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Association of TNF-α Promoter Region (-308 G/A, rs1800629) Gene Polymorphism with Psoriasis Vulgaris in Northern Iran

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A B S T R A C T

The present study aimed to investigate the association between the TNF-α promoter region polymorphism (-308 G/A, rs1800629) and psoriasis vulgaris in populations from western Mazandaran and eastern Guilan provinces in northern Iran. In this case–control study, whole blood samples were collected from 50 patients with psoriasis vulgaris residing in western Mazandaran and eastern Guilan, northern Iran, whose diagnosis had been confirmed by a dermatologist. Additionally, 30 whole blood samples were obtained from healthy individuals who met the inclusion criteria for the control group. Samples were collected from clinical laboratories located in the study regions. Genomic DNA was extracted from all samples, and genotyping of the TNF-α promoter region polymorphism (-308 G/A, rs1800629) was performed using the Amplification Refractory Mutation System–Polymerase Chain Reaction (ARMS-PCR) method. To validate the genotyping results and ensure the accuracy of the analysis, selected samples were further confirmed by DNA sequencing. The results of the statistical analyses revealed that the GG genotype (homozygous dominant) was the only genotype detected in both the patient and control groups. No individuals carrying the AA (homozygous recessive) or GA (heterozygous) genotypes were identified in either group. Consequently, the frequency of the A allele was zero in the study population. Overall, the findings demonstrated no significant difference in genotype or allele distribution between patients with psoriasis and healthy controls. Therefore, no statistically significant association was observed between the TNF-α rs1800629 polymorphism and susceptibility to psoriasis vulgaris in the studied population. Based on these results, this polymorphism cannot be considered a reliable genetic marker for the diagnosis or prediction of psoriasis in this region. Nevertheless, further studies involving larger sample sizes and broader populations are required to confirm these findings and clarify the potential role of this polymorphism in psoriasis pathogenesis.

Keywords: *Psoriasis vulgaris, TNF-α, rs1800629, Gene polymorphism, ARMS-PCR, Northern Iran.*

1. Introduction

Psoriasis is a chronic, progressive, immune-mediated skin disease (1) that most commonly presents as discrete, pink, scaly plaques that develop on various parts of the body (2). The most common type of psoriasis is psoriasis vulgaris (plaque), in which patients may have plaques of a certain size, coin-shaped, or almond-shaped (3).

Worldwide, approximately 100 to 125 million people suffer from psoriasis. The prevalence of this disease varies worldwide depending on the region and, according to reports, in Western countries it affects 2-4% of the population. While in Asian countries and some African countries, the lowest prevalence rate (between 0.3 and 1.2% in China) has been reported. On the other hand, in Scandinavian and Caucasian populations this rate reaches 11% (4-7). In Iran, its prevalence is between 1.3% and 2.5% (8).

The disease has a significant negative impact on health and quality of life, most notably in the emotional and social domains. In a recent National Psoriasis Foundation survey of 5,604 patients with psoriasis, 94% reported that psoriasis was a major problem in their daily lives (1). The prevalence of psoriasis varies by region and can appear at any age, suggesting that ethnicity, genetic background, and environmental factors influence the occurrence of psoriasis. In genetically predisposed individuals, a variety of stimulants can trigger the disease. In previous studies from 1982 to 2012, aggravating factors observed in Japanese individuals included stress, seasonal factors, infection, sun exposure, and beta-blockers (9).

Four decades of clinical and basic research on psoriasis have elucidated many of the underlying pathogenic mechanisms of the disease and paved the way for effective targeted therapies (10).

Three factors, genetic susceptibility, immune system imbalance, and environmental factors, are among the most important factors affecting the development of the disease and the differences that exist (11, 12). According to recent research, genetic factors are influential in the age of onset of the disease, clinical manifestations, type, and severity of the disease (13). Given the relatively high heritability of this disease, genetic analyses are being conducted worldwide to identify genes that affect the risk of developing psoriasis. According to studies, various single nucleotide polymorphisms (SNPs), which are involved in processes such as skin barrier function and regulation of immune and inflammatory responses, are associated with an increased risk of psoriasis (14).

Cytokines are bioactive proteins produced by many different cells of the immune system to regulate immune responses (15). Studies have shown that cutaneous and systemic overexpression of several proinflammatory cytokines, especially type 1 cytokines such as interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), and interferon gamma, are responsible for the initiation, maintenance, and recurrence of skin lesions including psoriasis (16). On the other hand, anti-inflammatory cytokines such as IL-1, IL-4, and IL-10 are relatively underexpressed in this disease (17).

Tumor necrosis factor-alpha (TNF-α) is a cell messenger protein involved in systemic inflammation and is known as a master regulator of the inflammatory response (18). This protein, is a 17-kDa proinflammatory cytokine that is produced by a variety of cell types in response to a variety of infectious and noninfectious stimuli. These cells include macrophages, T lymphocytes, B lymphocytes, natural killer cells, neutrophils, astrocytes, endothelial cells, and smooth muscle cells, but are mainly produced by activated macrophages. In general, TNF-α has a wide range of roles and, when expressed at normal levels, plays a physiological protective apoptotic role against some tumors and some infections, and activates control systems involved in cell proliferation, differentiation, inflammation, death, and immune regulation. Although normal levels of TNF-α are important for regulating immune responses, the persistence of an immune response caused by its inappropriate and excessive production can have deleterious effects, as evidenced by inflammatory, autoimmune, and proliferative disorders (19, 20). Studies have shown that inappropriate or excessive production of this proinflammatory cytokine can be harmful and lead to disease. Rheumatoid arthritis, inflammatory bowel disease, psoriatic arthritis, and psoriasis can be caused by abnormal TNF-α secretion. Therefore, TNF-α can be classified as a key factor in the pathological development of diseases (21). In psoriasis vulgaris patients, the level of tumor necrosis factor alpha (TNF-α) is generally increased (22) and by inducing and employing several cytokines, it activates the inflammatory processes of this

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disease and plays an important role in its development and pathogenesis (23). On the other hand, TNF-α inhibitors are used as drugs in the treatment of this disease (21).

One of the fundamental problems in clinical pharmacology is dealing with inter-individual variability in the effectiveness of drugs, both in terms of efficacy and safety. Pharmacogenetics is the study of genetic characteristics and their relationship to drug response, both in terms of efficacy and side effects. The first step in this process is to examine an individual's genetic variations. In the case of psoriasis, studies are attempting to identify genetic polymorphisms that act as markers or indicators of susceptibility to the disease. Given that many biological compounds for the treatment of this disease target the TNF-α protein, the study of polymorphisms in the TNF-α gene is of particular interest. TNF-α is located in a single copy on the short arm of chromosome 6 (6p.21.3) within the coding region of the major histocompatibility complex (MHC), HLA, and is very close to major histocompatibility complex B. This region is highly polymorphic, and up to 44 polygenic variants have been reported in this region, some of which have been associated with various diseases. In psoriasis, the most studied polymorphisms in TNF-α include substitutions of guanine for adenine at positions 238 and 308 (-238G→A, -308G→A), substitutions of cytosine for thymine at position 857 (-857C→T), and substitutions of thymine for cytosine at position 1031 (-1031T→C). The first two SNPs are located in the promoter region of the gene and have been shown to affect TNF-α expression and are associated with the occurrence of many diseases, including the severity of psoriasis. While the presence of -857T has been associated with an increased risk of psoriatic arthritis, not psoriasis. No definitive association between the polygenic position 1031 and this disease has been found (19, 20, 24). Although much effort has been devoted to investigating the association between TNF-α gene polymorphisms and psoriasis risk, the results obtained are inconsistent rather than consistent. Some studies have shown a significant association between TNF-α polymorphisms at positions -238 and -308 and psoriasis, but a number of them have also shown no significant association (25). The results obtained in this regard are very diverse and sometimes contradictory. According to some studies, the risk of psoriasis increases in the presence of the -238A allele, while it decreases in the presence of the -308A allele. Therefore, the -308A allele is protective in nature (22, 23, 25, 26). Rahman and colleagues showed in their study in 2006 that the -238A/G polymorphism increased the risk of developing psoriatic arthritis, while the -308A/G polymorphism decreased the risk, but the results were not significant (25). However, in a study published by Tsunemi et al. in 2003, they compared TNF-α gene polymorphisms between 163 affected patients and 96 healthy individuals in Japan, No significant association was observed between TNF-α gene polymorphisms at positions -308 G/A and -238 G/A and susceptibility to psoriasis (27).

There are many studies in this field, sometimes with contradictory results, which are beyond the scope of this section and will be discussed further.

Considering previous studies on the association of the -308(G/A) TNF-α polymorphism with psoriasis and various results obtained in different geographical regions, the aim of this study was to investigate this association in western Mazandaran and eastern Guilan in north of Iran, so that if this association is significant, it can be used as a diagnostic marker for psoriasis.

2. Methods and Materials

The study was a case-control study that was conducted after approval by the university's ethics committee under number IR.IAU.RASHT.REC.1398.012.

Sample preparation: The samples studied included 50 individuals with psoriasis and 30 control individuals, which were collected from western Mazandaran and eastern Guilan. To obtain whole blood from affected and control individuals, they were asked to fill out questionnaires containing information about age and gender and sign an informed consent form before sampling. After approval by the treating physician, the collected blood samples were transferred to the laboratory in EDTA-containing vials and stored in a -20°C freezer until DNA extraction and genetic studies.

DNA extraction: DNA was extracted from blood samples of patients and controls using a modified phenol-chloroform method. For extraction, cell lysis buffer was prepared containing Tris-Hcl 10mm/l, Sucrose 11% w/v, Mgcl2 5mm/l, Triton X-100(1%u/v), and nuclear lysis buffer was

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prepared containing Tris-Hcl 10mm/l, SDS 1% w/v, EDTA 10mm/l, Sodium citrate 10mm/l, and NACL 5mol.

Genomic DNA extraction was performed according to the protocol. The purity, quantity, and quality of the extracted DNA were evaluated using a biophotometer (Eppendorf-Germany) and 1% agarose gel. Samples with good quality and OD260/280 = 1.8-2 were used for further work.

Genotyping: To identify the polymorphism rs1800629 of the TNF-α gene at position -308(G/A), ARMS-PCR method was used. This method is based on the design of allele-specific primer pairs and amplification of the desired allele. To amplify the region containing the mutation, two primer pairs designed for the mutant allele and the normal allele, respectively, can be used (28).

The general characteristics of the primer pairs specific for the mutant and wild-type alleles are shown in Table 1. All primers used were designed using gene Runner and Oligo7 software based on the TNF-α gene sequence on chromosome 6. After selecting the primers, their sequences were compared with the human genome sequence in the Gene Bank database. In the primer design, in addition to the 3′ end mismatch, a base was changed in the third base of the 3′ end of the primers to ensure that the primer did not bind to the opposite allele. In order to optimize, the ARMS PCR reaction was performed in two separate vials, each containing 10µl of Master Mix 2x made in Denmark and 5µl of extracted DNA. To one of the vials, 1µl of each 10 picomoles primer pair of the wild type allele was added, and to the other vial, 1µl of each 10 picomoles primer pair of the mutant allele was added. Each vial was made up to 20µl with 3µl of distilled water. Then, polymerase chain reaction was performed using a BIORAD thermocycler. Initially, the reaction was performed with different DNA concentrations on different samples, and the optimal DNA concentration was obtained. To optimize the primer annealing temperature, the temperature was gradually changed between 50 and 70°C using a temperature gradient method until optimal conditions were achieved and the best annealing temperature was selected. The primer concentrations and other temperature conditions were also optimized. The PCR profile and thermal program are shown in Table 2. To check for contamination, a well containing all the test contents without DNA was considered as a negative control. After performing the PCR reaction to ensure the amplification of the desired fragment, the resulting product was electrophoresed on a 2.5% agarose gel. To better examine the homozygosity and heterozygosity of the alleles in each individual, the PCR samples corresponding to the normal allele and the mutant allele were loaded in two wells side by side and then examined.

DNA sequencing: In order to confirm the accuracy of the work for each genotype (AA-AG-GG), PCR Sequencing technique was used using the primers listed in Table 1. To perform this reaction, a vial containing 25 µl Master Mix, 2 µl of each primer, and 5 µl of extracted DNA was used and the volume was brought to 50 µl with 16 µl of distilled water. Then, this mix was placed in a thermocycler with the conditions mentioned above and the primer annealing temperature was 61 °C to perform the polymerase chain reaction.

After PCR, qualitative analysis was performed using 2.5% agarose gel and the remaining PCR products were sent to Taq-Kopenhagen (Denmark) along with the reverse primer for PCR Sequencing. The submitted sequence was analyzed using Chromas software and the known mutation was confirmed in the samples used.

Statistical analysis: Statistical analysis: After confirming the accuracy of the results, the data obtained from determining the genotype of the two patient and control groups were analyzed using SPSS24 software. Descriptive statistics of the variables, Kolmogorov-Smirnov test to examine the normal distribution of the age variable, parametric t-test to compare the mean age of the individuals in the control and patient groups, and chi-square test to examine the relationship between gender and the two control and patient groups were used. A significant value of $P< 0.05$ was considered.

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Table 1

Primers used and their general characteristics

Primers	Primer sequence (5'-3')	Tm (°C)	Length (bp)
TNF-α-nF	AGG CAA TAG GTT TTG AGA GGC AGG G	67	382
TNF-α-nR	GGG AAA GAA TCA TTC AAC CAG CGG AAA AC	67	382
TNF-α-mF	AGG CAA TAG GTT TTG AGA GGC AGC A	67	151
TNF-α-mR	AGT TGG GGA CAC ACA AGC ATC AAG GAT A	68	151
TNF-α SF(Sequencing Primer)	ACA CAG GCC TCA GGA CTC AAC ACA GCT T	71	317
TNF-α SR	TNF –mR primer	68	151

N=Normal, F=Forward, M=Motant, R=Reverse

Table 2

PCR program for amplification of the rs1800629 polymorphism of TNF-α gene at position (-308(G/A)

cycle number	time	temperature (°C)	stage
1	5 min	95	primary denaturation
30	45 sec	94	Secondary denaturation
	40 sec	62	annealing
	40 sec	72	extension
1	10 min	72	final extension

3. Findings and Results

In this study, by sampling 50 individuals with psoriasis and 30 healthy individuals, the association of the rs 1800629 polymorphism of the TNF-α gene at position -308 G/A with psoriasis was investigated. The genotypes AA, AG and GG and the alleles A and G were investigated in patients with psoriasis. The PCR products were examined on a 2.5% agarose gel with a DNA marker with a molecular weight of 100 bp. According to the designs, we should have seen a 382 bp fragment as the normal fragment and a 151 bp fragment as the mutated fragment. The results obtained from gel electrophoresis confirmed the presence of only the 382 bp fragment (normal fragment) (Figure 1).

Figure 1 shows the PCR product of three samples from the patient group, as can be seen in the image, all three samples are homozygous wild-type (GG).

Figure 2 shows the PCR product of four samples from the control (healthy) group, as can be seen in the image, all four samples are homozygous wild-type (GG).

Figure 1

PCR product of the rs 1800629 polymorphism of the TNF-α gene at position -308 G/A in three samples from the patient group.

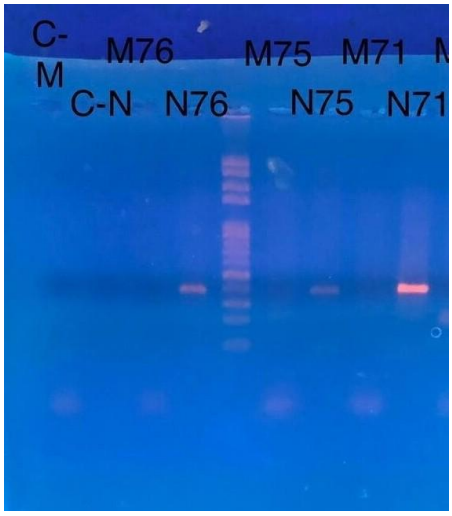

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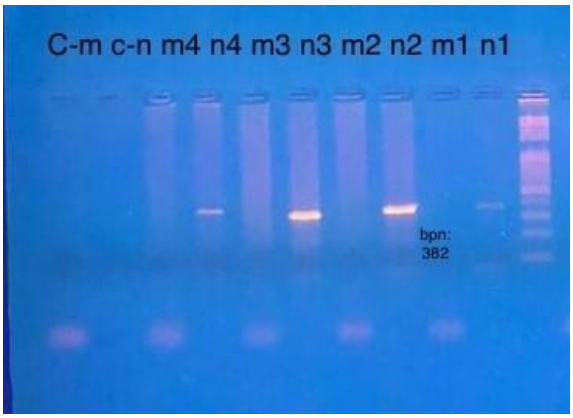
Figure 2

PCR product of the rs 1800629 polymorphism of the TNF-α gene at position -308 G/A in four samples from the control or healthy group.

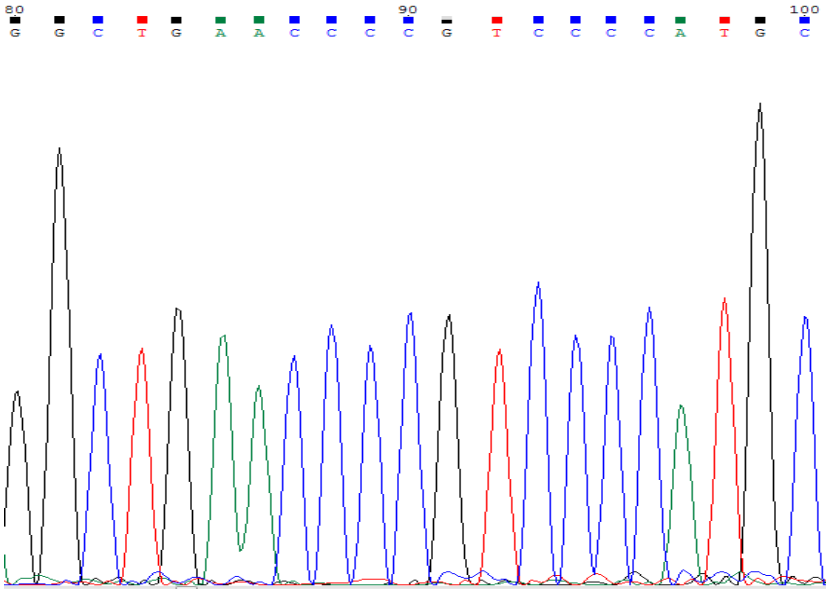


The results of statistical studies showed that the studied groups did not differ significantly in terms of gender and age ($p<0.05$). The GG genotype and G allele were examined in patients with psoriasis. The number and percentage of the homozygous wild-type GG genotype in the control and patient groups were (100%) 30 and (100%) 50, respectively. Also, the number and percentage of the G allele in the control and patient groups were (100%) 60 and (100%) 100, respectively. The number and percentage of the heterozygous AG genotype and the homozygous variant AA genotype in the control and patient groups were both zero. Therefore, the frequency of the A allele was also zero in both groups.

Overall, the results showed that there was no significant difference in the incidence of these alleles between the two study groups. Therefore, statistically, no significant association could be found between the rs1800629 polymorphism of the TNF-α gene and susceptibility to psoriasis.

Figure 3

DNA sequencing result for a homozygous wild-type (GG) sample from a patient. As shown, the C base is located at position 95 in the antisense strand.



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To analyze the sequence results, the sequence of the TNF-α gene

Variant type:

CAATAGGTTTTGAGGGGCATG(G/A)GGACGGGT TCAGCCTCAGGGTCCTAC

where the desired SNP is located in this sequence was used. The results obtained in the sequence are the antisense of the above sequence. The desired SNP is located at position 95. If the sample is homozygous wild-type genotype (GG), the base C should be located at the SNP position, and if it is homozygous variant genotype (AA), the base T should be located. If the sample is heterozygous (AG), one of the bases T or C is located, in this case two peaks are seen at this position. The accuracy of the PCR results and their correspondence with the results of sequencing can be seen in Figure 3.

4. Discussion and Conclusion

In this study, the association between the TNF-α gene polymorphism and psoriasis vulgaris was investigated in populations from western Mazandaran and eastern Guilan, northern Iran. The results demonstrated that the GG genotype (homozygous wild-type) was the only genotype detected in both the patient and control groups. No individuals carrying the GA (heterozygous) or AA (homozygous mutant) genotypes were identified. These findings suggest that the TNF-α promoter region polymorphism (-308 G/A, rs1800629) is not associated with susceptibility to psoriasis vulgaris in the studied population.

Single nucleotide polymorphisms (SNPs) characterize the smallest genetic differences between individuals and are increasingly being used in the post-genomic era to identify genetic markers for complex disease traits. Given that the regulatory regions of many genes are poorly understood, most efforts have focused on characterizing variations in and around the coding regions. The TNF-α gene provides a unique opportunity to study the distribution of SNPs in a genetic regulatory region where critical regions involved in the regulation of gene transcription are well characterized (29).

TNF-α is a key inflammatory mediator, and its expression has been implicated in the development and progression of psoriatic lesions (26). Several studies have suggested that functional polymorphisms located at positions −238 and −308 of the TNF-α gene may be associated with psoriasis susceptibility and disease progression. Although substantial efforts and resources have been devoted to investigating the relationship between TNF-α gene polymorphisms and the risk of psoriasis, the findings remain inconsistent and controversial. While some studies have reported a significant association between these polymorphisms and psoriasis, others have failed to demonstrate such a relationship.

Rajesh et al. conducted a study in 2017 titled Role of TNF-α polymorphism-308(G/A) in patients with psoriasis in India. This study was conducted on 74 patients with psoriasis and 74 healthy individuals using RFLP technique. The GG genotype was the dominant genotype observed in patients with psoriasis and healthy individuals. The frequency was 86.5% in patients and 82.4% in healthy individuals. The recessive allele (A) had a low frequency in both homozygous and heterozygous conditions. The distribution of genotypes in the two groups was compared using a probability table, and the two groups did not show a statistically significant difference. In this study, no association was observed between TNF-α polymorphism -308(G/A) and susceptibility to psoriasis (22), which is consistent with the results of our research.

In a similar study, Tsunemi et al. (2003) investigated polymorphisms at positions -238 and -308 of the TNF-α gene in Japan and their association with psoriasis vulgaris. This study included 163 patients with psoriasis vulgaris and 96 control subjects. No significant association was observed between genotypes and alleles of this SNP and susceptibility to psoriasis vulgaris (30).

Baran et al. also found no significant difference in the TNF-α -308 promoter polymorphism (genotypic distribution and allele frequency) between psoriasis patients and control subjects in a study conducted in Poland in 2006. Therefore, this polymorphism is not associated with susceptibility to psoriasis vulgaris. The most common genotype observed in both the patient and control groups was the GG genotype. This study confirmed the findings of previous studies that there was no association between the TNF-α -308 promoter polymorphism and susceptibility to psoriasis (31) and is consistent with our findings.

Nishibu et al. (2002) studied the association of TNF-238A and -308A with psoriasis vulgaris, psoriatic arthritis, and generalized pustular psoriasis (GPP). The study

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included 18 patients with psoriasis vulgaris, 11 with psoriatic arthritis, 2 with GPP, and 6 with GPP plus arthritis. Of these 37 patients, 36 had the GG genotype (97.3%) and 1 had the AA genotype (2.7%), and no GA genotype was observed (32).

Murdaca et al., in a 2014 study, examined 57 patients with psoriatic arthritis and 155 control subjects and did not observe a significant difference in the frequency of -308 and -238 SNPs between affected individuals and controls (33).

Also, Popadic et al. in 2015 investigated the association of the rs1800629 polymorphism of the TNF-α gene with psoriasis in Serbian patients. This study included 130 patients and 259 controls. They stated that the GG genotype was higher in patients compared to controls, but this increased frequency was not statistically significant (34).

In another study, Patricia et al. in 2019 studied the association between psoriasis vulgaris and the polymorphism of the TNF-α gene at position -308 in the Lebanese population and reported that this polymorphism was not associated with susceptibility to psoriasis vulgaris (35), and the results of all these studies were consistent with our findings.

In contrast to our findings, Aadil et al. (2018) investigated the association between the -238 and -308 polymorphisms of the proinflammatory cytokine TNF-α gene promoter in a North Indian population and concluded that the -308 polymorphism of TNF-α was associated with a reduced risk of psoriasis, and the -238 polymorphism of this cytokine was associated with an increased risk of psoriasis. In addition, serum TNF-α levels were increased in patients compared to controls (36).

Zhuang et al. also conducted a study in 2013 to comprehensively evaluate the association between TNF-α -308(G/A) and TNF-α -238(G/A) polymorphisms and the risk of psoriasis and stated that in general, TNF-α -308(G/A) polymorphism was significantly associated with a reduced risk of psoriasis. Subgroup analysis based on ethnicity showed that there was a significant association between this polymorphism and a reduced risk of psoriasis in both Caucasian and Asian populations (26).

In 2021, Hagg and colleagues investigated the association of gene polymorphisms at positions 308 and 238 with psoriasis. This study was conducted by Menoufia University in Egypt on 70 people with psoriasis and 70 healthy people. Genotyping results showed that the AG genotype and the A allele at position 238 were more common in patients than in healthy people, while conversely, at position 308, the AG genotype and the A allele were more common in the control group than in patients (20).

In a study conducted by Murchung et al., published in 2015, the effect of TNF gene polymorphism at position 308 on psoriasis was investigated and compared in 112 patients and 243 healthy controls in the Indian population. The results showed a strong association of the polymorphism of this gene at position 308 with psoriasis. In the patient group, the frequency of allele A and genotype AG was higher than in healthy individuals (37).

In a study conducted by Gulel et al. in 2018 in a Turkish population, they investigated the role of genes in susceptibility to psoriasis. In this study, 74 affected individuals and 74 healthy individuals were used. Genotyping results showed that the AA genotype at position -308 of this gene was significantly more frequent in patients. In light of this result, they stated that the A allele at position -308 has been shown to have greater potential as a transcriptional activator in vitro compared to the G allele. Therefore, the frequency of the A allele is associated with the risk of autoimmune disorders (38).

n a study published in 2021 by Wang and Zhou, they examined the association between different polymorphisms of the TNF-α gene and psoriasis by meta-analyzing 29 research articles. It was found that the TNF-α polymorphisms -238 G/A and -857 C/T were significantly associated with psoriasis in the general population. Subgroup analysis showed that the -238 G/A polymorphism was significantly associated with psoriasis in Caucasian and East Asian populations, and the 308 G/A polymorphism was significantly associated with psoriasis in East Asians (39).

In a similar study in Iran, Taj Sharghi et al. in 2015 examined the expression of TNF-α and IFN-γ genes in Iranian psoriasis patients using Real Time PCR and concluded that the gene expression of these two cytokines was increased in the skin lesions of patients compared to healthy individuals (40).

Overall, the results from different studies have been inconsistent. In many studies, the sample size was very small and they were not powered to detect the possible risk of

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TNF-α polymorphisms. In addition, selection bias is inevitable and may contribute to the results of the trial (25).

According to the results obtained in this study, the difference in the frequency of the TNF-α polymorphism (rs1800629) in the patient and control population was not significant after eliminating the factors of age and sex in this geographical area and this polymorphism cannot be used as a diagnostic marker for psoriasis. All genotypes observed in this study were GG and were normal homozygotes, which may have been due to the small number of samples, and perhaps if the number of samples increases, there is a possibility of observing the A allele.

Considering the different studies, it can be seen that one of the reasons for explaining the opposing and contradictory results could be the fact that these studies were conducted on different populations around the world (14). Furthermore, sample selection bias seems inevitable and may have contributed to the results. Demographic information may also not be well matched. Finally, genotype misclassification may affect the results because genotype quality control was not well performed in most studies (25).

Further research focusing on diverse populations is necessary to reach a definitive overall conclusion about this association. Other causes of different results in the study of gene polymorphisms include different gene pools, molecular methods used, and the size of the population studied (14). Using an appropriate sample size for each disease phenotype can better reflect the true impact of the polymorphism on the characteristics of that disease (41). However, further studies are needed to fully determine the molecular basis of susceptibility to psoriasis, which may differ for different races, and will certainly expand our knowledge of the pathogenesis of this disorder (31).

Authors' Contributions

All authors contributed substantially to the study and to manuscript development, and all approved the final version.

Declaration

The authors declare that artificial intelligence tools were used only to assist with language editing, translation, and improvement of the manuscript's readability. All conceptualization, study design, data collection, data analysis, interpretation of findings, and final approval of the manuscript were performed by the authors. The authors take full responsibility for the accuracy, integrity, and originality of the content.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

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Declaration of Interest

The authors report no conflict of interest.

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Ethics Considerations

The study placed a high emphasis on ethical considerations. Informed consent obtained from all participants, ensuring they are fully aware of the nature of the study and their role in it. Confidentiality strictly maintained, with data anonymized to protect individual privacy. The study adhered to the ethical guidelines for research with human subjects as outlined in the Declaration of Helsinki.

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