

The correlation TNF- α gene promoter region -238G, -308G, -857, and -1031 polymorphism with psoriasis vulgaris



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ABSTRACT

Background: Psoriasis vulgaris is a recurrent chronic skin disorder signed by hyperproliferation and epidermal inflammation. One of the etiology of psoriasis is genetic factors related to genetic polymorphism as disease susceptibility markers. This study was aimed to analyze the correlation of TNF- α gene promoter region polymorphism with psoriasis vulgaris.

Methods: An analytical observational study with cross-sectional design to identify correlation TNF-region promoter polymorphisms with psoriasis vulgaris. This study included 45 psoriasis vulgaris patients and 45 non-psoriasis vulgaris patients from April to October 2016 at Immuno-dermatology Polyclinic of Dermatology and Venereology/Haji Adam Malik Hospital, Medan. We isolated DNA from the blood sample then ran into the PCR process with specific primers. PCR results were examined by electrophoresis with 2% agarose. Chi-Square test was used to test the hypothesis of a relationship between the TNF- α promoter region and psoriasis vulgaris at a significance of $P < 0.05$.

Result: Analysis by Chi-Square test found a significant correlation of polymorphism in TNF- α gene promoter region with psoriasis vulgaris in -308G ($p=0,001$) and 1031 ($p=0,002$) loci.

Conclusion: TNF- α gene promoter region polymorphism TNF- α gene -1031 was more frequent in the case group, -308G was commonly found in the control group. Both of them were significantly correlated with psoriasis vulgaris.

Keywords: promoter region, TNF- α gene, psoriasis vulgaris

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INTRODUCTION

Psoriasis is a skin disease characterized by hyperproliferation and inflammation of the epidermis with a clinical picture of erythematous plaques and stratified scales, which are chronic residuals. Psoriasis can affect $\pm 2.5\%$ of the world's population, about 20-30% suffer from moderate to severe psoriasis.^{1,2} The prevalence of psoriasis varies widely in several countries. It is estimated to range from 1% to 3% of the population in the world. The incidence in the United States is 2-2.6%, in Central Europe around 1.5%.³ During 2000 to 2002, 338 psoriasis patients (2.39%) were found in the Dermatology and Venereal Disease Polyclinic, dr. Cipto Mangunkusumo, Jakarta.⁴ Based on medical records of the Haji Adam Malik Hospital, Medan, for the period January to December 2015, there were 3,021 psoriasis patients, of which

89 patients were diagnosed as psoriasis vulgaris. Of these, 31 patients (34.9%) were male, and 58 patients (65.1%) were female.⁵ The prevalence of this disease in Indonesia has not been recorded, but the incidence in Asia itself is said to be low (0,4%).⁶

Psoriasis can interfere with the patient's quality of life. Treatment is often not satisfactory, resulting in social and economic burdens. Various studies over the last few decades have added to the knowledge of psoriasis' pathogenesis, with the ultimate goal of finding therapies that are more effective or cure.⁷⁻¹²

CD8 + T cells are found in the psoriasis epidermal layer, while CD4 + T cells and dermal dendritic cells are found in the superficial dermis layer. Psoriasis is considered as an immune system-mediated disease characterized by the presence of T helper (Th) 1 cell predominantly in skin

lesions with elevated levels of interferon-gamma (IFN- γ), tumor necrosis factor- α (TNF- α), IL -2 and IL-18.¹³⁻²⁰

Polymorphisms of -238G bp and -308G bp of the TNF- α promoter region were reported in several studies to associate psoriasis vulgaris and rheumatology diseases, e.g., rheumatoid arthritis and ankylosing spondylitis.²¹⁻²⁹ While polymorphisms at -857 bp were also associated with psoriasis vulgaris accompanied by psoriasis with rheumatoid arthritis. In these three loci, psoriasis cannot arise by itself but must be preceded by comorbid systemic diseases.³⁰⁻³³

From the above explanation, it can be concluded that the relationship of the TNF- α promoter region gene polymorphism with the incidence of psoriasis vulgaris has not shown consistent results. None of the studies have focused on psoriasis vulgaris, so the researchers are interested in conducting this study.

METHODS

Study Design

This study was an analytical observational study using a cross-sectional design to identify the association of TNF-region promoter polymorphisms with the incidence of psoriasis vulgaris and controls. This study used 45 psoriasis vulgaris patients who came for treatment at the Immuno-dermatology Polyclinic of Dermatology and Venereology/Haji Adam Malik Hospital, Medan from April 2016 to October 2016. This research was conducted after obtaining ethical clearance from the Faculty of Medicine's ethical commission, Universitas Sumatra Utara number 347/TGL/KEPK FK USU-RSUP HAM/2016. On the other hand, the study's control group was 45 individuals without psoriasis vulgaris who met the inclusion and exclusion criteria. The inclusion criteria for case-patients such as all patients diagnosed clinically as patients with psoriasis vulgaris type 2, in the range of age between 30-65, are willing to participate in research and sign informed consent. The exclusion criteria were psoriasis vulgaris patients who are pregnant and breastfeeding, suffer from fibrosis, chronic inflammation, malignancy, and autoimmune diseases (systemic lupus erythematosus, Sjogren's syndrome, Churg-Strauss syndrome, idiopathic thrombopenic purpura and allergies. The inclusion criteria for control, such as do not suffer from psoriasis, in the range of age between 30-65, are willing to participate in the study by signing the informed consent. We excluded the controls who are pregnant and breastfeeding, suffer from fibrosis, chronic inflammation, malignancy, and autoimmune diseases (systemic lupus erythematosus, Sjogren's syndrome, Churg-Strauss syndrome, idiopathic thrombopenic purpura, and allergies.

Study Procedure

The study was started with informed consent to the case patients and control. Researchers carried out the recording of basic data at the Immuno-dermatology polyclinic of Dermatology and Venereology Department, Haji Adam Malik Hospital, Medan, such as name, gender, place/date of birth, address,

telephone number, and occupation. Simultaneously, the clinical diagnosis of psoriasis vulgaris was confirmed by the researcher and the supervisor at the Immuno-dermatology Polyclinic of Dermatology and Venereology Haji Adam Malik Hospital, Medan. This study was conducted using Invitrogen Polymerase Chain Reaction (PCR) and Sequencer. The primer sequences were used for both polymorphism (polymorphism -857 was conducted using primer -308F and -238R (5'-CAGCGGAAAACCTTCCTTGG-3'), primer -857F (5'AGGAATGGGTTACAG GAGAC-3') and -857R (GTCCCCTGT ATTCCATACCT) while polymorphism -1031 was conducted using primer 1031F (5'TCAGAGAGCTTCAGGGATAT-3') and 1031R (5'ACATGTGGCCATATCTC CCA-3').

Officers took blood samples at the Clinical Pathology Installation of Haji Adam Malik Hospital, Medan. The method of taking blood is from the median cubital vein using a 5 ml sterile syringe. 5 ml of blood was drawn. After the blood sample is taken, the sample is immediately given an identity label then DNA isolation (Invitrogen kit) is carried out.

Two hundred µl of blood was taken and put into a 1.5 ml microcentrifuge tube, then 20 µl of Proteinase K and 20 µl of RNase A were added, then vortexed (for even mixing) then the sample was incubated

for 2 minutes at room temperature (20-25°C). Then 200 µl of Lysis Buffer was added to the tube, then vortexed and incubated at 55°C for 10 minutes. Then 200 µl of absolute ethanol was added and then vortexed. Next, 640 µl of lysate was added to the tube and put into the spin column connected to the collection tube. The tubes were then centrifuged at 10,000 rpm for 1 minute. After the centrifugation process is complete, the collection tube is discarded, and a new collection tube is prepared on the spin column.

Furthermore, 500 µl of wash Buffer I was added to the tube and centrifuged at 10,000 rpm for 1 minute. The process was repeated with 500 µl wash buffer II and then centrifuged again at a maximum speed for 3 minutes. The collection tube was again discarded, and the spin column was placed in a 1.5 ml microcentrifuge tube. Furthermore, 25-200 µl of Elution Buffer was added to the tube and incubated for 1 minute at room temperature. Then the tube was again centrifuged at maximum speed for 1 minute. In the final stage, the spin column is removed, and the DNA has been filled at -20°C.

Isolated DNA then went into PCR procedure. PCR was conducted with the temperature setting at 94°C for the denaturation process, 58°C for the annealing process, 72°C for the extension and further extension processes, and 40c

Table 1. Demographic Characteristics

Characteristics	Percentage (%)	
	Cases (n = 45)(%)	Control (n=45)(%)
Gender		
Male	14 (31,1)	14 (31,1)
Female	31 (68,9)	31 (68,9)
Age		
30-39	17(37,8)	17(37,8)
40-49	15 (33,3)	15 (33,3)
50-59	12 (26,7)	12 (26,7)
60-65	1 (2,2)	1 (2,2)
Mean (SB)	43,38 (7,90)	43,38 (7,90)
Tribe		
Batak	16 (35,6)	16 (35,6)
Jawa	15 (33,4)	15 (33,4)
Melayu	6 (13,3)	6 (13,3)
Aceh	3 (6,7)	3 (6,7)
Cina	2 (4,4)	2 (4,4)
Minang	2 (4,4)	2 (4,4)
India	1 (2,2)	1 (2,2)

for the soaking process repeated for 35 cycles.

The gene amplification results were then examined using the agarose electrophoresis technique with 2% agarose on a casting tray with a capacity

of 32 samples with a volume of 130 ml. The next reading results will be checked by sequencing at the first base of Kuala Lumpur using chroma V1.45 software; numbers 1 to 4 show the polymorphism mutants TNF- α -238G, -308G, -857, and -1031.

Table 2. The Genotype Difference Locus -238G between Case and Control Group

Allele Sequence	Cases (n = 45)(%)	Control (n = 45)(%)	P
G-A	14 (31,1)	9 (20)	0,227
Non G-A	31 (68,9)	36 (80)	

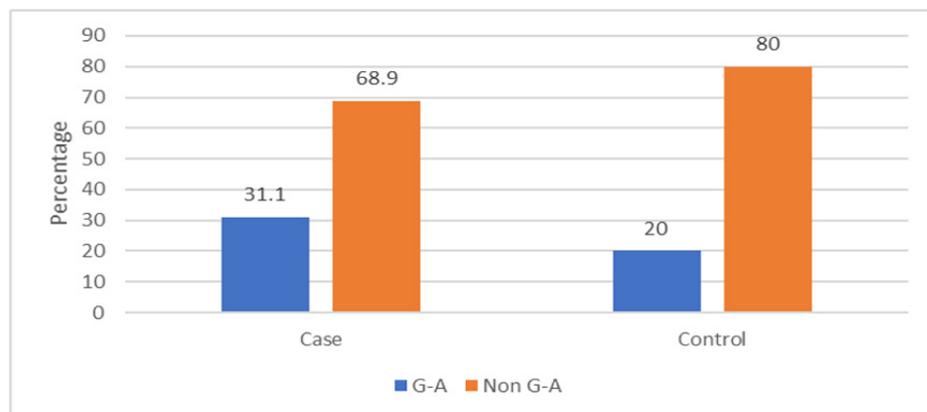


Figure 1. The Bar Graph of Differences in Allele Sequences at Locus -238G Based on Case and Control Groups

Table 3. The Genotype Differences between -308G Locus Genotype between Case and Control Group

Allele Sequence	Cases (n = 45)(%)	Control (n = 45)(%)	P
G-A	6 (13,3)	21 (46,7)	0,001
Non G-A	39 (86,7)	24 (53,3)	

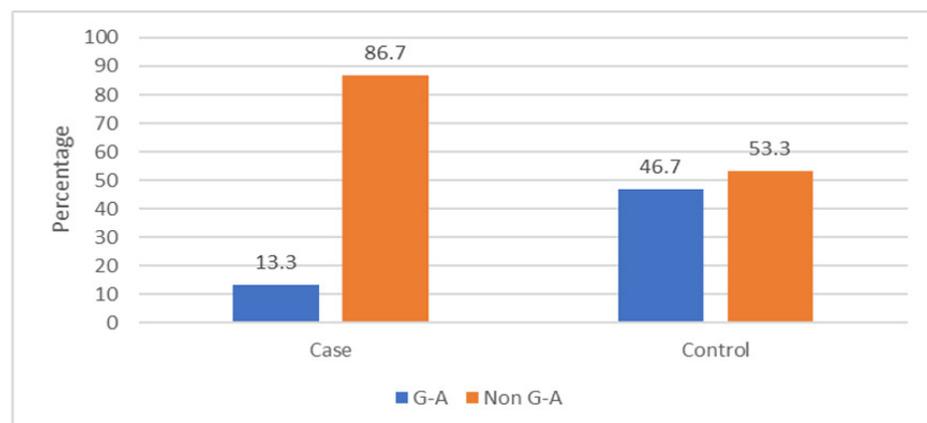


Figure 2. The Bar Graph of Differences in Allele Sequences at Locus -308G Based on Case and Control Groups

Processing and Data Analysis

The collected data were analyzed using a computer. Categorical data (nominal scale) are presented by displaying frequency distribution and percentage. Chi-Square test was used to test the hypothesis of a relationship between the TNF- α promoter region and psoriasis vulgaris at a significance of $P < 0.05$ by displaying the Odds Ratio (OR) value 95% confidence interval.

RESULTS

In this study, subjects included were psoriasis vulgaris patients and healthy individuals as controls who met the inclusion and exclusion criteria, amounting to 45 subjects each. Patient and control group demographic data were adjusted accordingly (Table 1).

This study was followed by 45 subjects with psoriasis vulgaris who came to the immuno-dermatology polyclinic, Haji Adam Malik Hospital, Medan, who met the inclusion and exclusion criteria. All control subjects had been matched based on sex, age, and ethnicity. The subjects were mostly female, amounting to 31 people (68.9%) with a mean age of 43.38 years and the majority of the subjects were Batak as many as 16 people (35.6%).

The age of psoriasis vulgaris patients in this study was 30-65 years old, with the largest age group between 30-39 years (37.8%), 40-49 years (33.3), 50-59 years (26.7 %), and followed by 60-65 years (2.2%).

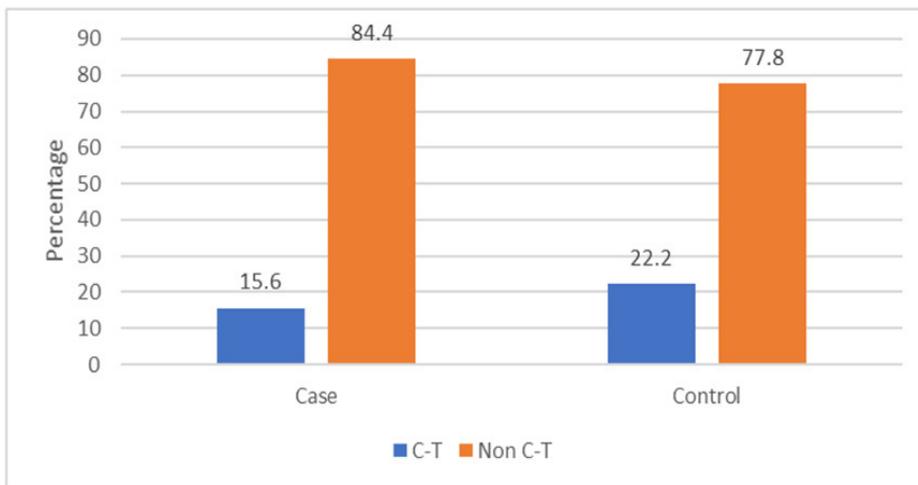
Most ethnic groups in the study were Batak with 16 people (35.6%), Javanese 15 people (33.4%), Aceh 3 people (6.7%), Chinese 2 people (4.4%), Malay 6 people (13.3%), Minang 2 people (4.4%) and India 1 person (2.2%). Until now, data has not been found on the largest number of tribes who experience psoriasis vulgaris.

The results showed that the genotypic allele sequence locus -238G was G-A as many as 14 people (31.1%), while in the control group, there were nine people (20%) (Figure 1). The analysis results using the Chi-Square test showed no significant differences in allele sequences between cases and controls at locus -238G ($p = 0.227$) (Table 2).

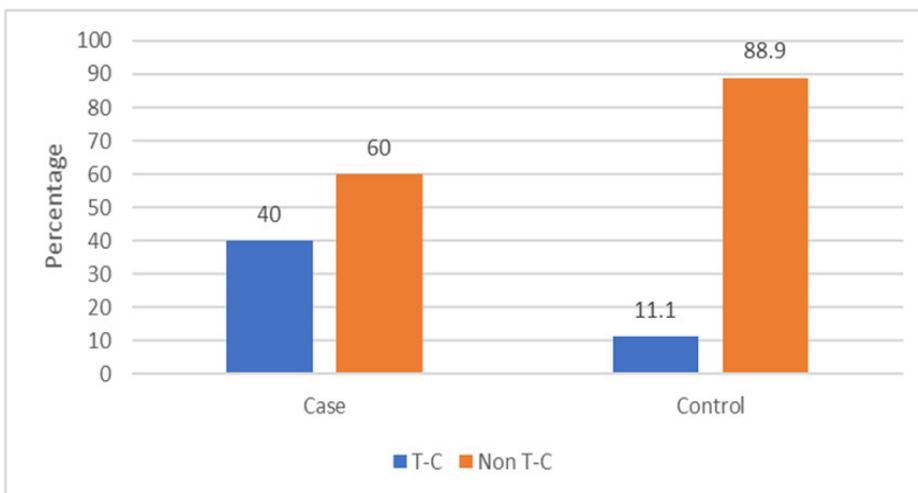
The results showed that the genotype allele sequence locus -308G was G-A only

Table 4. The Genotype Differences in locus genotype -857 between cases and controls

Allele Sequence	Cases (n = 45)(%)	Control (n = 45)(%)	<i>p</i>
C-T	7 (15,6)	10 (22,2)	0,419
Non C-T	38 (84,4)	35 (77,8)	

**Figure 3.** The Bar Graph of Differences in Allele Sequences at Locus -857 Based on Case and Control Groups**Table 5.** The 1031 Locus Genotype Differences between Case and Control Groups

Allele Sequence	Cases (n = 45)(%)	Control (n = 45)(%)	<i>p</i>
T-C	18 (40)	5 (11,1)	0,002
Non T-C	27 (60)	40 (88,9)	

**Figure 4.** The Bar Graph of Differences in Allele Sequences at Locus 1031 Based on Case and Control Groups

as many as six people (13.3%), while in the control group, there were 21 people (46.7%) (Figure 2). The chi-square test analysis showed significant differences in allele sequences between the case and control groups at the -308G locus ($p = 0.001$) (Table 3).

The results showed that the genotype allele sequence locus -857 was C-T as many as seven people (15.6%), while in the control group, there were ten people (22.2%) (Figure 3). Using the Chi Square test, the analysis results showed no significant difference in allele sequences between cases and controls at locus -857 ($p = 0.419$) (Table 4).

The results showed that the allele sequence of the genotype locus 1031 was T-C as many as 18 people (40%), while in the control group, there were only five people (11.1%) (Figure 4). Using the Chi-Square test, the analysis results showed a significant difference in allele sequences between the case and control groups at locus 1031 ($p = 0.002$) (Table 5).

DISCUSSION

In a systematic study paper, Parisi reported no difference in psoriasis vulgaris in men and women based on studies conducted on populations in Taiwan, the United States, and Norway. To date, there is no consensus on the effect of gender on the prevalence of psoriasis vulgaris.³⁴

Gelfand et al. demonstrated that psoriasis's high prevalence at younger ages gradually increased at 30-39 years of age. Psoriasis rarely occurs in those younger than ten years, with a prevalence of 0.55%.³⁵ Otherwise, Siniah et al. reported that psoriasis vulgaris patients in a study in Malaysia were found mostly in the 40-60 years age group (17.2%), and a smaller percentage was found in the younger age group and the age group over 60 years (8.1%).³⁶

Based on epidemiological studies worldwide, it is estimated that psoriasis' prevalence varies from region to region. The prevalence of children ranged from 0% in Taiwan to 2.1% in Italy. Whereas in adults in the United States, 0.98% to 8% are found in Norway. In Indonesia, ten major hospitals have recorded the prevalence rates in 1996, 1997 and 1998, respectively 0.62%, 0.59% and 0.92%.

Psoriasis continues to experience an increasing number of visits to health services in Indonesia.³⁷

According to E Gallo's study et al., TNF- α gene locus -238G was found more frequently in patients (92.6%) than in controls (83.1%). The TNF α -238G gene mutant allele was also seen more frequently in patients than in controls, presumably associated with an increased risk of genotype-related psoriasis in some mutant alleles (GA / AA). However, a recent study concluded that the -238G genotype was found more frequently in severe psoriasis patients.³⁸

Research by E. Gallo et al. Concluded that there was no significant association of the TNF α -308 genotype. However, they found a recurring frequency of the TNF α -308G gene in moderate to severe psoriasis cases and often occurred in early-onset psoriasis patients.³⁸ On the other hand, a meta-analysis study by Li et al. 2007 included 997 psoriasis cases for the TNF α -238 gene and 943 controls where each subject was drawn from 8 case-control studies, while the TNF α -308 gene involved 1,156 psoriasis patients and 1,083 controls and each. Subjects drawn from 10 case-control studies concluded that the wild-type G allele was found, which may act as a protective factor against psoriasis.³² In line with those findings, Le Zhuang's 2013 meta-analysis study concluded that the TNF α -308 gene was a polymorphism associated with decreased risk factors for psoriasis while the TNF α -238 gene was associated with an increased risk for psoriasis.³⁹

According to the study of E. Gallo et al., TNF gene polymorphism α -857 involved 89 psoriasis patients and 76 controls; there was no difference in the distribution in their study.³⁴ Meanwhile, a similar study conducted by K. Reich et al. in 2007 in other populations also found no difference in this polymorphism but found a higher frequency of TNF α -857 in arthritis psoriasis patients than in controls.⁴⁰

According to the study of E. Gallo et al. Found differences in the genotype distribution of the TNF α -1031 gene between patients and controls, where the frequency of wild-type GG was higher in patients; this indicates that this mutation plays an active role in the pathophysiology

of psoriasis.³⁸ According to J.L. Oestreicher et al., differences in population and race can cause the difference in TNF- α gene polymorphism in a study.⁴¹

This research can be continued by focusing on the ethnicity/race of psoriasis vulgaris patients. Further research is needed to develop psoriasis vulgaris treatment by gene engineering (Repairing Gene) methods based on mutations and gene loci in psoriasis vulgaris.

CONCLUSION

The analysis results using the Chi-Square test found a significant relationship between the TNF- α promoter region promoter polymorphism and the incidence of psoriasis vulgaris at locus -308G and 1031.

DISCLOSURES

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Conflict of Interest

The authors declared no conflict of interest regarding this research.

Author Contribution

All authors have contributed to designing research concepts, taking sample data, analyzing data, and preparing the published manuscript.

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