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The Relation of rs2981572 Polymorphism and IL-20 Levels in Asthma Patients Infected With Streptococcus

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Abstract

One frequent chronic autoimmune illness that affects many people is asthma. The current study examined the relationship between the genetic polymorphisms of interleukin 20 (rs2981572) and asthma chronic disorder among Iraqi patients who had *Streptococcus pneumonia* in both controls and cases. For the current study, 300 participants were split into two groups: a case group and a control group. In regard to patients, the blood and sputum specimens were collected together, while for the control group, only blood samples were collected. Each participant in the current work was given 8 ml of venous blood, which was then divided into two parts: 4 ml was immediately transferred into EDTA tubes for DNA extraction and detection of the rs2981572 polymorphism, and the remaining 4 ml of blood was put in a gel tube and left to clot for serum separation by centrifuge. To estimate IL-20, the enzyme-linked immunosorbent test was employed. IL-20 and rs2981572 were detected using the tetra-primers amplification refractory mutation system-polymerase chain reaction assay. According to the findings of the rs2981572 polymorphism, the genotypes TT (OR = 0.07; 95% CI = 0.04-0.12) were found to have highly significant protective factors (P = 0.0000). For the TG genotype, the P-value is highly significant, OR=9.54, 95% CI= 5.49–16.58, so the results suggested the TG genotypes are highly significant etiological factors and are associated with asthma disease as a risk factor. IL-20 levels in study population sera were found to be significantly higher in cases (P =0.0001) than in controls (1389.92 ± 31.84 vs. 797.67 ± 31.11 pg/ml) respectively.

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1. Introduction

One of the most serious pathogens with a high rate of morbidity and mortality worldwide is *Streptococcus pneumoniae* [1]. *S. pneumoniae* also colonizes the human nasopharynx and is a very important pathogen in causing respiratory diseases and invasive infections and is the most common pathogen. On the other hand, *S. pneumoniae* has been associated with rheumatoid arthritis at the age of 7 years [2]. A group of clinical symptoms characterizes chronic asthma, such as airway hyper-responsiveness, inflammation, and obstruction, and may be reversible [3]. From other side, the disease is also most common chronic disorder in children, and like other diseases, it is affected by many factors, including exposure to microbes [4]. It is worth noting that *S. pneumoniae* cause a group of infections in the respiratory tract for example middle ear infections and pneumonia, which cause common attacks of asthma in children in particular [5]. In general, interleukins act as an interacting network to regulate airway inflammation and bronchoconstriction caused by asthma [6]. It is clear that the genetic polymorphisms in cytokines play a crucial role in many diseases, whether inflammatory or regulatory, for example, the role of the IL-20 in

kidney disease appears to be clear in patients compared to controls [7]. In addition, it has been observed that genetic polymorphisms in the IL-13 gene contribute to the worsening of renal cell carcinoma patients [8]. Moreover, study [9] about genetic polymorphisms in the interleukin-4 gene was presented its crucial role in the exacerbation of lung cancer. Aberrant gene expression of IL-20 may play a role in many inflammatory diseases [10]. In addition, the process of facilitating communication among hematopoietic cells and epithelial cell interactions was done by interleukins, including IL-20 [11]. On the other hand, some studies have suggested that interleukin 20 is a potential target for treating inflammatory diseases [12, 13]. In addition, many inflammatory interleukins like IL-8 have been associated with the risk of diseases such as recurrent urinary tract infections in patients [14]. Dhabaan *et al.* explain that genetic factors playing a significant role disease development [15]. Because asthma is a chronic inflammation of the bronchial tubes and causes dysfunction of the airway [16], inflammatory cytokines may have a decisive role in combating such infections, hyperoxia, bronchopulmonary responses to inspiration of dry gas, acute and chronic inflammation, and perhaps atelectasis [17]. This study highlights the role of genetic polymorphism and interleukin 20 level in asthma and demonstrates the genetic association with the disease.

2. Materials and Methods

2.1. Study design

In the current study, the experiment work was designed between cases and control to find the correlation between the rs2981572 polymorphism in IL-20 and asthma patients were infected by *S. pneumonia*. The current study included 300 participants, who were divided evenly into two groups. The patient group represented 150 participants, while the other half represented the control group. In accordance with the Ethics Committee of the University of Iraq, College of Education, and in cooperation with the Karkh Health Department, the study was completed. The ethical number of the research was 27/485 in 11/8/2024.

2.2. Selection the study groups

a. Patients' group selection

A total of hundred and fifty patients suffering from asthma and diagnosed with *Streptococcus* bacteria were visited at Baghdad Teaching Hospital in Baghdad Governorate. The cases were diagnosed by specialists at Baghdad Karkh Health Department. All cases were diagnosed with asthma after a clinical examination by a specialist physician and laboratory investigations.

b. Controls' group selection

The health group in this work was carefully chosen to eliminate bias and confounding. In this study, 150 healthy individuals were selected as a control group. Some essential criteria were used to determine the control group sample. These characteristics indicated no family history of the condition, no other health issues or comorbidities, the study population from the same population area and under the same conditions, there are no health problems suffered by the control group in general, and they do not have any immune diseases or other

c. Specimen collection

Two types of specimen's blood and sputum were collected from all participants in the current work. From all individuals in the present work, 8ml of peripheral blood was collected. For DNA extraction, only 4 ml of peripheral blood was transferred immediately into EDTA tubes. The leftover blood was transferred into gel tubes to estimate the levels of IL-20.

2.3. Bacterial isolation and detection

a. Samples collection:

All patients participating in the current study donated a sample of sputum, which was collected in sterile cub tube for the purpose of isolating the *S. pneumonia*.

b. Isolation of bacteria

The blood agar plate (BAP) was prepared in accordance with the company's instructions (Himedia/India), and then it was autoclaved at standard conditions of sterilization (121°C/ 15 psi for 15 minutes). After that, the bacterial media were cooled down to 45°C, and 5% of red blood cells from humans were thoroughly mixed to get a final concentration of 5% of blood agar and transferred into sterile Petri dishes under sterilization conditions. The Petri dishes were then ready for primary isolation of bacteria. During the incubation period overnight with approximately 5% of CO_2, each plate was examined. In 5% blood agar, *S. pneumoniae* shows α-hemolytic activity.

c. Confirm the diagnosis of bacteria

All pneumococci were selected based on their phenotypic characteristics on blood agar media and α-hemolysis production. The initial diagnosis was confirmed by using Gram stain for appearing the morphological features for all isolate.

d. Phenotypic identification systems

The Vitek2 compact automated system using the gram-positive card for the rapid Strep identification strips (bioMérieux) was performed to confirm the *S. pneumonia* identification according to the manufacturer's recommendations.

2.4. Identification of rs2981572 T/G.

a. DNA extraction

The DNA genomic kit (Bioneer/Korean) was utilized in order to extract DNA according to manufacturer recommendations. The purity of DNA was determined via a nanodrop device, and the acceptable range of DNA purity was estimated between 1.6 and 1.8. All samples were kept at minus 20 degrees before use.

b. Primers preparing and selection

A tetra-primer ARMS-PCR method was used for the detection of the IL-20 gene and two specific alleles (*T* and *G*) of the rs2981572 polymorphism. Nuclease-free water was used to dilute the specific primers in order to prepare 100µM as the final concentration, and then the stock solution of primers was kept at -20°C before usage. For two alleles of rs2981572 T/G polymorphism, two inner-specific primers (Table 1), created via Bioneer/Korean, were utilized for the detection of *T* and *G* genotypes.

c. Reaction conditions of PCR assay

The final volume of PCR amplification was 25µl, which comprised 10µl of PCR premix (Bioneer/Korean), 7µl of DNA template, 2µl for both outer and reverse primers(10µM), and nuclease-free water to obtain a final volume of 25µl. The final product size of IL-20 was 320 bp for two outer primers. Regarding rs2981572 allele detection, the final product of the PCR reaction, the IL-20 gene, was used as a DNA template. The Eppendorf tubes (0.2 ml) were placed in the PCR device. For rs2981572 polymorphism detection, the cycling parameters of PCR were run under the following conditions: one cycle of the primary denaturation step at 95°C for 5 min, thirty-five cycles of the denaturation step at 95°C for 30 sec, annealing at 70°C for 30 sec, and 30 sec at 72°C as the extension step. One cycle was run for the final extension step at 72°C for 10 min, and then one cycle for the infinite step was run at 4°C in order to end the PCR reaction.

d. Estimation of IL-20 levels

For the estimation of IL-20 in populations in the current study, serum was isolated from whole blood that collected in a gel tube via centrifuge for all blood samples. Following sample collection, the serum was kept frozen at -20°C until the ELISA technique was applied to estimate the IL-20 level. According to the recommendation of manufacturing, a human ELISA kit of IL-20 (Biotech/Korea) was used for estimation of IL-20 levels.

e. Statistical analysis

Statistically, BMI SPSS version 25.0 and Win Pepi version 11.65 was used to analyze all data of the current study for homogeneity, normality, normal distribution, and mean ± SE of mean. Using Fisher's exact test ($P<0.05$), the rs2981572 polymorphism was compared to control groups to determine its association with asthma disease. The odds ratios (OR) and confidence intervals (CI) were calculated using the WinPepi software. The Hardy-Weinberg equilibrium was used to determine the outcomes of the preventative and etiological fractions.

Table 1: Primer sequences of the IL-20 gene rs2981572 using TARMS-PCR

Target Gene	Primer	Primer sequences (5`→ 3`)	Size (bp)
IL-20 gene	Outer F	ACTCATCAATAATATTTTCATCATATGCT	320
	Outer R	AGTTTTAAGATAAAATAATAATGGGCTG	
rs2981572 T/G	T allele: Inner F	TTGTCATAAGCTTTTAATTCATTCTT	156
	G allele: Inner R	CAAGATAAAAATATTTTAGTGCAATGTC	219

*All primers in the present work were used according to [18].

3. Results

a. Detection of bacteria

In the present findings, the pathogenic bacteria were isolated and then primary diagnosed by using BAP, microscopic examination, biochemical tests, and then VITEK automated system. The first identification was completed *in situ* at the hospital using morphological characteristics on culture media. All isolates were given α-hemolysis on BAP with linear or irregular arrangements of Gram-positive cocci, which were considered possible streptococci. According to the findings of biochemical tests and culture media, all isolates were also subjected to the VITEK automated system for precise and accurate diagnosis of the isolates at generic and species level. The results came to ensure the previous identification.

b. rs2981572 T/G polymorphism detection

The specific band positions of the *T* and *G* alleles of the rs2981572 polymorphism in the IL-20 gene are shown in figure 1 at 156 and 219 bp, respectively.

Figure 1 reflects the results of two specific bands of rs2981572 genotypes as well as IL-20 for the controls and cases groups. In Table 2, the significant differences of genotypes and allele frequencies for the rs2981572 polymorphism in patients and controls are shown. Alongside the frequencies of all genotype forms, including homozygote and heterozygote, the Hardy-Weinberg equilibrium (HWE) showed strong agreement. Chi-square analysis was used to statistically examine the allele frequencies and genotype distribution. Furthermore, a statistical analysis was conducted using the odds ratio (OR) and its 95% confidence interval (CI).

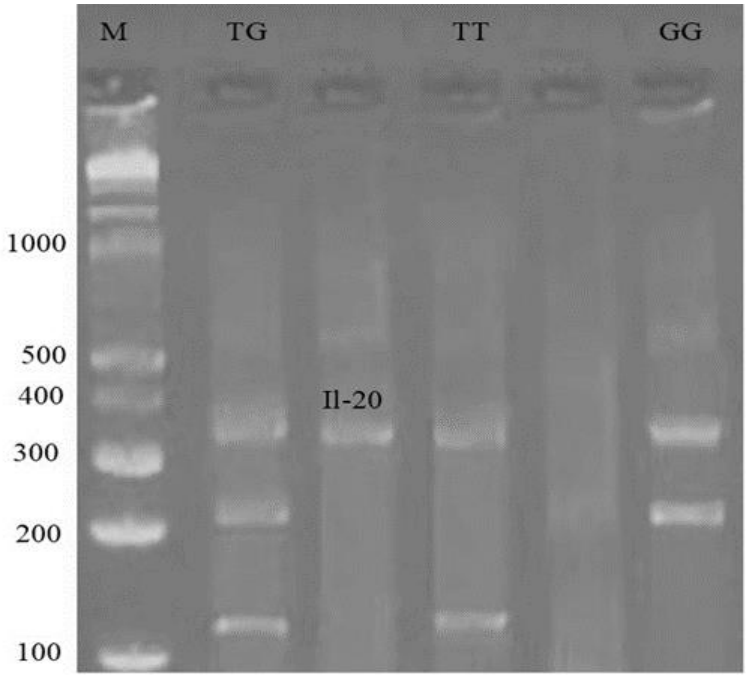

Figure 1: The results of the size amplicon for rs2981572 alleles and IL-20 gene. The product size of IL-20, *G* and *T* alleles of rs2981572 polymorphisms were 320 bp, 219 bp and 156 bp respectively. UV light was used to illustrate the bands. A 100 bp molecular weight DNA marker is shown by the M lane.

Table 2: The allele frequencies and rs2981572 genotyping results in patients and controls.

Genotypes	Cases (n=150)				Control (n=150)				OR (95%CI)	RF	*P*
	Observed		Excepted		Observed		Excepted				
	No	%	no	%	No	%	no	%			
TT	15	10%	26.04	17.36%	94	62.7%	74.2	49.5%	0.07(0.04 – 0.12)	0.58	0.0000**
TG	95	63.3%	72.92	43.2%	23	15.3%	62.6	41.7%	9.54(5.49–16.58)	0.56	0.0000**
GG	40	26.7%	51.04	10%	33	22 %	13.2	8.8%	1.29 (0.76- 2.19)	0.21	0.4
Total	150	100	150	100	150	100	150	100			

OR= Odds ratio, CI= Confidence Interval, RF=Risk factor, P<0.05 by Fisher's test, **highly significant, p-value of TT and TG =1.2×10-22** and 7.2×10-18**respectively.

In addition to the more common genotype and allele frequency, the results in Table 2 also shed light on the percentage of the dominant genotype in patients and the control group for IL-20 (rs2234671). The TG genotype recorded 63.3% of total cases, while the GG and TT genotypes were noted to constitute 26.7% and 10%, respectively. In regard to the control group, the dominant homozygous TT genotype recorded a higher rate of 62.7% than the other genotypes, GG (22%), and TG (15.3%). Regarding the TT genotype, the risk factor (0.58) is regarded as a highly significantly protective factor (*P* =0.0000) because the OR was 0.07 (95% CI = 0.04-0.12). However, because the OR for the TG genotype was 9.54 (95% CI= 5.49–16.58), the risk factor (0.56) is regarded as a highly significant etiological factor (*P* = 0.0000). The OR of GG genotype was 1.29 (95% CI= 0.76-2.19), accordingly

is considered insignificant (P = 0.4) etiological factor. Furthermore, the results in Table 3 indicated that the G allele (58%) frequency is higher than that of the T allele (42%) in the case group. In contrast to the control, the T and G alleles recorded 67.3% and 32.7%, respectively. Furthermore, risk factor (0.49) is considered a highly significant protective factor (P =0.0000), and the OR of G allele frequency was 3.32 (95% CI = 2.37-4.65), indicating that risk factor (0.4) is a highly significant etiological factor (P =0.0000). In contrast, the OR of T allele frequency was 0.3 (95% CI = 0.22-0.42). Based on these results, individuals with the G allele and TG genotype are significantly more likely to have asthma. Conversely, the T allele and dominant TT genotype offer significant protection against the illness. The proportion of prevented and etiological fractions among study groups is shown in Table 4. For the TT and GG genotypes as well as *the* T allele, the proportion of prevented fractions in the population was 58.5%, 6%, and 49.1%, respectively. About the TG genotype and G allele, the proportions of the etiological fraction were 56.7% and 40.8%, respectively.

c. Measurement of IL-20 levels

IL-20 levels in study population sera were found to be significantly higher in cases (P =0.0001) than in controls (1389.92 ± 31.84 vs. 797.67 ± 31.11 pg/ml, respectively). The present work findings illustrated that there are notable distinctions between patients and healthy individuals. Albeit the presence of these significant differences, the current results recorded an interference in IL-20 levels between the study groups. Another words, Fig2 shows approximately 33.3% of the interference between cases and controls.

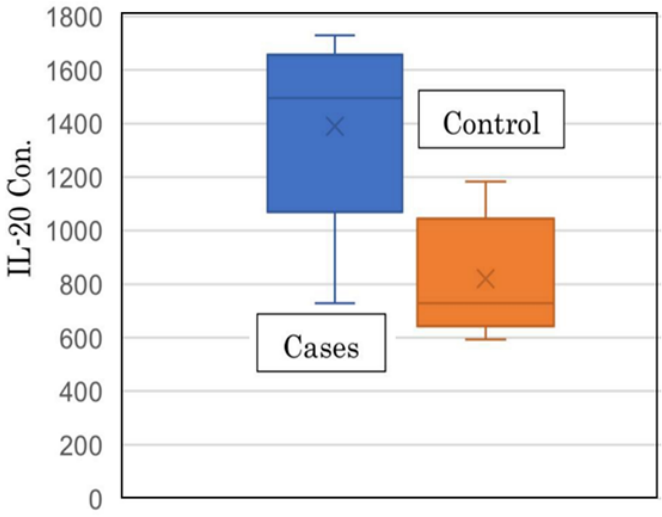

Figure 2: IL-20 levels in the case and control groups are displayed in a box plot. The orange and blue boxes, respectively, display the values for the controls and cases. The asterisks represent the mean. Below and above the box range, respectively, are whiskers that indicate the maximum and minimum values.

Thereby, the remaining percent (67.7%) of patients who had greater IL-20 levels than controls, may be a useful immunological indicator for asthma. This information needs to be confirmed by more research.

Table 3: The allele frequencies of IL-20 gene polymorphisms (rs2234671 T/G) in patients and controls.

Specific target Gene	Allele	*Asthma patients* number (%)	Control group Number (%)	OR (95%CI)	RF	*P*
IL-20 gene rs2234671 T/G	*T*	125 (58%)	211 (67.3%)	0.3 (0.22- 0.43)	0.49	0.000**
	G	175 (42%)	89 (32.7%)	3.32 (2.34 – 4.72)	0.4	0.000**

=highly significant, p-value for T and G allele is 1.9×10^{-12} for both of them.

Table 4: The proportion of the etiological and protective fraction in populations for the genotypes and allele frequencies of the rs2234671 T/G polymorphism in the IL-20 gene in patients and controls

Target Gene	Genotypes and alleles	Prevented fraction %	Etiological fraction %
IL-20 gene rs2234671 T/G	TT	58.5%	-
	TG	-	56.7%
	GG	6%	-
	T allele	49.1%	-
	G allele	-	40.8%

d. The levels of IL-20 in patients and according to genotypes.

According to rs2981572 genotypes, the significant variation in IL-20 levels between cases and control are shown in Table 5. The findings in Table 5 noted highly significant variation among controls and cases in IL-20 levels according to the genotypes of rs2981572 polymorphisms. The results in Table 5 showed clear significant variation between patients and control groups among all genotypes, where the results for the TT, TG, and GG genotypes recorded significant differences of 0.0001, 0.00002, and 0.0003, respectively. The significant differences ($P < 0.05$) in IL-20 levels between cases group according to rs2981572 genotype are shown in Table 6. The result in Table 7 reported insignificant differences between all patients' groups according to their genotyping.

Table 5: The distribution of rs2981572 genotyping allele frequencies in patients relative to controls

Genotypes	IL-20 levels concentration (Mean ± SE)		*p*-value
	Cases	Control	
TT	(1551.62±81.58)	(787.83±43.74)	0.0001
TG	(1393.11±34.37)	(823.28±48.71)	0.00002
GG	(1319.89±79.39)	(806.69±70.62)	0.0003

Table 6: The levels of IL-20 levels distribution according to rs2981572 genotyping alleles frequencies in cases group.

Genotypes	IL-20 levels concentration (Mean ± SE)		*p*-value
TT vs TG	(1551.62±81.58)	(1393.11±34.37)	0.12
TT vs GG	(1551.62±81.58)	(1319.89±79.39)	0.06
TG vs GG	(1393.11±34.37)	(1319.89±79.39)	0.4

4. Discussion

A complex interplay between environmental and genetic variables causes a chronic asthma illness. The physiological symptoms of asthma are diverse, and can occur in several patterns, such as T2 (allergic or non-allergic, eosinophilic) and T2 (non-eosinophilic). Although there are differences in the origins of these patterns, there is strong evidence that environmental factors, particularly exposure to microbes, during childhood play a role [19]. Microbial imbalance can occur as a result of loss of beneficial microorganisms, increase in pathogenic microorganisms, or decreased microbial diversity. This imbalance may increase susceptibility to asthma by causing changes in the immunological development of mucosal tissues [20]. In a study of the nasopharyngeal microbiome in Australia, which included 234 infants and continued to analyze their urine multiple times during the first two years of life, the results showed that the increased risk of asthma was associated with repeated early colonization with staphylococci associated with infants attending daycare and receiving antibiotics [21]. The findings of this study offer the first proof that asthma and the rs2981572 genotype are related in Iraqi individuals who have a pneumococcal infection. The results of this study demonstrated that the rs2981572 genotype is linked to a higher chance of developing the autoimmune illness asthma. According to [18], the rs2981572 genotypes were substantially linked to multiple sclerosis, another autoimmune disease, which is consistent with the current findings. Many studies on autoimmune diseases such as rheumatoid arthritis, lupus nephritis, ulcerative colitis, atherosclerosis, and asthma have shown a link and involvement of IL-20 in these diseases [22]. Important factors in the development of autoimmune diseases such as allergic asthma are immune parameters such as interleukins and antibodies [23]. In general, overexpression of high levels of the IL-20 in patients is evaluated in cases of autoimmune diseases. In

recent years, it has been observed that levels of interleukin 20 increase in patients with rheumatoid arthritis [24]. Wu *et al.* [25] reported high levels of expression and concentration of IL-20 in the airway epithelium of asthma patients. Moreover, the findings of Madouri *et al.* [26] recorded during infection, there was an initial increase in the mRNA and protein expression of the cytokine IL-20 in the lung tissue. There are many factors that affect human health, including genetic factors, lifestyle conditions such as social behaviors, economic conditions, and environmental factors associated with that lifestyle, in addition to the possibility of obtaining health care and treatments for a particular disease [27]. In medicine, pathology, epidemiology, and clinical immunology, genetic polymorphisms are considered major contributors to genetic diversity among humans and are identified as valuable biomarkers in the related sciences, and ethnic studies. Although genetic mutations are rare and are usually known to cause genetic diseases, from another perspective, genetic polymorphism is not necessarily linked to a specific disease [28]. Genetic diversity within the population, including polymorphic genes, is essential for developing personalized treatment protocols. The appropriate drug must be accessible for the right genotype at the right dosage [29]. Research on the connection between the development of lung illnesses, such as asthma, and the microbiome is still underway. It is essential that the microbiome is colonized during the first three years of life for general health because it plays a crucial role in this for the body. Early microbial imbalance may be associated with many factors affecting this balance, including cesarean sections during childbirth, excessive use of antibiotics, and perhaps even artificial nutrition. Studies have shown that the intestinal microbiome and respiratory tract in children and young people have a relationship between microbial imbalance and the development of asthma in them later in life [30]. Genetic polymorphisms may not be associated with disease development in some cases due to the size of the samples studied or perhaps genetic diversity associated with the geographic region as another reason to explain this lack of association [31]. It is worth mentioning that other molecular studies suggest a close association with genetic predisposition to the disease (see for example references [32], [33]).

5. Conclusion

According to this study, the TG genotype and *G* allele in the rs2981572 polymorphism in the IL-20 gene may be linked in asthma. However, much more investigation is needed to confirm this connection.

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Conflicts of Interest: The authors declare no conflict of interest pertaining this work.

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