

Tumor Necrosis Factor- α 308 G/A polymorphism and psoriasis risk

A pooled analysis in different populations

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Abstract

More and more researches have been carried out on the association between the tumor necrosis factor- α (TNF- α) 308 G/A polymorphism and psoriasis, however, controversial results have emerged in these studies. This meta-analysis was performed to quantitatively clarify the relationship between TNF- α 308 G/A polymorphism and the risk of psoriasis in different populations. Databases of PubMed, Springer Link, Ovid, Chinese Wanfang Data Bases, Chinese National Knowledge Infrastructure and Chinese Biology Medicine were investigated until June 2019. The association between the TNF- α 308 G/A polymorphism and psoriasis was evaluated by calculating the pooled odds ratio (OR) and 95% confidence intervals (CIs). A total of 26 studies including 3657 patients and 3197 controls were screened out. In the overall population, the pooled results showed a reduced psoriasis risk with the TNF- α 308 G/A polymorphism (A vs G: OR=0.77, 95% CI=0.67-0.89; AA+GA vs GG: OR=0.72, 95% CI=0.61-0.86). In the subgroup analysis stratified by geographic locations, the TNF- α 308 G/A polymorphism was significantly associated with a reduced risk of psoriasis in Germany (A vs G: OR=0.67, 95% CI=0.57-0.78; AA+GA vs GG: OR=0.62, 95% CI=0.52-0.75), as well as in China (AA+GA vs GG: OR=0.71, 95% CI=0.52-0.98) and Poland (A vs G: OR=0.61, 95% CI=0.38-0.97; AA+GA vs GG: OR=0.59, 95% CI=0.35-0.99). This study indicated a significantly reduced psoriasis risk associated with the TNF- α 308 G/A polymorphism in Germans, as well as in Chinese and Poles populations compared with other populations. Ethnicity and geographic locations probably play a pivotal role in the genetic association of psoriasis.

Abbreviations: CIs = confidence intervals, OR = odds ratio, TNF- α = tumor necrosis factor- α .

Keywords: meta-analysis, polymorphism, psoriasis, tumor necrosis factor- α

1. Introduction

Psoriasis is a very common inflammatory skin disease which affects about 3% total populations in the world.^[1,2] The pathogenesis of psoriasis is still unclear and need further studies.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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However, the prevalence rates vary greatly between individuals of different ethnic backgrounds and geographic locations.^[3] Reasons for these variations are likely to be both genetic and environmental.^[4,5] Recently, some commonly inherited low-penetrance genes have been recognized as the genes possibly responsible for the susceptibility to psoriasis. One of the major representative genes is tumor necrosis factor- α (TNF- α) gene, which is an important inflammatory mediator and its expression has been shown to be involved in the development of psoriatic lesions. There are several common single nucleotide polymorphisms in the TNF- α gene, including -238 (rs361525), -308 (rs1800629), and -857 (rs1799724) positions, and the most studied polymorphism is a G to A transition in the promoter at position -308. However, the results are not frequently reproducible and the relationship is still poorly understood. These different results might be caused by racial and regional differences of the enrolled patients, as well as by the small sample size in each study. Whether the association in different populations differs according to geographic locations remains elusive. This meta-analysis was performed to quantitatively clarify the relationship between TNF- α 308 G/A polymorphism and the risk of psoriasis in different populations.

2. Materials and methods

2.1. Identification of eligible studies and data extraction

All studies that investigated the association between TNF- α 308 G/A polymorphism and psoriasis published before May 2019 were considered in this meta-analysis. PubMed, Springer Link,

Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure and Chinese Biology Medicine databases were used for literature searching. The search keywords were (TNF 308 G/A or rs1800629 or TNF- α) and (psoriasis or psoriatic) and (polymorphism or variant or mutation). All database searches were restricted to human subjects with no language limitation. All references cited in these studies were also reviewed to identify additional published works not indexed by these databases. Inclusion criteria contained:

- (1) case-control studies describing the association between TNF- α 308 G/A polymorphism and psoriasis,
- (2) reporting genotype frequencies of TNF- α 308 G/A polymorphism to calculate the odds ratio (OR).

Exclusion criteria were defined as follows:

- (1) studies containing incomplete data,
- (2) case reports,
- (3) editorial articles,
- (4) review articles and meeting abstracts.

The following data were extracted from each study: first author's name, publication year, geographic locations, sample size, and available genotype information with TNF- α 308 G/A polymorphism. The protocol was approved by the Ethics Committee of Henan University of Chinese Medicine First Affiliated Hospital.

2.2. Statistical analysis

The association between TNF- α 308 G/A polymorphism and psoriasis risk was evaluated by calculating the pooled OR and

95% confidence intervals (CIs). This meta-analysis examined the overall association between the A allele with the risk of psoriasis relative to the G allele; and the comparison between homozygote AA and GG, the comparison between AA and (GG+GA), and the comparison between (AA+GA) and GG. The heterogeneity test were assessed by chi-square based Q-test. When there was no significant heterogeneity between studies, OR was pooled using the fixed-effects model. Otherwise, the random-effects model was used. We compared the consistency between fixed-effects model and random-effects model to assess the sensitivity analysis. The funnel plot was used to assess the potential publication bias and the Egger test was applied to evaluate the funnel plot asymmetry. All statistical analyses were conducted using the Stata, version 12 (StataCorp LP, College Station, TX). A *P* value less than .05 was considered to be statistically significant.

3. Results

3.1. Description of included studies

According to the inclusion and exclusion criteria, twenty-five articles^[6–30] on the association between TNF- α 308 G/A polymorphism and the risk of psoriasis were included. The publication year of the involved studies ranged from 1997 to 2016. A total of 3657 patients and 3197 controls were included in this meta-analysis. The main characteristics of the included studies are listed in Table 1. Ten national groups including Germany, Japan, UK, Spain, China, Korea, Poland, Canada, Egypt and Brazil were enrolled in this meta-analysis. The pooled analysis was not performed for Korea and Egypt because only 1 study was searched for these groups.

Table 1
Characteristics of studies included in the meta-analysis.

First author and publication year	Geographic locations	Case number	Control number	Cases			Controls		
				GG	GA	AA	GG	GA	AA
Hohler 1997	Germany	122	99	99	18	5	73	20	6
Reich 1999	Germany	151	123	113	38	0	79	42	2
Hamamoto 2000	Japan	20	87	20	0	0	83	3	1
Kaluza 2000	Germany	47	43	42	5	0	33	10	0
Craven 2001	UK	81	66	63	14	4	44	21	1
Gonzalez 2001	Spain	52	73	44	8	0	58	15	0
Al-Heresh 2002	UK	124	101	79	38	7	71	27	3
Li 2002	China	123	165	92	30	1	104	61	0
Zhang 2002	China	87	128	77	10	0	112	16	0
Reich 2002	Germany	231	345	178	53	0	238	103	4
Kim 2003	Korea	103	125	96	7	0	107	18	0
Tsunemi 2003	Japan	163	96	161	2	0	92	4	0
Chang 2003	China	105	160	92	13	0	132	27	1
Long 2004	China	77	82	73	4	0	71	11	0
Mossner 2005	Germany	239	135	197	41	1	95	39	1
Baran 2006	Poland	78	74	62	16	0	57	16	1
Rahman 2006	Canada	225	103	146	75	4	67	33	3
Rahman 2006	Canada	203	101	144	53	6	69	25	7
Nedoszytko 2007	Poland	166	65	141	24	1	46	18	1
Reich 2007	Germany	729	370	558	152	19	253	107	10
Settin 2009	Egypt	46	98	9	28	9	6	81	11
Magalhaes 2010	Brazil	69	70	57	12	0	53	17	0
Gallo 2012	Spain	84	76	70	14	0	60	16	0
Zhou 2012	China	100	100	92	8	0	92	8	0
Wu 2012	China	107	110	97	9	1	104	6	0
Cardili 2016	Brazil	125	202	88	34	3	170	29	3

3.2. Meta-analysis results

The primary results of this meta-analysis on the association between TNF- α 308 G/A polymorphism and psoriasis were illustrated in Table 2. In the overall population, the pooled results showed a reduced psoriasis risk with the TNF- α 308 G/A polymorphism (A vs. G: OR=0.77, 95% CI=0.67–0.89; AA+GA vs. GG: OR=0.72, 95% CI=0.61–0.86) (Table 2, Fig. 1).

Six studies including 1519 cases and 1115 controls identified an association between the TNF- α 308 G/A polymorphism and psoriasis risk in Germany. Six studies including 599 cases and 745 controls were performed in China, and 2 studies including 244 cases and 139 controls in Poland. The TNF- α 308 G/A polymorphism was significantly associated with a reduced risk of psoriasis in Germany (A vs G: OR=0.67, 95% CI=0.57–0.78; AA+GA vs GG: OR=0.62, 95% CI=0.52–0.75), as well as in China (AA+GA vs GG: OR=0.71, 95% CI=0.52–0.98) and Poland (A vs G: OR=0.61, 95% CI=0.38–0.97; AA+GA vs GG: OR=0.59, 95% CI=0.35–0.99) (Table 2, Fig. 1). However, the significant results were not found in Japan, UK, Spain, Canada and Brazil (Table 2, Figure 1).

Table 2
Association of the TNF- α 308 G/A polymorphism and psoriasis susceptibility.

Analysis model	n	OR _f (95%CI)	OR _r (95%CI)	P _h
A vs G				
Total analysis	26	0.77 (0.67–0.89)	0.77 (0.69–0.86)	.046
Germany	6	0.67 (0.57–0.78)	0.67 (0.57–0.78)	.880
Japan	2	0.31 (0.07–1.36)	0.32 (0.07–1.43)	.874
UK	2	1.04 (0.58–1.87)	1.09 (0.75–1.60)	.140
Spain	2	0.75 (0.42–1.34)	0.75 (0.42–1.34)	.920
China	6	0.77 (0.55–1.08)	0.76 (0.56–1.02)	.334
Poland	2	0.60 (0.35–1.05)	0.61 (0.38–0.97)	.239
Canada	2	0.88 (0.65–1.20)	0.88 (0.65–1.48)	.530
Brazil	2	1.23 (0.43–3.50)	1.47 (0.98–2.21)	.022
AA vs. GG				
Total analysis	17	0.77 (0.52–1.16)	0.77 (0.52–1.13)	.794
Germany	5	0.66 (0.36–1.22)	0.61 (0.34–1.10)	.634
UK	2	2.27 (0.70–7.39)	2.29 (0.71–7.42)	.830
China	3	1.73 (0.27–11.07)	1.71 (0.33–8.94)	.629
Poland	2	0.32 (0.04–2.62)	0.32 (0.04–2.65)	.977
Canada	2	0.47 (0.19–1.17)	0.47 (0.19–1.17)	.680
AA vs GG+GA				
Total analysis	17	0.96 (0.65–1.41)	0.94 (0.65–1.36)	.681
Germany	5	0.74 (0.40–1.36)	0.768 (0.38–1.22)	.635
UK	2	2.28 (0.71–7.34)	2.31 (0.72–7.40)	.681
China	3	1.85 (0.29–11.82)	1.83 (0.35–9.54)	.618
Poland	2	0.35 (0.04–2.90)	0.35 (0.04–2.87)	.920
Canada	2	0.47 (0.19–1.15)	0.47 (0.19–1.15)	.686
AA+GA vs GG				
Total analysis	26	0.72 (0.61–0.86)	0.73 (0.64–0.82)	.017
Germany	6	0.62 (0.52–0.75)	0.62 (0.52–0.75)	.903
Japan	2	0.32 (0.07–1.42)	0.33 (0.07–1.50)	.791
UK	2	0.91 (0.39–2.10)	0.98 (0.63–1.52)	.068
Spain	2	0.73 (0.40–1.34)	0.73 (0.40–1.34)	.918
China	6	0.73 (0.51–1.04)	0.71 (0.52–0.98)	.333
Poland	2	0.60 (0.30–1.18)	0.59 (0.35–0.99)	.182
Canada	2	0.95 (0.66–1.35)	0.95 (0.66–1.35)	.718
Brazil	2	1.26 (0.38–4.18)	1.53 (0.98–2.38)	.015

OR_f = Odds ratio for fixed-effects model, OR_r = Odds ratio for random-effects model, P_h = P value for heterogeneity test, TNF- α = tumor necrosis factor- α .

3.3. Sensitivity analysis and publication bias diagnosis

To evaluate the sensitivity of this meta-analysis, we compared the consistency between fixed-effects model and random-effects model. All the significant results were not materially altered except for China and Poland, suggesting that the data for overall population and Germany were stable (Table 2). The Begg's funnel plot and Egger's test were used to evaluate the publication bias. As shown in Figure 2, the shape of the funnel plot did not reveal obvious asymmetry. Similarly, the Egger test indicated that there was no evidence of obvious publication bias in all the included studies ($t=-0.46$, $P=.646$, Fig. 3).

4. Discussion

Although the multifactorial nature of psoriasis is well known, genetic factors are considered to be strong determinants of these diseases, thus encouraging researchers to search for the responsible genes. TNF- α gene has been implicated in the pathogenesis, activity and severity of psoriasis. In 1997, Hohler and co-workers firstly analyzed the relationship between psoriasis and TNF- α 308 G/A polymorphism.^[6] Subsequently, a number of studies were conducted to investigate the association between TNF- α 308 G/A polymorphism and psoriasis in different populations. Till now, several published meta-analyses have analyzed the relationship between TNF- α 308 G/A polymorphism and psoriasis risk.^[31–34] They all identified a significant association between TNF- α 308 G/A polymorphism and decreased risk of psoriasis in both Caucasians and Asians.^[31–34] However, these meta-analyses did not consider geographical differences. Therefore, we conducted this meta-analysis to assess the relationship between TNF- α 308 G/A polymorphism and psoriasis risk in different populations according to geographic locations. In this meta-analysis, 26 studies from ten ethnic groups consisting of 3657 patients and 3197 controls were included. The results showed a reduced psoriasis risk with the TNF- α 308 G/A polymorphism in the overall population.

The exact mechanism of ethnic discrepancy is uncertain, but the study of differences in the underlying genetic background and social factors among different populations may be of significance. Ethnically diverse subjects may have unique cultures and lifestyles that can contribute to different genetic characteristics and susceptibility to specific diseases. In this meta-analysis stratified by geographic locations, we found that the TNF- α 308 G/A polymorphism was significantly associated with a reduced risk of psoriasis in Germany, as well as in China and Poland. However, we did not find a significant association in Japan, UK, Spain, Canada, and Brazil. Therefore, the relationship between TNF- α 308 G/A polymorphism and psoriasis might be susceptible in different populations. Because there is only 1 study from Korea and Egypt, we fail to discuss the association between the TNF- α 308 G/A polymorphism and psoriasis among these populations in the current meta-analysis. Compared with previous meta-analyses,^[31–34] psoriasis patients and controls were selected from more ethnic groups in the present meta-analysis. And the effects of different populations upon the risk of psoriasis risk were also evaluated by stratified analysis of geographic locations.

This meta-analysis is strengthened by investigating the impact of different populations on the risk of psoriasis and the TNF- α 308 G/A polymorphism. The findings provide additional

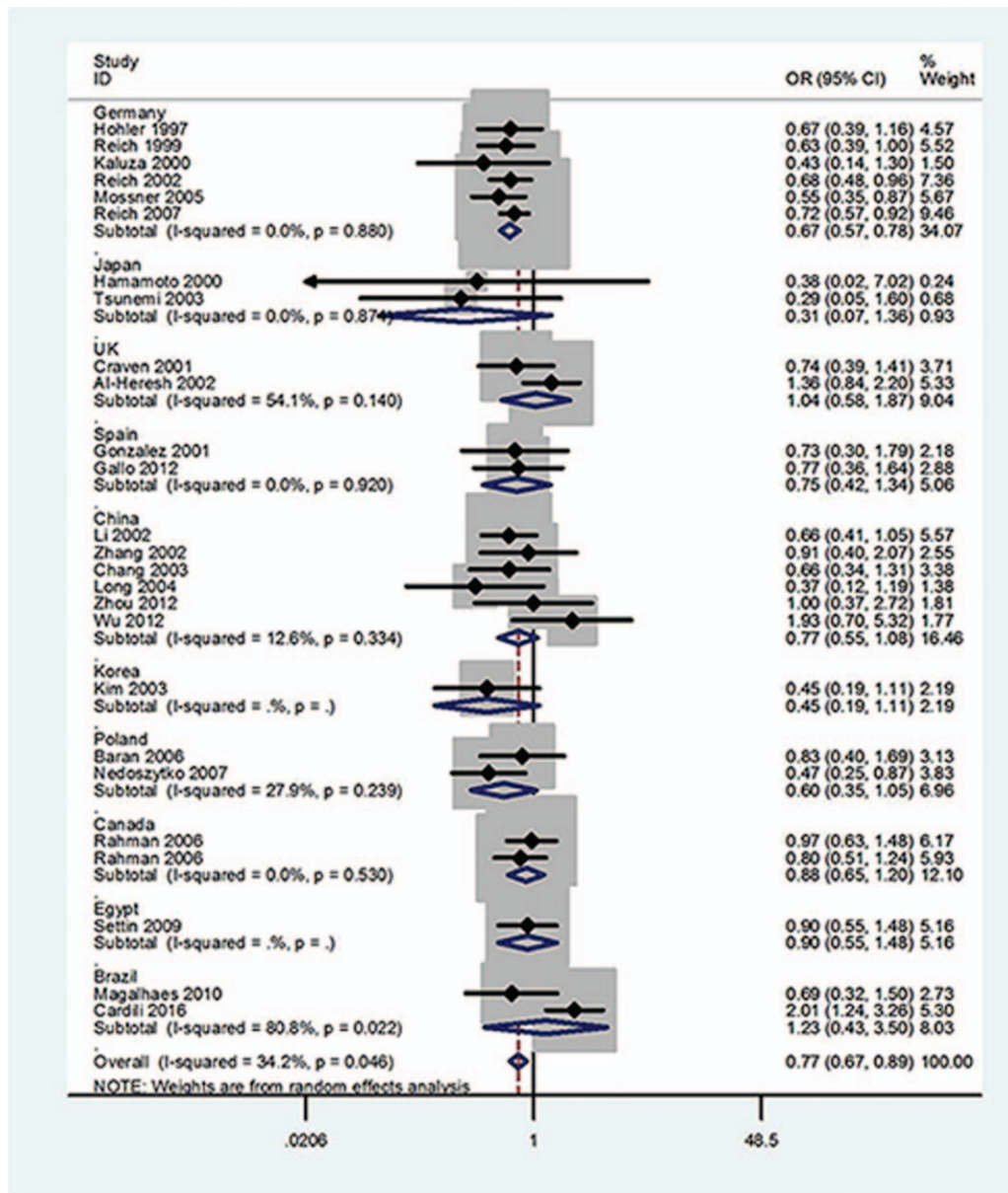


Figure 1. The forest plots of all selected studies on the association between TNF- α 308 G/A polymorphism and psoriasis susceptibility under (A vs. G) model.

evidence for the possible association between the TNF- α 308 G/A polymorphism and psoriasis risk in Germans, as well as in Chinese and Poles populations. In this meta-analysis, no significant publication bias was found in all the included studies. However, several limitations have to be acknowledged in this meta-analysis. First, only English and Chinese databases were used for literature searching, articles/databases in other language were not included. Therefore, further studies are needed to assess the association in other populations. Secondly, the etiology of psoriasis is complex and mediated by the activities of multiple genes. The effect of any single gene might exert a limited impact on psoriasis risk than anticipated. Moreover, due to insufficient information, we failed to conduct subgroup analyses stratified by other factors, such as gender, smoking status and ethnicity, *etc* and we planned to perform this

in the future study. Finally, as there are significant differences in the incidence rates of psoriasis in countries with different latitudes,^[35] we cannot exclude the role of latitude in the association of TNF- α polymorphism with psoriasis in different countries.

In conclusion, this meta-analysis indicated a significantly reduced psoriasis risk associated with the TNF- α 308 G/A polymorphism in Germans, as well as in Chinese and Poles populations compared with other populations. Ethnicity and geographic locations probably play a pivotal role in the genetic association of psoriasis. Subsequent studies are urgently required to validate this conclusion in other populations. Whether there are racial differences between the enzyme polymorphisms and clinical prognosis in other diseases remains to be elucidated.

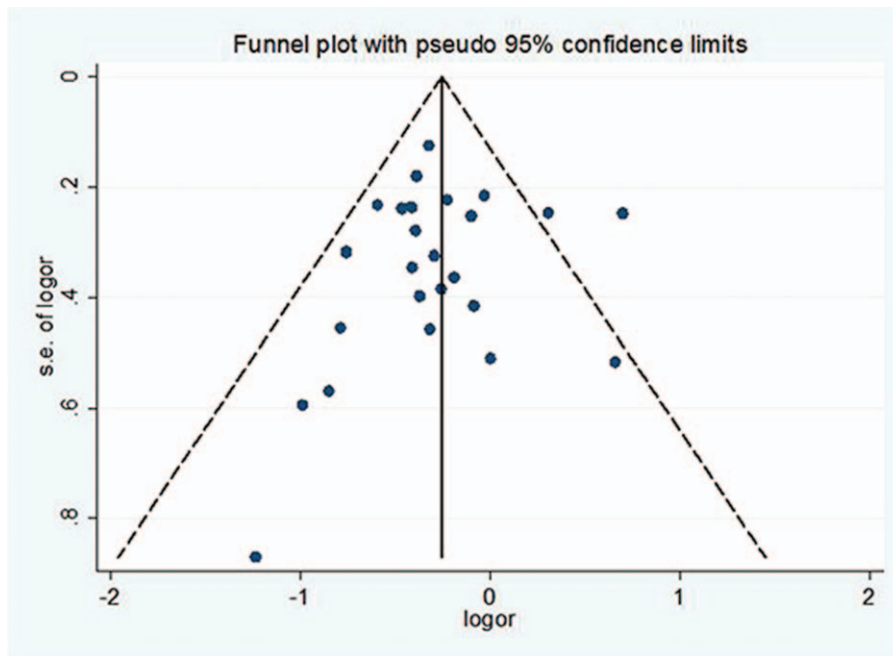


Figure 2. Publication bias assessment of TNF- α 308G/A polymorphism and psoriasis susceptibility with Begg funnel plot.

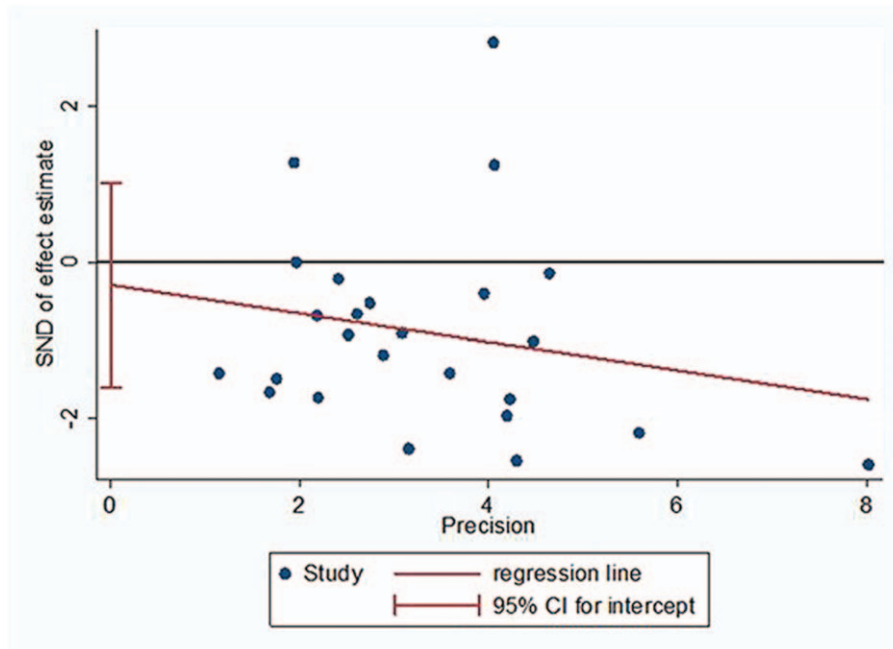


Figure 3. Egger's linear regression for the Begg funnel plot.

Author contributions

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References

- [1] Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009;361: 496–509.
- [2] Menter A, Griffiths CE. Current and future management of psoriasis. *Lancet* 2007;370:272–84.

- [3] Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007;370:263–71.
- [4] Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013;133:377–85.
- [5] Bowcock AM, Barker JN. Genetics of psoriasis: the potential impact on new therapies. *J Am Acad Dermatol* 2003;49:S51–6.
- [6] Hohler T, Kruger A, Schneider PM, et al. A TNF-alpha promoter polymorphism is associated with juvenile onset psoriasis and psoriatic arthritis. *J Invest Dermatol* 1999;109:562–5.
- [7] Reich K, Westphal G, Schulz T, et al. Combined analysis of polymorphisms of the tumor necrosis factor-alpha and interleukin-10 promoter regions and polymorphic xenobiotic metabolizing enzymes in psoriasis. *J Invest Dermatol* 2002;41:525–30.
- [8] Hamamoto Y, Tateno H, Ishida T, et al. Lack of association between promoter polymorphism of the tumor necrosis factor-alpha gene and psoriatic arthritis in Japanese patients. *J Invest Dermatol* 2000;115:1162–4.
- [9] Kaluza W, Reuss E, Grossmann S, et al. Different transcriptional activity and in vitro TNF-alpha production in psoriasis patients carrying the TNF-alpha 238A promoter polymorphism. *J Invest Dermatol* 2000;114:1180–3.
- [10] Craven NM, Jackson CW, Kirby B, et al. Cytokine gene polymorphisms in psoriasis. *Br J Dermatol* 2001;144:849–53.
- [11] Gonzalez S, Brautbar C, Martinez-Borra J, et al. Polymorphism in MICA rather than HLA-B/C genes is associated with psoriatic arthritis in the Jewish population. *Hum Immunol* 2001;62:632–8.
- [12] Al-Heresh AM, Proctor J, Jones SM, et al. Tumour necrosis factor-alpha polymorphism and the HLA-Cw*0602 allele in psoriatic arthritis. *Rheumatology (Oxford)* 2002;41:525–30.
- [13] Li B. Tumor Necrosis Factor-A Gene Polymorphism and Psoriasis. PhD Thesis. Shenyang: China Medical University, 2002. (article in Chinese)
- [14] Zhang AP. Experimental Studies on HLA Genotyping in Patients with Psoriasis Vulgaris in Chinese Han Population. PhD Thesis. Nanjing: Nanjing Medical University, 2002. (article in Chinese)
- [15] Reich K, Mössner R, König IR, et al. Promoter polymorphisms of the genes encoding tumor necrosis factor alpha and interleukin-1 beta are associated with different subtypes of psoriasis characterized by early and late disease onset. *J Invest Dermatol* 2002;118:155–63.
- [16] Kim TG, Pyo CW, Hur SS, et al. Polymorphisms of tumor necrosis factor (TNF) alpha and beta genes in Korean patients with psoriasis. *Arch Dermatol Res* 2003;295:8–13.
- [17] Tsunemi Y, Nishibu A, Saeki H, et al. Lack of association between the promoter polymorphisms at positions 308 and 238 of the tumor necrosis factor alpha gene and psoriasis vulgaris in Japanese patients. *Dermatology* 2003;207:371–4.
- [18] Chang YT, Tsai SF, Lee DD, et al. A study of candidate genes for psoriasis near HLA-C in Chinese patients with psoriasis. *Br J Dermatol* 2003;148:418–23.
- [19] Long F, Sun C, Deng D, et al. TNF-238A is associated with juvenile onset psoriasis in patients of Han population in southwest China. *J Dermatol Sci* 2004;36:109–11.
- [20] Mossner R, Kingo K, Kleinsang A, et al. Association of TNF 238 and 308 promoter polymorphisms with psoriasis vulgaris and psoriatic arthritis but not with pustulosis palmoplantaris. *J Invest Dermatol* 2005;124:282–4.
- [21] Baran W, Szepietowski JC, Mazur G, et al. A 308 promoter polymorphism of tumor necrosis factor alpha gene does not associate with the susceptibility to psoriasis vulgaris. No difference either between psoriasis type I and type II patients. *Acta Dermatovenerol Alp Panonica Adriat* 2006;15:113–8.
- [22] Rahman P, Siannis F, Butt C, et al. TNF-alpha polymorphisms and risk of psoriatic arthritis. *Ann Rheum Dis* 2006;65:919–23.
- [23] Nedoszytko B, Szczerkowska-Dobosz A, Zablotna M, et al. Associations of promoter region polymorphisms in the tumour necrosis factor-alpha gene and early-onset psoriasis vulgaris in a northern Polish population. *Br J Dermatol* 2007;157:165–7.
- [24] Reich K, Huffmeier U, König IR, et al. TNF polymorphisms in psoriasis: association of psoriatic arthritis with the promoter polymorphism TNF*-857 independent of the PSORS1 risk allele. *Arthritis Rheum* 2007;56:2056–64.
- [25] Settin A, Hassan H, El-Baz R, et al. Association of cytokine gene polymorphisms with psoriasis in cases from the Nile Delta of Egypt. *Acta Dermatovenerol Alp Panonica Adriat* 2009;18:105–12.
- [26] Magalhaes RF, Biral AC, Pancoto JA, et al. Human leukocyte antigen (HLA) and single nucleotide polymorphisms (SNPs) tumor necrosis factor (TNF)-alpha -238 and -308 as genetic markers of susceptibility to psoriasis and severity of the disease in a long-term follow-up Brazilian study. *Int J Dermatol* 2010;49:1133–40.
- [27] Gallo E, Cabaleiro T, Roman M, et al. Study of genetic polymorphisms in the tumor necrosis factor alpha promoter region in Spanish patients with psoriasis. *Actas Dermosifiliogr* 2012;103:301–7.
- [28] Zhou X, Zhuo Y, Pan RW. Using PCR-RDB in association of tumor necrosis factor (TNF)-alpha gene polymorphism with psoriasis vulgaris in Southern han population. *Modern Pract Med* 2012;24:1099–101.
- [29] Wu H, Guo J, Pan A, et al. Association between polymorphism of tumor fatality factor alpha and beta genes and psoriasis vulgaris. *J Clin Dermatol* 2012;41:658–60. (article in Chinese).
- [30] Cardili RN, Deghaide NS, Mendes-Junior CT, et al. HLA-C and TNF gene polymorphisms are associated with psoriasis in Brazilian patients. *Int J Dermatol* 2016;55:e16–22.
- [31] Li C, Wang G, Gao Y, et al. TNF-alpha gene promoter -238G>A and -308G>A polymorphisms alter risk of psoriasis vulgaris: a meta-analysis. *J Invest Dermatol* 2007;127:1886–92.
- [32] Zhu J, Qu H, Chen X, et al. Single nucleotide polymorphisms in the tumor necrosis factor-alpha gene promoter region alter the risk of psoriasis vulgaris and psoriatic arthritis: a meta-analysis. *PLoS One* 2013;8:e64376.
- [33] Zhuang L, Ma W, Cai D, et al. Associations between tumor necrosis factor- (polymorphisms and risk of psoriasis: a meta-analysis. *PLoS One* 2013;8:e68827.
- [34] Jia Y, Qin HJ, Zhang JX, et al. Association of the tumour necrosis factor- (polymorphisms rs361525 and rs1800629 with susceptibility to psoriasis: a meta-analysis. *Clin Exp Dermatol* 2013;38:836–44.
- [35] Jacobson CC, Kumar S, Kimball AB. Latitude and psoriasis prevalence. *J Am Acad Dermatol* 2011;65:870–3.