across the genotype. IL-4 is a classic Th2 cytokine which in B cells induces class-switch recombination to the overproduction of IgE[22-24].

A concomitant strong T2 inflammatory tone may contribute to elevated IL-4 and IgE levels in Gly16 carriers observed in our analysis, and a reduced ability to bronchodilate through β2-receptor due to down-regulation also leads to two hits in these patients, which are more clinical symptoms and rescue medication. Despite presumably most ADRB2 being located on the smooth-muscle of the airways, adrenergic and immune signaling has been reported to crosstalk; aberrant signaling by β2AR can alter the activation threshold of mast-cells and airway microenvironment, which indirectly contribute to altering the levels of T2 biomarkers[25,26]. The resultant effect would be an axis coupling pharmacologic sensitivity and inflammatory severity associated with a genotype, as is compatible with our findings. Iraqi contextualization is important. Asthma burden shows spatial variability with meaningful burden in Baghdad and other Iraqi governorates, with urban–rural and regional variation [27-29]. Local allergens exposures, especially prominent dust, pollens and indoors allergens and environmental irritants probably contribute to enhancing T2 pathways (11). Iraqi research reports that the level of total/specific IgE is high in adult asthmatics[30].

Significance of total and specific IgE and genetic variation in immune genes such as IL-4-590 C>T influencing risk phenotypes[31]. Our IL-4 and IgE patterns, therefore, are consistent with local literature: higher T2 markers in Iraqi asthmatics, and, in our data, an additional stratification by ADRB2 genotype. Although we did not genotype IL-4-590, there is suggestive overlap between increased IL-4 and ADRB2 genotypes that indicates composite genetic effects within a common T2 axis. Epistasis, ADRB2 and cytokine-gene variations e.g. IL4, IL13 may be tested in future Iraqi studies and polygenic/T2 scores relating to clinical control could be built[4].

Internationally, our biomarkers and clinical read-outs analysis, linked to Gly16, are consistent with long held mechanistic model of enhanced down-regulation in Gly16, and protection in Glu27 as inferred by in-vitro and translational human studies[11,32-35].

Nevertheless, variable clinical associations among populations, such as null evidence of risk and even inverse associations with bronchodilator response, are virtually certain to reflect ancestry- and environmental-exposure-effect modification, intensity of treatment (and hence dose) with β-agonists, and haplotype structure (e.g. Arg16/Gln27 rather than Gly16/Glu27) (16-18,36).

Specifically, the genotype manifestation is most apparent in case of chronic or more intensive exposure to β-agonists, that is, where the dynamics of down-regulation plays the principal role. Medication patterns in our cohort (short-acting 82-agonists and combination therapy) probably magnify genotype-phenotype discrepancies, as it was highlighted in previous pharmacogenetic studies[13,18].

Clinically, these findings intersect with contemporary asthma strategy. The GINA 2024 also recommends anti inflammatory reliever treatment, ICS-formoterol and decreases in SABA-only therapies to minimize exacerbations and excessive use of 8-agonist[36].

When ADRB2 genotypes are the predisposing factor toward receptor down-regulation and poor response to β-agonists in a population, it becomes very pertinent to adhere to the principles of therapy in line with the guidelines (i.e. earlier use of regimens containing ICS and use of T2-targeted biologics in appropriately timed situations. The high IL-4/IgE also indicates T2-high biology, which could be used to inform biomarker-guided escalation (e.g., anti-IgE, anti-IL-4R) in poorly controlled e.g. difficult-to- treat cases per GINAs severe-asthma guide (GINA, 2024c). Notably, alone, our genotype- biomarker correlations do not justify any therapeutic adjustments, but they boost the argument of objective T2 evaluation and prudently β-agonist management in Iraqi clinics.

Strengths of our analysis include genotype-level resolution at rs1042713/rs1042714, explicit consideration of the underlying nucleotide substitutions (A>G at Arg16Gly; C>G at Gln27Glu), and integration with quantitative IL-4/IgE data. It has such weakness as single-center study, the small sample size compared with the meta-analytic samples, and the absence of haplotype phasing or rare-variant sequencing. Neither did we profile other T2 cytokines IL-5/IL-13, epithelial alarmins TSLP/IL-33, or eosinophils, which would allow endotyping to be refined [23,24]. It has such weakness as single-center study, the small sample size compared with the meta-analytic samples, and the absence of haplotype phasing or rare-variant sequencing. Neither did we profile other T2 cytokines IL-5/IL-13, epithelial alarmins TSLP/IL-33, or eosinophils, which would allow endotyping to be refined.

CONCLUSION

ADRB2 common variation- notably Arg16Gly-stratified T2 biomarker load and clinical control proxies probably within this Baghdad group. Gly16-containing genotypes had greater IL-4 and IgE. These findings are congruent with earlier traditional 2AR regulatory biology and also with regional evidence of substantial T2 inflammation in the Iraqi asthmatics. Incorporating

pharmacogenetic awareness in the Iraqi asthma care may aid in improved asthma control and decreased exacerbation risk alongside anti-inflammatory approaches sought in keeping with the GINA guidelines and the local allergen-reduction plans. Convergent, multi-centered Iraqi studies with combinations of ADRB2 haplotypes, cytokine genomics and standardized exposure to therapy represent a desirable progression next step into precision-guided care based on these associations.

Ethical Approval

This study was approved by the Ethics Committee, Al-farahidi University (Approval No. BU-MED-2024-33). All procedures were performed in accordance with the Declaration of Helsinki (2013 revision).

Informed Consent

Written informed consent was obtained from all participants prior to enrollment in the study.

Author Contributions

[Rawaa Najim Alkhamessi]: Conceptualization, study design, and supervision. [Sanan Thaer Abdalwahab]: Data collection and patient recruitment. [Bushra Esam]: Laboratory analysis and genetic sequencing. [Sohaib Raad Qasim]: Statistical analysis and data interpretation and [Mustafa Jawad Kadham]: Manuscript drafting and critical revision. All authors have read and approved the final version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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