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Polymorphism in the *Toll-like Receptor 2* Subfamily and Risk of Atopy: A Population Study in Zanjan, Iran

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ABSTRACT

Background & Objective: Atopy is an allergic state with manifestations of asthma, atopic dermatitis, and allergic rhinitis. There was a genetic tendency to atopy, and the genetic polymorphisms in the *TLR*s had been shown as a causal factor. The objective of this research was to examine the association between *TLR2* rs7656411 polymorphism and atopic individuals in Zanjan Province.

Materials & Methods: Total genomic DNA was extracted from the whole blood of atopic and non-atopic individuals (100 atopic patients and 50 healthy control subjects) who were referred to the Allergy Clinic at Mousavi Hospital of Zanjan University of Medical Sciences Zanjan, Iran. PCR amplification and direct sequencing methods were employed for genotyping of *TLR2* rs7656411 in all patients and controls.

Results: In this study, the GG genotype was higher in the patients than in the controls (15% vs. 8% in non-atopic subjects). However, this difference was not significant (P-value = 0.21). We also did not find any significant difference between the frequency of alleles (G and T) in the patients and controls.

Conclusion: Our study showed that *TLR2* rs7656411 polymorphism are not significantly associated with atopy in an Iranian population, but the GG genotype might be a risk factor for atopy.

Keywords: Asthma, *TLR2*, Single Nucleotide Polymorphism, Atopy

1. Introduction

Allergy-associated diseases are the most common chronic diseases in developed countries. There has been a consistent rise in the percentage of the population experiencing allergies over time. A recent study in Zanjan showed that about one-third of school children had at least one symptom of allergy (1-3).

The remarkable increase in allergies and asthma observed in the developed world today, particularly in recent decades, cannot be solely attributed to genetic changes occurring within this brief timeframe. Given these conditions, there seems to be a global epidemic of allergic diseases that may be due to environmental changes, improved public health, and a wide range of genetic susceptibilities (4-6).

Therefore, in most countries, allergy treatment should be the major concern (7). Allergies involve an abnormal immune response to environmental antigens such as pollen, peanuts, wool, or animal dander (8). The reason for the recent increase in allergic diseases is most likely the bio-environmental effect on microbiota changes. For example, there is evidence to suggest that the gut microbiomes modulate the function of Th1/Th2 cells, which may be effective in inducing the immune tolerance against antigens (9). The molecular basis of the allergic process is not fully understood. Nonetheless, various mechanisms have been suggested, one of which is related to the perturbation of the function and structure of epithelial barriers. Under normal circumstances, dendritic cells (DCs) can process antigens from epithelial barriers by spreading between epithelial cells and tight binding proteins. However, if the epithelial barrier is damaged, antigens can penetrate the sub-epithelium and activate the innate and acquired immune response (10, 11).

Another suggested mechanism is that allergens stimulate the protease receptors located on epithelial cells, which in turn triggers the production of innate cytokines and ultimately leads to the activation of T cells, especially Th2 (11). Activation of APCs (antigen presenting cells) in turn activates the *TLR*s (Toll-like receptors) signaling pathway and initiates an immune response (10). In allergic individuals, activated APCs migrate to the lymph node for depletion, where they polarize T cells to prepare them for defending against environmental allergens (12). Antigen-specific T cells infiltrate the tissue and produce Th2 cytokines that cause the appearance of allergy symptoms (13). Polarized Th2 cells support IgE-switched B cells and cause mast cell and eosinophils infiltration (10, 11). Maturation and activation of innate immune cells are mediated by *TLR*s that are essential for maintaining immune homeostasis, but they can also derive allergic responses. *TLR*s are a family of membrane protein receptors essential for innate immune activation, consisting of conserved leucine-rich repeat domains. *TLR*s are one of the first lines of defense of the body, activated by pathogen-associated molecular patterns (PAMPs), and these molecular structures are specific to the pathogens and do not occur in the host. Eleven types of *TLR* (*TLR*1-*TLR*11) have been identified in humans, all of them except for *TLR*11 are functional (12, 13). *TLR*s directly and indirectly modulate the function of Treg cells that play an important role in immune responses. Activation of *TLR*s is accomplished by the activation of antigen-presenting cells (APCs) and the release of cytokines, both of which strongly modulate Treg-mediated immune suppression (14). In addition, recent investigations indicate that there is an unknown pathway in which *TLR*s expressed on Treg cells modulate immune responses by interfering with the suppressive activity of Tregs (15-17). Many studies have shown that Tregs play a critical role in the development of atopic diseases and that *TLR* signaling pathways influence the function and number of Tregs in umbilical cord blood (18-21). Therefore, *TLR*s play a key role in recognizing the microbiome environment and thus modulating allergy-related symptoms. Polymorphisms of these receptors may influence the exacerbation of atopic diseases (22-24). The A896G polymorphism of *TLR*4 is associated with hypersensitivity to inhaled endotoxins (25). Polymorphisms in *TLR2* show an association with atopic diseases in rural children (26). In general, genetic studies of *TLR2* polymorphisms and allergic diseases show inconsistent results (26, 27). Genetic variations in *TLR*1, *TLR*6, and *TLR*10 have been associated with childhood asthma exacerbation (28) whereas the C1237T polymorphism in *TLR*9 has been associated with atopic eczema (29).

However, the immunological mechanisms of this gene polymorphisms and the development of atopic diseases are not well understood. On the other hand, the prevalence of these diseases has been increasing in recent decades, especially in children, and imposes a high cost on the health care system. The objective of this study was to evaluate the association of rs7656411 (g.27215T>G) polymorphism in the *TLR2* receptor with atopic diseases in the affected patients in Zanjan province of Iran.

2. Materials and Methods

This study is a cross-sectional study involving 100 patients with allergic rhinitis or allergic asthma (confirmed by skin tests) or those with childhood dermatitis and asthma who were over 15 years of age and were referred to the Allergy Clinic at Mousavi Hospital of Zanjan University of Medical Sciences. Patients were included in the study after obtaining informed consent. It should be noted that DNA samples from 50 non-atopic healthy individuals were used as controls. The study was conducted in accordance with the approval of the Institutional Ethical Committee (Ethical code: ZUMS.REC.1395.62).

2.1 Blood Sampling

After collecting 3 ml of venous blood, samples were stored at -20 °C until DNA extraction.

2.2 DNA Extraction

A DNA extraction kit (Favorgen Biotech, Taiwan) was used for DNA extraction according to the manufacturer's protocol. To assess the quality of the DNA, the optical density ratio at 260 nm to 280 nm was measured by Biophotometer Plus (Eppendorf, Germany), and its concentration was determined.

2.3 PCR-sequencing

The rs7656411 (g.27215T>G) polymorphism in the *TLR2* gene fragment was amplified utilizing gene-specific oligonucleotide primers that were designed using Primer 3, and the specificity of these primers was verified through Primer-BLAST (https://www.ncbi.nlm.nih.gov/tools/primer-blast). The sequences of the primers and the conditions for PCR are detailed in Table 1.

PCR reactions were conducted in 40 µL mixtures that included 200-500 ng of genomic DNA, 0.4 µM of each

primer, and 20 µL of 2x Master Mix (Yektatajhiz, Iran), which contained 0.5 IU Taq DNA polymerase, 1.5 mM MgCl2, 0.2 mM dNTPs, and reaction buffers. The PCR products were examined using 1% agarose gel electrophoresis and were visualized under UV light. Subsequently, 25 µL of each PCR product, along with the forward primer, were dispatched for sequencing (Macrogen, South Korea). The resulting sequences were analyzed utilizing BLAST, Clustal X2, and Chromas V2.4 software packages.

2.4 Statistical Analysis

For the examination of genetic data, SNPStats was utilized (30). A Hardy-Weinberg equilibrium assessment was performed for the SNP in both the patient and control groups, followed by the application of logistic regression models to derive odds ratios (ORs), 95% confidence intervals (CIs), and *p* values.

Table 1. Primer sequences and PCR conditions for amplification of rs7656411 region.

Sequence of primers (5′-3′)	PCR Product size	PCR conditions
Forward: TCTGGATCTGTCTTTCTGGCT Reverse: TGGTACTCTTGCCCTCAACA	843 bp	ID: 95°C/ 2 min (1 cycle) D: 95°C/ 30 sec (40 cycles) A: 59°C/ 30 sec (40 cycles) E: 72°C/ 40 sec (40 cycles) FE: 72°C/ 7 min (1 cycle)

3. Result

As described in the methods section, total of 150 subjects, including 100 atopic patients (44 males and 56 females) and 50 non-atopic as controls (24 males and 26 females) with ages between 15 and 55 years, were selected for this study. After amplification of the target gene (Figure 1), the allele and genotype frequency of the polymorphism in the *TLR2* gene (rs7656411 (g.27215T>G)) was detected via the Sanger sequencing method (Figure 2).

3.1 TRL2 Polymorphisms Allele and Genotype Frequency

The allele and genotype frequencies of g.27215T>G are indicated in Table 2. As shown in Table 2, these frequencies were not significantly different between atopic patients and controls. The allele frequencies of T and G were 0.7 and 0.3, respectively, in both atopic and non-atopic subjects. The frequencies of g.27215T>G genotypes were not significantly different between atopic patients and the control group, except for a higher frequency of the GG genotype in patients. Fifty-four (0.54) patients were homozygous for T (TT), 31 (0.31) were heterozygous (GT), and 15 (0.15) were homozygous for G (GG), while the numbers and frequencies of TT, GT, and GG genotypes in healthy subjects were 25 (0.5), 21 (0.42), and 4 (0.08), respectively. Therefore, the homozygous GG genotype may confer a higher risk than the heterozygous genotype.

3.2 Relationship Between Genotype and Inheritance Models

In this research, we analyzed the correlation between the genotypes of the aforementioned polymorphism and inheritance models of the subjects. Table 3 indicates the relationship between the above-mentioned genotypes and different inheritance models in patients and controls. The result suggests that despite the differences in the frequency of GG genotypes in atopic and healthy groups, there is no significant difference. The calculated OR for the GG genotype (1.74) indicates that this genotype might be a risk factor for atopy but is not statistically significant.

3.3 Interaction Analysis with Covariate Sex

As indicated in Table 4, there is no significant difference between genotypes in females and males. It should be noted that the number of female and male subjects in this study is not equal. As indicated in Table 4, the GG genotype has a higher frequency in male patients than in controls which might be a risk factor for atopy in males.

3.4 Hardy-Weinberg Equilibrium

Finally, the Hardy-Weinberg equilibrium (HWE) was estimated in the study population (Table 5). The result shows that allele and genotype frequencies in all subjects and cases were not in HWE.

Table 2. Allele and genotype frequencies of *TLR2* rs7656411 (g.27215T>G) in patients with atopy and controls.

SNP allele frequencies (n=150)						
	All subjects		Control		Case	
Allele/Genotype	Count	Proportion	Count	Proportion	Count	Proportion
T	210	0.7	71	0.71	139	0.7
G	90	0.3	29	0.29	61	0.3
GG	19	0.13	4	0.08	15	0.15
TG	52	0.35	21	0.42	31	0.31
TT	79	0.53	25	0.5	54	0.54

SNP: Single nucleotide polymorphism

Table 3. The relationship between rs7656411 (g.27215T>G) genotypes and risk of atopy.

Genotype	Control	Case	OR (95% CI)	P-value
TT	25(50%)	54 (54%)	1.00	
GT	21 (42%)	31 (31%)	0.68 (0.33-1.42)	0.27
GG	4 (8%)	15 (15%)	1.74 (0.52-5.77)	

Table 4. SNP and sex cross-classification.

	F			M		
Genotype	Control	Case	OR (95% CI)	Control	Case	OR (95% CI)
TT	9	30	1.00	16	24	0.45 (0.17-1.20)
GT	14	19	0.41 (0.15-1.12)	7	12	0.51 (0.16-1.70)
GG	3	7	0.70 (0.15-3.28)	1	8	2.40 (0.26-21.84)

Interaction P-value = 0.18

Table 5. SNP exact test for Hardy-Weinberg equilibrium.

	TT	GT	GG	T	G	P-value
All subjects	79	52	19	210	90	0.034
Control	25	21	4	71	29	1
Case	54	31	15	139	61	0.0089

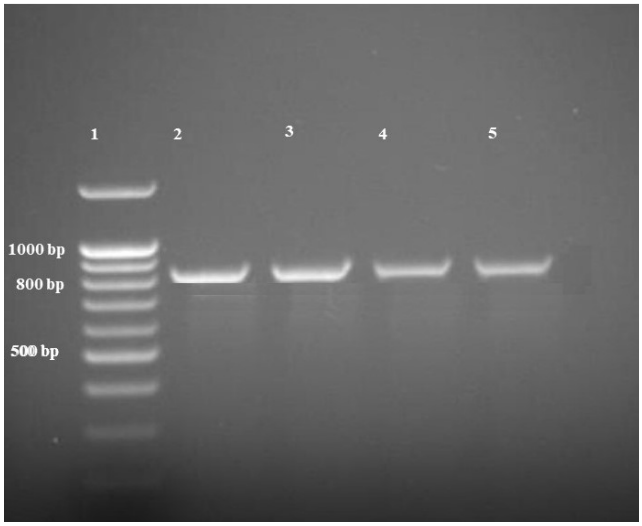

Figure 1. Gel electrophoresis of PCR products of amplified target gene. Lane 1, 100 bp DNA marker; lanes 2, 3, 4, and 5 show the 843 bp PCR product (**Designed by Authors, 2025**).

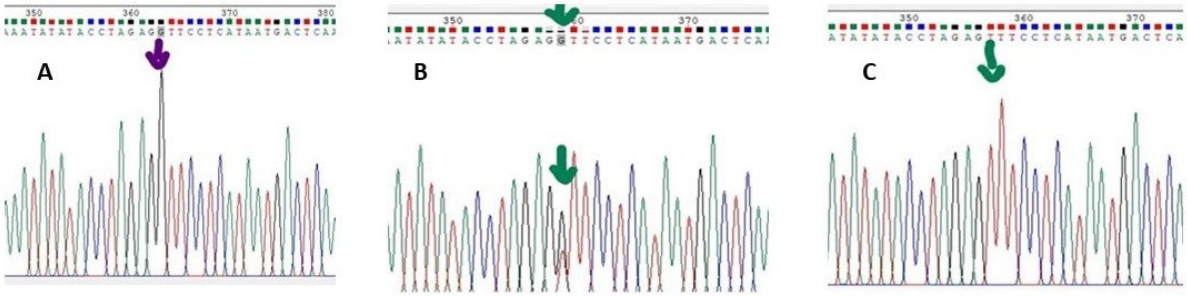

Figure 2. Analysis of single nucleotide polymorphism (SNP) using Sanger sequencing. (A) Homozygous normal allele (TT) (B) Heterozygous allele (GT) (C) Homozygous mutant allele (GG) (**Designed by Authors, 2025**).

4. Discussions

Atopy is a fairly prevalent chronic condition globally, especially in industrialized and semi-industrialized societies. Most of these individuals have a positive family history, and genetic factors make a person susceptible to the disease. In recent years, the prevalence of the disease has been on the rise, especially in children. Atopic disease imposes high costs on the healthcare system. In addition, psychological costs to patients and families should also be considered. There are many genetic factors that contribute to this disease, one of the well-known factors is Toll-Like Receptors (*TLR*s) that are involved in innate immunity **(31, 32)**. In the present research, which aimed to examine the association of the rs7656411 polymorphism (g.27215T>G) in *TLR2*, 100 atopic patients over 15 years of age were compared with 50 non-atopic healthy individuals for this polymorphism. The T allele is the normal allele, and the G allele is the variant. In this study, the frequency of the T allele in all subjects was 0.7, and the frequency of the G allele was 0.3. Allele frequencies in atopic and non-atopic individuals showed no significant differences. In this study, the frequency of GG, GT, and TT genotypes in all subjects was 0.13, 0.35, and 0.53, respectively. The frequency of the GG genotype in atopic patients was higher than in healthy individuals, and the GT genotype frequency was higher in healthy individuals than in atopic individuals, but there was not a significant difference in the frequency of the TT genotype between these two groups. Despite the difference in GG genotype frequency (about twice as high in atopic individuals), this difference is not significant. This difference means that the GG genotype might be a risk factor for atopy.

In this study, no association was found between the frequency of alleles and genotypes considered with sex. Recently, studies have been done on the association of polymorphism in *TLR*s with autoimmune and infectious diseases, cancers, and chronic hereditary diseases **(33-35)**. Studies on *TLR2*'s association with asthma and atopic diseases are relatively few.

Koponen et al **(36)** examined *TLR*1-rs5743618 and *TLR*6-rs5743810 polymorphisms in 133 children under 6 months of age who were hospitalized for bronchitis. The incidence of asthma and atopy in these children was also investigated up to the age of 6 years. They found that 24% of children with the GG genotype in *TLR*1-rs5743618 were diagnosed with asthma by age 6, compared with

38% of children with the GT/TT genotype with asthma who had been diagnosed up to 6 years of age. Similarly, 18% of children with the CT genotype in *TLR*6-rs5743810 developed asthma compared with 49% of children with other genotypes. In this study, *TLR*1-rs5743618 polymorphism was associated with asthma (p-value = 0.04) (36).

In the study by Liu et al (37), the *TLR2*-rs4696480 variant was associated with atopic disease and asthma in GG/GA carriers compared to AA genotype carriers (p-value < 0.03). IgE levels were also higher, which was attributed to immune system alterations in atopic individuals (37).

Zuo et al (38), in an investigation into *TLR* expression in asthmatic patients, highlighted the association between *TLR*s and airway inflammation in asthmatic patients. Moreover, they reported that the strongest association was between *TLR2* and *TLR*4 in asthma patients. It was also demonstrated that overexpression of these *TLR*s as well as overproduction of cytokines (such as IL-1β, TNF-α, IL-6, IFN-γ, and CXCL10) were associated with *TLR2* and *TLR*4 activation (p-value < 0.005) (38).

In another study by Qian et al (39) on the same polymorphism discussed in this study and its effects on asthma, the findings also showed that the frequency of the GG and GT/TT genotypes in controls were 26.2% and 73.8%, respectively. This prevalence rate in asthmatic patients was 32.5% and 67.5%, respectively. This study revealed that the homozygous G allele of this polymorphism was associated with a reduced risk of asthma (p-value=0.036). It was also reported that the cause of decreased risk of asthma in these individuals was a decline in immune activity and a decrease in the production of inflammatory factors such as IgE (39). In the present study, in contrast to the aforementioned study, the frequency of GG genotype was higher (about twice) in atopic individuals. The differences between the data in this study and the study by Qian et al (39) may be due to differences in the studied populations and their genetic backgrounds. Considering the differences in the two studies, further studies on this SNP may help to better understand the factors contributing to the incidence and control of the disease. All these studies indicate the importance of *TLR*s in asthma and atopic patients and the severity of symptoms in these patients. Although these studies show that even if there is a significant difference between those with and without these polymorphisms, these SNPs alone cannot be the cause of the disease and other environmental and genetic factors are involved. However, the significance of these genetic changes in *TLR*s cannot be ignored.

5. Conclusion

This study found no statistically significant association between the *TLR2* rs7656411 polymorphism and atopy in this Iranian population sample. While a trend toward increased GG genotype frequency was observed in atopic patients, the finding was not statistically significant and should be interpreted cautiously given the study's limitations, including small sample size and Hardy-Weinberg equilibrium violation in cases. Future research should include larger, well-powered studies with diverse Iranian populations and address potential population stratification issues.

6. Declarations

6.1 Acknowledgments

We thank research deputy of Zanjan University of Medical Sciences for financial support of this study.

6.2 Ethical Considerations

The study was conducted in accordance with the approval of the Institutional Ethical Committee (Ethical code: ZUMS.REC.1395.62).

6.3 Authors' Contributions

Akefeh Ahmadiafshar and Ali Ramazani conceived and designed the study. Fatemeh Mohajer wrote the initial manuscript and carried out the methods and analysis. Roghayeh Arezumand Edited the manuscript. Nima Motamed carried out the statistical analysis. All authors reviewed, edited, and approved the final version of the manuscript.

6.4 Conflict of Interest

The authors have no conflict of interest.

6.5 Fund or Financial Support

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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