Genetic Association of IL-17 rs2275913G/A or 197 A>G Gene Polymorphism in Patients with Respiratory Allergies in Basra Governorate / Iraq

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Introduction:

Allergies and asthma are major global health problems in many countries and cases of respiratory diseases have increased around the world in recent years, as epidemiological studies and many recent studies have shown that allergic rhinitis has a significant impact on asthma and that its treatment may affect asthma control as the majority of asthma patients were suffering from allergic rhinitis and it is an increased risk factor for asthma [(1)] These diseases occur as a result of interaction between environmental causes and genetic factors and the multiplicity of genetic forms (Polymorphism) of genes of the most important genetic factors, which is intended to vary in the sequence (sequence) of deoxyribonucleic acid (DNA) found between individuals of the same type and is the most common variation of genetic diversity found throughout the human genome It can also be expressed as the presence of two or more alternative forms of allele in an individual's genome, resulting in characteristic phenotypic patterns in the same population and frequency in the population of at least 1% [(1,2)] Continuous or repeated exposure to harmful environmental factors leads to allergic diseases, which later develop into asthma, where epithelial cells stimulate the release of a group of interleukins that are considered an inflammatory response to allergens [(3)] Where the term InterLeukin (IL) is a description of a group of cytokines (Cytokines), which are cellular motor proteins with complex immune functions that are manufactured by different cells, but mainly by CD 4+ cells of T cells, and the activity of interleukins varies according to their members, but in general they stimulate the growth, reproduction, maturity, migration, differentiation and development of T and B cells and other blood cells, These proteins play an important role in the differentiation and activation of immune cells, the term interleukin (IL) was first described in 1979 in a letter to the editor of the Journal of Immunology to describe a number of leukocyte secreting molecules (Leukocytes) and also described as originating from lymphocytes and therefore sometimes referred to as lymphokins. [(1,4)] Allergy in general is an abnormal immune reaction that occurs as a result of an antigen or foreign body, and allergy is not a disease but a series of immune reactions that lead to known symptoms of allergy. Allergic diseases are caused by allergens, whose chemical composition affects the human body through their effect on the immune system, which leads to an allergic reaction Asthma is defined as a chronic inflammation of the airways in which many cells and cellular elements play a role. Chronic inflammation is associated with airway overresponse, which leads to frequent episodes of wheezing, chest tightness, shortness of breath and coughing, especially in the early morning and at night.

Interleukin Gene 17A (IL -17A):

This gene belongs to the family of interleukin-17 genes consisting of six genes starting from IL-17F - IL-17 A and this gene family is encoded into a group of motor proteins (cytokines) that have an active role in inflammatory diseases. Cytokines from IL-17A to IL-17F are responsible for the pathogenic activity of T subcells (Th17). The IL-17 A gene is located on the short arm of chromosome 6 i Package 12.2 (6p12.2) [(5-7)] This gene codes for a glycoprotein of 155 amino acids. The motor protein (IL-17A) is expressed by fibroblasts, epithelial cells, myeloid cells, vascular endothelial cells, T and B cells, and it works on a group of different cells. It stimulates cells to secrete chemicals by regulating them to express pro-inflammatory stitokines and works to attract neutrophil cells to the site of inflammation to defend against various pathogens [(8)]. The IL-17A gene has the genetic form rs2275913G/A or 197 A>G in the promoter region, so the two lilys region are (G, A) and three structures (GG, GA, AA) and has an effective effect on the production of interleukin-17 and is associated with bronchial sensitivity and asthma events. [(9-11)]

Materials and methods:

Samples

150 human blood samples were collected in a volume of (1-3 ml) in EDTA tubes distributed into two groups, the first group was represented by patient samples, and the number of blood samples was 100 blood samples divided into 50 blood samples from people with allergies and 50 blood samples from people with asthma patients, depending on the diagnosis of the specialist doctor and from the Allergy and Asthma Center, as well as from workers at the Nahran Omar site of the South Oil Company. As for the second group, it is the control group (healthy people), which included 50 blood samples from healthy people who do not have allergies and asthma, and the samples of the two groups included both sexes (males and females) and different age groups ranging between (20-70) years and for a period from March 2022 to September 2022.

Extracting DNA from the blood:

DNA extraction from samples from the two groups (patients and control) using a DNA extraction kit prepared by Genaid Company.

Tetra Primer ARMS – PCR (Amplification Refractory Mutation System Polymerase Chain Reaction):

The polymorphism of the interleukin-17 gene (IL-17) was studied using the following prefixes shown in the table (1).

Table (1): The prefixes used for the IL-17 gene illustrate the genetic form rs2275913 G/A [6]

Gene	Primer name	Primer sequences	Length	*TA
IL-17	Outer F	GGTACATGACACCAGAAGACCTACA	25	*59*
IL-17	Outer R	CCTGCTATGAGATGGACAAAATGT	24	
IL-17	Inner F	TTCCCATTTTCCTTCAGACGA	21	
IL-17	Inner R	CCCAATGAGGTCATAGAAGAATCTATC	27	

*TA :- Annealing Temperature

The method of work was carried out with a reaction mixture with a volume of 20 microliters and as shown in Table (2) based on the leaflet attached with Bioneer Master Mix manufactured by the reaction mixture company here all the prefixes are added together in one tube for each sample to be studied.

Table (2) represents the chemicals of the reaction mixture and their volumes (IL-17)

Chemicals	Volume
Master Mix	
Outer Premier Forward	2 µl (10pc/ml)
Outer Premier Reverse	2 µl (10pc/ml)
Premier Forward	2 µl (10pc/ml)
Premier Reverse	2 µl (10pc/ml)
DNA	5 µl
D.W.	7 µl

Total	20 µl

After completing all the additions, the samples were shaken slightly by the rapid shaking device for 5 seconds to ensure the homogeneity of all materials, then the samples were placed with a PCR Sprint Thermal Cycler device and the device was filled according to the following program for the interleukin 17 gene as in Table (3).

Table (3) shows the PCR program for the IL-17 gene

Steps	C° Temperature	time/cycle	The number of cycle
Initial Denaturation	95	5 min	**1**
Denaturation	95	1min	**30**
Annealing	59	30sec	
Extension	72	1min	
Final extension	72	5min	**1**
Final extension	72	5min	

After the end of the work of the device, the samples were electrophoresis migrated using agarose gel at a concentration of 2% and after detecting the beams with an ultraviolet light device and then recording the results.

Statistical Analysis:

Fisher test was performed to test the homogeneity of the samples used and the Genepop program was used to estimate some genetic parameters of the studied samples.

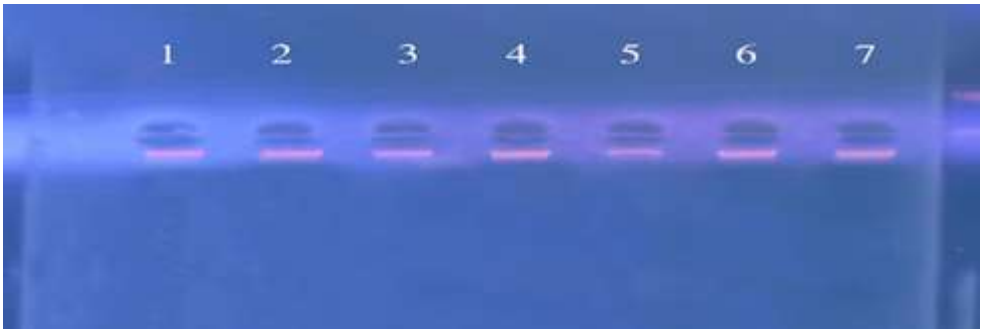
Results and discussion:

Polymorphism of cellular motor genes

DNA extraction The genomic DNA of human blood:

Use samples was extracted for the three groups of allergy, asthma and control as in Figure (1).

Figure (1) shows the electrophoresis of the DNA genome on acarrose gel at a concentration of (0.8%)



Interleukin-17 gene polymorphism for mutation site rs2275913 G/A:

The results of the electrical migration of the gene to the G/A mutation site enlarged with ARMS-PCR Tater technology showed the emergence of three bundles, the first was a size of 375 bp, represented by a part of the 17A gene, which carries the mutant genetic form, and the second bundle, the natural allele G, with a size of 246 bp, while the mutant allele A represented the third bundle, with a size of 177 bp, as shown in the figures below.

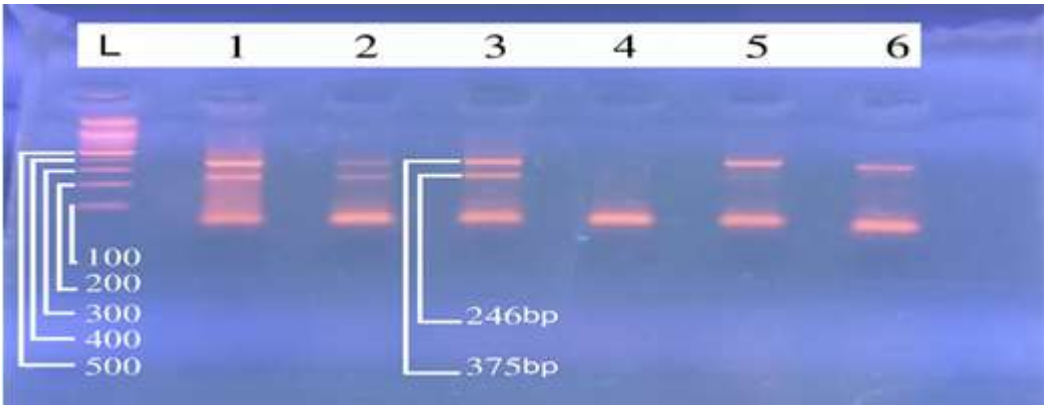


Figure (2) shows the electrophoresis of the PCR products of the interleukin-17 gene at the site of the mutation rs2275913 G/A on the acarrose gel at a concentration of (2%) and the results show a beam of size 246bp, which represents the genotype GG.

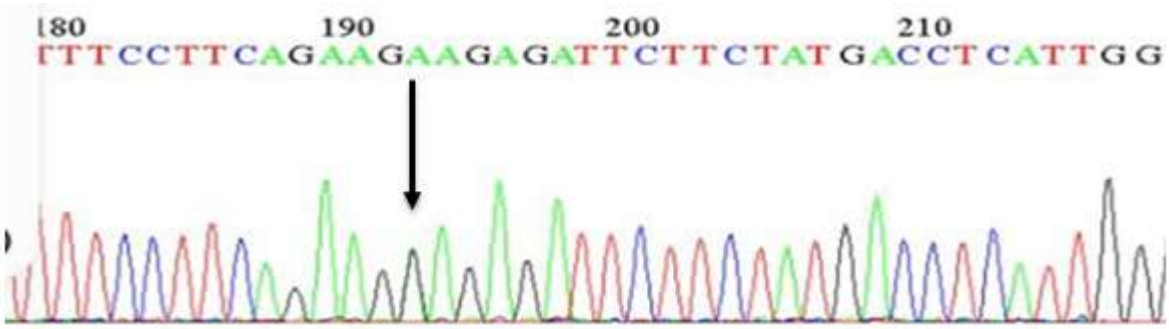


Figure (3) shows the results of the Sequenc for part of the Promoter region of the IL-17 gene The indicator part represents the location of the G allele, which represents the genotype Homozygous; Wild type GG

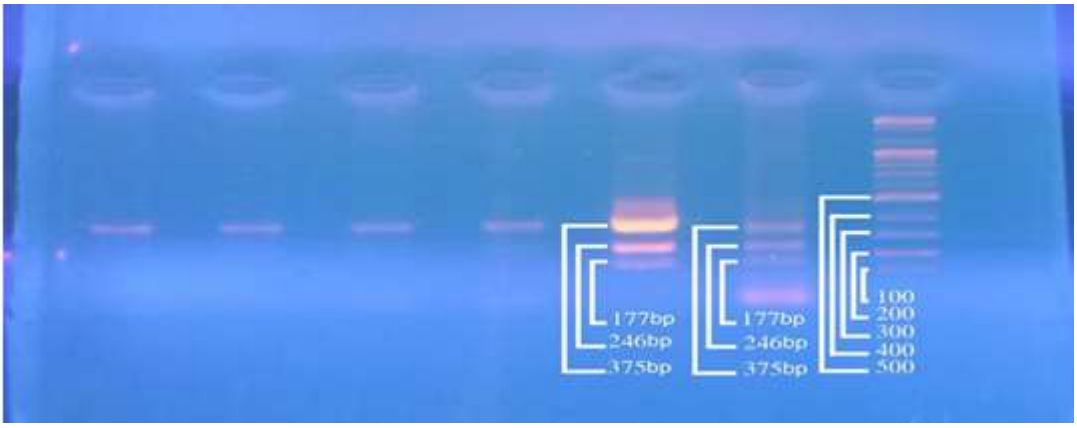


Figure (4) shows the electrophoresis of the PCR products of the interleukin-17 gene at the site of the mutation RS2275913 G/A on the acarrose gel at a concentration of (2%). The letter L (Ladder) indicates that the numbers (1-4) represent only the samples with a size of 375bp the size of the genetic region containing heterogeneity While the numbers (5 and 6) represent the samples containing the first three packages refer to the genetic region containing heterogeneity with a size of 375bp, the second bundle with a size of 246bp represents the G allele and the third bundle with a size of 177bp represents the allele A.

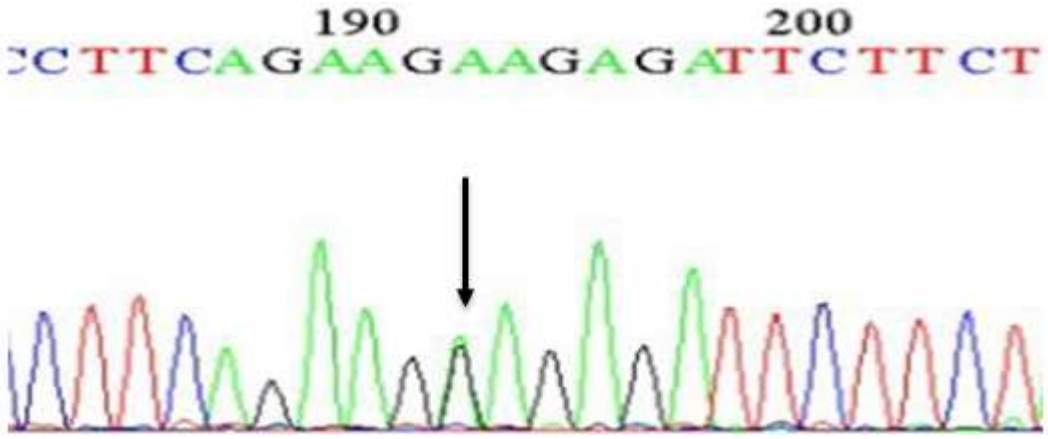


Figure (5) shows the results of the Sequence for part of the Promoter region of the IL-17 gene The indicator part represents the location of the Heterozygous GA hybrid state.

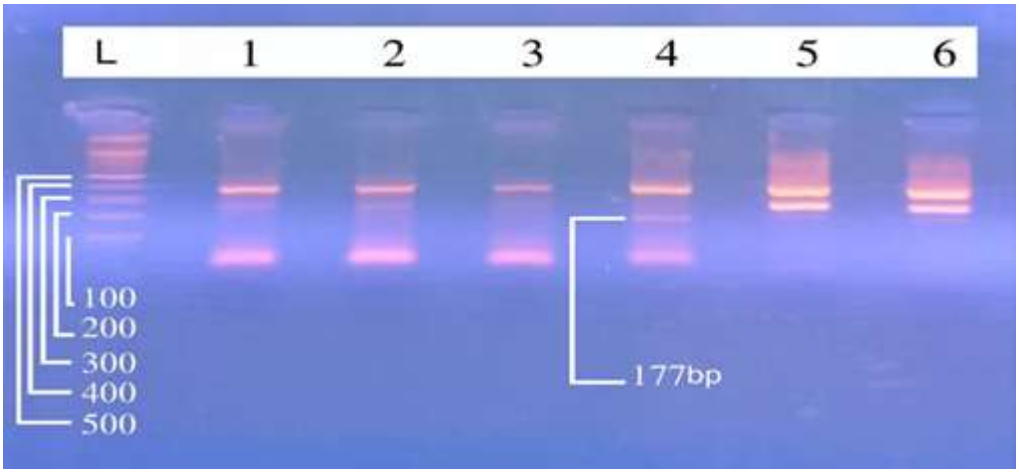


Figure (6) shows the electrophoresis of the PCR products of the interleukin-17 gene at the site of the mutation RS2275913 G/A on the agarose gel at a concentration of (2%). The letter L (Ladder) and the numbers (1-3, 5 and 6) indicate the appearance of the bundle of the genetic region containing heterogeneity of size 375bp and allele G of size 246 bp, while the number (4) represents the sample containing allele A and size 177bp.

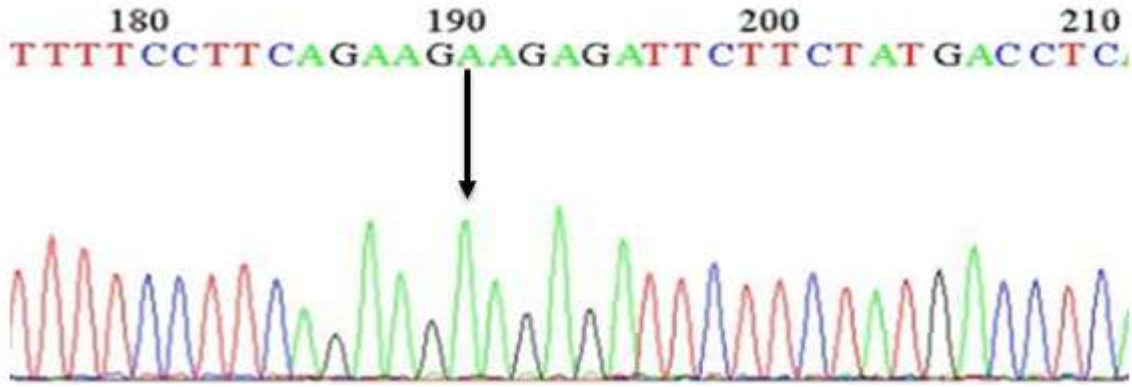


Figure (7) shows the results of the Sequence for part of the Promoter region of the IL-17 gene, the indicator part representing allele A and mutant genotype AA.

The results of the frequency distribution of alleles G and A for the IL-17 gene using the Hardy-Weinberg equilibrium law showed heterogeneous results between samples of allergies and asthma patients and the control group, if allele A was recorded (17% and 14%) in each of the two groups of allergy and asthma patients respectively compared to the G allele for the same two groups by (83% and 86%) respectively, while the frequency of allele A was recorded by 0.0%

compared to allele G Record 100% in the control group as in Table (4) Which shows that there are no significant differences between the three groups and the frequency distribution of the alleles, although there is a variation in the frequency of allele lines between the patient and control groups. The results show that allele A was not shown to be associated with allergies and asthma using the Fisher s test. The critical ratio (OR) Odds Ratio was 0.6287 for the allergy group and 0.5029 for the asthma group with confidence intervals (CI) under 95% ranging between (0.02458 – 16.0844) for allergy patients and (0.01953 – 12.952) for asthma patients, while the results showed that allele G was associated with the control group by one and a half times compared to allergy. The critical ratio (1.5905=OR) with a 95%CI (0.0622 - 40.6872) was at a probability level P = 0.7791 and almost twice as high as asthma and the critical ratio (1.9885 = OR) with a 95%CI (0.07721 - 51.2142) at a probability level P =0.6783.

Table (4) shows the relationship between the allele iterations of the genetic form rs2275913 G/A IL-17 and the three groups.

***P Value**	**OR* (95%CI) ***	**Allele frequency**		**Allele**
		control	allergy	
0.7791	1.5905 (0.0622 - 40.6872)	1.0	0.83	**G**
	0.6287 (0.02458 – 16.0844)	0.00	0.17	**A**
*P Value	OR* (95%CI) *	Allele frequency		**Allele**
		control	asthma	
0.6783	1.9885 (0.07721 – 51.2142)	1.00	0.86	**G**
	0.5029 (0.01953 – 12.952)	0.00	0.14	**A**

Statistical analysis of the results of our current study showed that the single genetic form of the IL-17 G/A gene is not associated with susceptibility, but we believe it is associated with allergy and asthma patients and evidence of the appearance of the mutant allele A in the two patient groups and its non-appearance in the control group. can be attributed to the location of the genetic profile within the catalyst region of the IL-17 gene, which modifies the binding of nuclear transcription factors of active T cells and thus affects the rate of copying of the IL-17 gene (9-13)This is consistent with the study of [6,14], which indicates that allele G of IL-17A rs 2275913 was associated with a lower risk of asthma, i.e. has a protective role for asthma, and allele A for the genetic form rs 2275913 was associated with abnormal lung function and the total level of IgE in asthma patients The presence of this genetic form in patients confers genetic susceptibility to childhood asthma in southwestern China populations and its use as a specific genetic trait to assess the risk of asthma, especially populations with bronchitis [9].

In an analysis of five previous studies reported that there was no significant association between the genetic form Il-17 197 G/A and the risk of asthma in gene analysis among the general population and dependent on ethnic group [15]The analysis of the studies stated that there is no significant association between the genetic form and the risk of asthma, perhaps this indicates the appearance of allele A in the patient group, but in a small percentage, and this is consistent with the results of the current study A study

[13]also showed that nucleotide 197A was strongly associated with the development of asthma, as it appeared at a high rate in the patient group and did not appear in the control group, and the researcher indicated that the development of asthma may be due to the exclusive spread of this genetic variant (allele A) at the beginning and development of allergic disease in the population of Dhi Qar Governorate - Iraq.

The results of our current study contradict the study conducted by [10,16], which found that the frequency of the G allele is at a significantly higher frequency in pediatric asthma patients and that asthma is positively associated with the frequency of the G allele may be due to differences in the patient's demographics, sample size, environmental factors, and genetic background, all of which can lead to different results between studies. Also, a study [17] showed no significant association between the genetic form IL-17 197 G/A and the risk of asthma in the Turkish population. Also, [18] stated that there were no statistically significant differences between the normal allele G and the mutant allele A between asthma patients and the control group. The results of the genetic analysis of the results of the ARMS-PCR Tater technology for the genetic form IL-17 rs2275913 G/A and using the Hardy-Weinberg law as in Table (3-7) showed three genotypes in the two groups of patients, namely GG, GA, AA and one genotype, which is the original in the control group GG, although there was a clear difference in the frequencies of genotypes between the two groups of patients compared to the control group, especially the frequency of the genotype GA in allergy patients was (0.28) and in asthma patients (0.24) compared to control set (0.0) Now this difference is insufficient for the latest variation in the frequency of genotypes statistically between the two groups of patients and the control group at the probability level P = 0.900 and P = 0.9935, and when using the Fisher test, it was shown that any of the genotypes was more associated with the appearance of the disease. The critical ratio of genotype heterotype OR=1.2302 GA with confidence interval (95% CI 0.0487 - 31.1063) in allergy patients and the critical ratio in asthma patients OR=0.9866 with confidence interval (95%CI 0.03891-25.0166) was recorded These results show that the GA genotype is associated with the onset of allergy and asthma by one time compared to the control group.

The results also recorded the highest genotype among the three genotypes, the original genotype GG, and it was 0.69 and 0.74 in the two patient groups, respectively, compared to the control group, which appeared by 100%, but it did not show a significant difference between the three groups at P = 0.900 and P = 0.993. Statistical analysis using the Fisher test showed that GG genotype replication may have a protective role against the disease.

While the results showed that the AA genotype is the least frequent among the three types in the groups of allergy and asthma patients (0.03 and 0.02) respectively, but it is possible that it has a role in the latest disease, even by a very small percentage. The reason for this is that it did not appear in the control group and was 0% at the probability level P = 0.2725 and P = 0.1908, as well as for the Fisher test, the association of the genotype with the onset of the disease was not recorded, this may be due to the small size of the sample taken in each group.

Table (5): Shows the relationship between the genotypes of the genetic form RS2275913 and the three groups

***P Value**	**OR* (95%CI) ***	**genotype frequency**		**genotype**
		control	allergy	
0.900	0.8129 (0.0321 - 20.5535)	1.00	0.69	**GG**
	1.2302 (0.0487 - 31.1063)	0.00	0.28	**GA**
	0.1511	0.00	0.03	**AA**

0.2725	(0.0052 - 4.4194)			
*P Value	OR* (95%CI) *	genotype frequency		**genotype**
		control	asthma	
0.9935	1.0136 (0.03997 -25.7019)	1.00	0.74	**GG**
	0.9866 (0.03891- 25.0166)	0.00	0.24	**GA**
0.1908	0.1707 (0.00322 – 3.1319)	0.00	0.02	**AA**

A statistical analysis of the results of our current study showed that the original genotype GG has a protective role against asthma, while the hybrid genotype GA and mutant genotype AA can have a role in causing the disease. The exclusive prevalence of this variant in patient samples may be due to the possible involvement of this genetic change in the onset and progression of allergic disease[13]. Genetic polymorphism in noncoding regions may have important functional consequences These differences are able to affect either the expression or activity of the resulting protein and therefore the susceptibility or severity of several disorders will be affected by the possession of certain alleles of polymorphic genes.

The presence of IL-17A in the 6P region, a genomic region associated with asthma [19,20] which contains the VEGF gene that has been shown to be associated with asthma severity [21]. The current results are consistent with the study [6,16,22] who indicated that the GA hybrid genotype is significantly elevated with asthma. [12] reported that people with the genotype GG expressed lower levels of interleukin 17 than people with the genotype GA and AA.

A study (9)indicated that Chinese children with AA genotype are 2.29 times more likely to develop asthma than others, especially populations with bronchitis, as well as a study conducted by [23], which revealed that Saudi asthma patients with AA genotype express high levels of interleukin-17 In a comparison between the two groups of patients, it was found that the AA genotype was recorded less frequently in the asthma group compared to the allergic rhinitis group, and the researchers pointed out that interleukin-17 is derived from inflammatory leukocytes, which target the epithelial cells of the airway, Expression of the mucosal mucosa has been associated with the pathophysiology of allergic rhinitis, including disease severity and increased localized eosinophils [24]and also associated with an elevated level of interleukin-17 in serum of Babylonian allergic rhinitis patients with AA genotype compared to the healthy group.

Thus, the researchers pointed out that the genetic form IL7 A is a risk factor for allergic rhinitis and it is important to measure the level of interleukin-17 in the serum of patients in severe cases [25] It contradicts his study [11] which found an association between polymorphism IL -17 A rs 2275913) and asthma and found that asthma is less common in people with the genotype GA, AA and that the most affected people are those who carry the genotype GG. [10] found that the GG genotype is at a significantly higher frequency in asthma patients.

The study [26], which suggested that GA and GG genotypes have protective effects against allergic rhinitis and asthma development,is consistent with our study in terms of the genotype GG has a protective role and contradicts the current study in terms of the GA genotype. While there were no significant differences between the GG,AA genotypes and the incidence of the disease, unlike the genetic makeup, which showed a significant association with asthma compared to the control group [18].

Conclusion:

Place The results of the current study recorded no association for age groups, sex, allergies and asthma, although there were differences in the percentages of patients between allergies and asthma compared to the control group. 4- The results of the current study showed that the allele G is not associated with allergies and asthma for the genetic form (IL-17 rs2275913G<A) and is considered as a protective source of the disease, while the results recorded the appearance of allele A and both genetic types ((AA, GA in patients with allergies and asthma, but in small proportions and not appearing in the control group, so it can be noted that allele A is associated with disease events.

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