Association of rs610604 in TNFAIP3 and rs17728338 in TNIP1 gene polymorphisms with psoriasis susceptibility: A meta-analysis of case-control studies

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Abstract

Background: To date, the pathological mechanisms underlying the occurrence and development of psoriasis are still unanswered questions. Genome-wide association surveys have revealed that TNFAIP3 and TNIP1 were key biomarkers for psoriasis. This study aimed to investigate the association between TNFAIP3 and TNIP1 gene polymorphisms with psoriasis susceptibility.

Methods: Comprehensive literature search was undertook across four online databases—PubMed, Embase, Cochrane Library, and China National Knowledge Infrastructure (CNKI) up to August 25, 2019. Allele model of inheritance was used to analyze the original data. Newcastle–Ottawa scale (NOS) was used to evaluate the risk bias of each study. Pooled odds ratios and 95% confidence intervals were calculated using the RevMan 5.3 software.

Results: In all, 13 case-control studies comprising 13,908 psoriasis patients and 20,051 controls were identified and included in this meta-analysis. The results demonstrated that rs610604 in TNFAIP3 polymorphism was significantly associated with psoriasis risk using random effect model (G vs. T, OR = 1.19, 95% CI: 1.09–1.31, P = 0.0002), and a significant association between rs17728338 in TNIP1 polymorphism and psoriasis vulnerability using fixed effect model (A vs. G, OR = 1.69, 95% CI: 1.58–1.80, P < 0.00001).

Conclusions: This meta-analysis indicated that rs610604 in TNFAIP3 and rs17728338 in TNIP1 gene polymorphisms were associated with psoriasis susceptibility.

Introduction

Psoriasis is currently regarded as a chronic, inflammatory skin disease associated with systemic conditions. As with other dermatoses, the patients who suffered from it also have to face the huge psychological burden because of visible disfiguration. Considerable comorbid diseases often occur in psoriasis patients, including psoriatic arthritis, metabolic syndrome, cardiovascular disorders, gastrointestinal diseases, mood disorders as well as other emerging comorbid diseases. Psoriasis affects approximately 2%–3% of the population world-wide, and its prevalence is much higher in western countries. To data, five types of psoriasis have been identified: psoriasis vulgaris, guttate or eruptive psoriasis, inverse psoriasis, erythrodermic psoriasis and pustular psoriasis.
As a complex inflammatory disorder, the etiology and pathogenesis of psoriasis is widely thought to be caused by the interplay of intrinsic and environmental factors. Numerous triggers and aggravations for psoriasis occurrence have been identified, such as mild localized trauma, drugs, HIV infection and streptococcal pharyngitis. However, intrinsic factors such as genetics may play a more important role. Thanks to the powerful genome-wide association studies (GWAS) as well as other genetic studies, more than 60 regions of the human genome have now been identified to be correlate with psoriasis. Tumor Necrosis Factor Alpha-Induced Protein 3 (TNFAIP3) and TNFAIP3 Interacting Protein 1 (TNIP1) are among them, they were first discovered to be associated with psoriasis in 2009. After that, numerous studies on the association of single nucleotide polymorphisms in TNFAIP3 and TNIP1 with the risk of psoriasis have conducted. However, the conclusions of these studies may be incomprehensive and contradictory. Thus, our aim was to undertake a meta-analysis to comprehensively analyze these studies.

TNFAIP3 gene is located on human chromosome 6q23.3, another aliases for TNFAIP3 is A20. While TNIP1 is located on 5q33.1. They are all Protein Coding genes encode ubiquitin-editing enzyme A20 and A20-Binding Inhibitor Of NF-Kappa-B Activation 1 (ABIN-1), which interact with each other to influence intracellular signaling. Polymorphisms of the two genes may alter their protein coding, and thus to have an impact on their closest functional protein partners. The interrelation network of TNFAIP3 and TNIP1 with their nearest associated functional protein partners were illustrated on Fig. 1. Over the years, accumulating evidence indicated that genetic variations in the genes TNFAIP3 and TNIP1 are strongly associated with vulnerability to numerous inflammatory diseases. Considering that study sample sizes were small and the statistical effect was limited of an individual study, this meta-analysis is meant to provide the most comprehensive and precise evaluation on the association of TNFAIP3 and TNIP1 polymorphisms with psoriasis vulnerability.

Materials And Methods

Search strategy

Two of our investigators (Hai-bo Gong and Shu-tao Gao) independently searched four major
databases—PubMed, Embase, Cochrane library, CNKI—for papers published before August 25, 2019. The search strategy for PubMed was as follows: (((Psoriasis) OR "Psoriasis"[Mesh])) AND (((((("Tumor Necrosis Factor alpha-Induced Protein 3"[Mesh]) OR Tumor Necrosis Factor alpha-Induced Protein 3) OR Zinc Finger Protein A20) OR A20) OR TNF Alpha-Induced Protein 3)) OR ((((((“TNIP1 protein, human” [Supplementary Concept]) OR TNIP1) OR TNFAIP3 Interacting Protein 1) OR A20-Binding Inhibitor Of NF-Kappa-B Activation 1) OR VAN protein, human) OR TNFalpha-induced protein 3-interacting protein 1, human) OR ABIN-1 protein, human))) AND (((((single nucleotide polymorphism) OR Polymorphism) OR Alleles) OR SNP) OR Variation) OR gene).

**Inclusion and exclusion criteria**

The PICOS (population, intervention, comparison, outcome, and study design) principle was used to generate the inclusion criteria for the present study, which were as follows: case control studies on humans; published studies on the association of TNFAIP3 or TNIP1 polymorphisms with psoriasis susceptibility; and available data to calculate the odds ratios (ORs) and 95 % confidence intervals (95 % CIs). In contrast, Studies met the following criteria should be excluded: reviews, non-human studies, lack of sufficient data to evaluate ORs and CIs, and duplicated articles.

**Data extraction**

Hai-bo Gong and Shu-tao Gao independently evaluated and extracted all necessary data from each candidate article including: first author, year of publication, Ethnicity of study population, numbers of cases and controls, and the allele frequencies of the TNFAIP3 or TNAP1 polymorphisms, Hardy-Weinberg equilibrium (HWE) results.

**Quality assessment**

Newcastle–Ottawa Scale (NOS) was used to assess all included studies in accordance with its criteria.

“Score system” was applied to judge every included study on three broad aspects: Selection of case and control groups (0–4 points); Comparability of case and control groups (0–2 points); and Ascertainment of exposure for included studies (0–3 points). Studies with ≥ 5 scores were considered as a high quality. If there were discrepancy in this process, the two authors would discuss and arrive at consensus with the third author (Xiong-ming Pu).
**Statistical analysis**

The preferred Reporting Items for systematic Review and Meta-analyses (PRISMA) was used to complete this meta-analysis\(^{15}\). We perform this Meta-analyses using allele model of inheritance owing to the lack of sufficient information. The association between rs610604 in TNFAIP3 and rs17728338 in TNIP1 polymorphisms with psoriasis was calculated by merging ORs with 95 % CIs. Q-statistical test and \(I^2\) test were used to evaluate the heterogeneity among all included studies\(^{16}\). The random effect model was used to combine the data in the cases of heterogeneity \((P < 0.1, I^2 > 50\%)\) or fixed-effect model was used when it was out of heterogeneity \((P > 0.1, I^2 < 50\%)\).\(^{17,18}\) The Hardy–Weinberg equilibrium results were extracted from original studies or calculated using the original data. We used leave-one-out sensitivity analysis to judge the robustness and reliability of the results. Revman 5.3 software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Sweden) was used to generate Forest plots. Egger's test was used to evaluated the publication bias (Stata version 12.0, Stata Corp LP, U.S.A).

**Functional predictions**

To explore the annotations of the human non-coding genome. Functional analyses were performed using the in silico tool HaploReg 4.1 (http://pubs.broadinstitute.org/mammals/haploreg/haploreg.php).

**Results**

**Study characteristics**

The primary search of the four databases harvested 206 records: 72 from PubMed, 80 from Embase, 11 from Cochrane library, and 43 from China National Knowledge Infrastructure (CNKI). After removed duplicated and irrelevant records. 13 articles were ultimately went into the process of meta-analysis. The detailed process of the literature search and screen is shown in Figure 2. Of the 13 articles, 11 articles containing original data for rs610604. These studies were performed in UK\(^{19}\), Egypt\(^{20}\), India\(^{21}\), China\(^{22-25}\), Pakistani\(^{26}\), USA\(^{27}\), Sweden\(^{28}\), México\(^{29}\). In all, These studies included 11,556 psoriasis patients and 16,720 controls. As for rs17728338, there were 9 articles involved in them, they were conducted in UK\(^{19}\), Europe\(^{30}\), China\(^{22,23,31}\), India\(^{21}\), Pakistani\(^{26}\), USA\(^{27}\), México\(^{29}\). In all, these studies
containing 11,776 psoriasis patients and 17,631 controls. The detailed characteristics of every study for rs610604 and rs17728338 are shown in Table 1 and Table 2 respectively. The methodological quality of each study evaluated using NOS for nonrandomized controlled trials is shown in Table 3.

**Meta-analyses results**

**Rs610604 polymorphism and psoriasis susceptibility**

We used random effect model to evaluate the association between rs610604 polymorphism and psoriasis vulnerability owing to a significant heterogeneity among the included studies ($P < 0.0001$, $I^2 = 70\%$). The results demonstrated that rs610604 was significantly associated with psoriasis risk (G vs. T; OR = 1.19, 95% CI: 1.09–1.31, $P = 0.0002$; Fig. 3).

**Rs17728338 polymorphism and psoriasis susceptibility**

Heterogeneity was small among all the studies for rs17728338 ($P = 0.41$, $I^2 = 4\%$). therefore, fixed-effect model was used to conduct the meta-analysis. Our results revealed a significant association between rs17728338 polymorphism and psoriasis vulnerability (A vs. G; OR = 1.69, 95% CI: 1.58–1.80, $P < 0.00001$; Fig. 4).

**Sensitivity analysis and publication bias**

The significance of pooled ORs and 95% CIs was not affected when we take out one study at a time, indicating that the results were stable and robust. Sensitivity of rs610604 and rs17728338 analysis were visually illustrated by Figs. 5 and 6. Publication bias were shown by the Egger’s test plots of rs610604 ($P = 0.755$) and rs17728338 ($P = 0.616$) (Figs. 7 and 8), suggesting no statistically significant publication bias.

**Functional analysis**

The results of functional analysis conducted using HaploReg are shown in Figure 9.

**Discussion**

Although the precise mechanism of human psoriasis remains somewhat enigmatic. It is increasingly recognized that strong genetic predisposition act as intrinsic factor for psoriasis pathogenesis, and SNPs in human genome may be one of the keys to unlock insights into genetic basis for the occurrence, development and relapse of psoriasis$^{32,33}$. As intrinsic factors, polymorphisms in TNFAIP3
and TNIP1 gene has garnered considerable attention over the past decade by different research teams all over the world.

Our meta-analysis results indicated that psoriasis patients had a statistically significant higher frequency of the rs610604 G allele. Most individual studies were in accordance with the results analysis by synthesis. The outcome of the meta-analysis remained stable after we conducted the leave-one-out sensitivity analysis. For rs17728338, The pooled outcome illustrated that the A allele of rs17728338 have an significantly increased risk for psoriasis. To further explore the underlying mechanisms of the interaction of TNFAIP3 and TNIP1, the HaploReg 4.1 online database was used to predict the functions of the two loci in silico. According to HaploReg, enhancer histone marks for rs610604 were found in 5 different human tissues, while enhancer histone marks for rs17728338 were found in 9 different human tissues. Both rs610604 and rs17728338 were in linkage disequilibrium with numerous other loci using a threshold of \( r^2 \geq 0.8 \). Regulatory motifs changed were found in both rs610604 and rs17728338. These in silico information may help to have a better understanding of the functions of the two loci, functional experiments are strongly need to validate these hypotheses in the future.

A20 was first characterized as a cytokine-inducible factor by a seminal study of Dixit, V. M. et al in 1990\(^{34}\). After that, in the year of 2004, Dixit and co-workers discovered that A20 was involved in TNF-induced NF-κB activation by playing a role of dual ubiquitin-editing enzyme\(^{35,36}\). Dysregulation of A20 expression was found to be associated with inflammatory and autoimmune disease such as psoriasis as well as the pathogenesis of cancer over the past few years. Jiang et al.’s study\(^{37}\) suggested that TNFAIP3 mRNA expression level significantly correlated with the severity and pathology of psoriasis. Other studies on systemic lupus erythematosus (SLE) and type 2 diabetes reported that some of the single nucleotide polymorphisms (SNPs) can influence expression level of the TNFAIP3\(^{38,39}\). As for cancer involvement, A20 mRNA was found to be upregulated in the poorly differentiated head and neck squamous cell carcinomas (SCCs) of the skin while no A20 mRNA is observed in normal tissues samples\(^{40}\). The molecular mechanism of A20 functions underlying these biological processes is
generally characterized as inhibitory effect of NF-κB activation by editing the ubiquitylation status of its numerous proximal signaling proteins such as receptor-interacting protein serine/threonine kinase 1 (RIPK1), TNF Receptor Associated Factor 6 (TRAF6), Mucosa-Associated Lymphoid Tissue Lymphoma Translocation Protein 1 (MALT1), etc. Apart from NF-κB signaling pathway, A20 is also been reported to be involved in the regulation of other signaling circuits including Wnt pathway, interferon regulatory factor (IRF) pathway, etc. There were also studies focusing on blocking autophagy and anti-apoptotic activities by deubiquitination. However, the exact mechanisms by which it does this remains unclear. More researches are needed to explore the mechanisms underlying them.

One of the most important A20 binding protein is TNFAIP3 Interacting Protein 1 (TNIP1), which has another alias of ABIN-1. It has been reported that TNFAIP3 and TNIP1 physically interact with each other to inhibit cell death and NF-κB signaling pathway. Similar with TNFAIP3, more than 3 genome-wide association studies (GWAS) indicated that TNIP1 have been implicated in numerous inflammatory disease, including psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE), systemic sclerosis (SSC), rheumatoid arthritis (RA). It is probably that A20 collaborate with TNIP1 to be involved in the pathophysiology of these disease.

To date, this is the most comprehensive meta-analysis on the correlation between TNFAIP3 and TNIP1 polymorphisms and psoriasis vulnerability. However, several drawbacks should not be overlook. First, As far as the small study number and sample size is concerned, although we have gathered all the currently available evidences, false negatives of our study may exist. Second, the genetic factor for psoriasis is composed of a synergetic effect of multiple relevant genes and loci. However, we only focused on rs610604 in TNIP1 and rs17328338 in TNFAIP3. Third, only allele model was used to analyzed the data. Other genetic models are strongly recommend to be used as long as there are enough future relevant researches. Fourth, HWE of some included studies were missing, thus may lead to Information bias. Finally, only studies published in English were included in the present study, the lack of potential relevant articles written in other language may lead to selection bias.

Conclusions
The present study suggested that G allele of rs610604 polymorphisms in TNFAIP3 and A allele of rs17728338 polymorphisms in TNIP1 were estimated to have an increased risk for psoriasis susceptibility by using the allele model.

Declarations
Competing interests
The authors declare that there was no conflict of interests.

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Author Contributions
Gong, H. B produced the idea and the did the first version of this paper. Gong, H. B and Gao, S. T did the literature search respectively. Kang, X. J and Wu, X. J was involved in the revising of the manuscript and provided some important intellectual ideas in our original manuscript. Pu, X. M critically revised the final manuscript and takes the responsibility for all the data analysis.

Compliance with Ethical Standards
All analyses in the present work were based on previous published literatures and online public databases, there were no human participants included in our study. Therefore, this work does not need any ethical approval and patient consent.

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Abbreviations

| Abbreviations | Full name |
|---------------|-----------|
| SNP           | Single nucleotide polymorphism |
| CNKI          | China National Knowledge Infrastructure |
| NOS           | Newcastle–Ottawa scale |
| TNFAIP3       | Tumor Necrosis Factor Alpha-Induced Protein 3 |
| TNIP1         | TNFAIP3 Interacting Protein 1 |
| OR            | Odds ratio |
| CI            | Confidence interval |
| HWE           | hardy-weinberg equilibrium |
| GWAS          | Genome-wide association study |
| RIPK1         | Receptor-interacting protein serine/threonine kinase 1 |
| TRAF6         | TNF Receptor Associated Factor 6 |
| MALT1         | Mucosa-Associated Lymphoid Tissue Lymphoma Translocation Protein 1 |
| IRF           | Interferon regulatory factor |
| SLE           | Systemic lupus erythematosus |
| SSC           | Systemic lupus erythematosus |
| RA            | Rheumatoid arthritis |

Tables

Table 1. Main characteristics of included studies
| Study            | Year | Country | Ethnicity  | Case/Control |   |   |
|------------------|------|---------|------------|--------------|---|---|
|                  |      |         |            | M            | W |

**Table 2. Main characteristics of included studies**

| Study            | Year | Country | Ethnicity  | Case/Control |   |   |
|------------------|------|---------|------------|--------------|---|---|
|                  |      |         |            | M            | W |

**Table 3. Quality assessment of included studies according to the Newcastle-Ottawa Scale**

M, mutant allele; W, wild allele; HWE, Hardy-Weinberg Equilibrium; NA, Not Available
| Item/Study | Adequate definition of cases | Representativeness of cases | Selection of control subjects | Definition of control subjects | Control for important factor or additional factor |
|-----------|----------------------------|-----------------------------|-----------------------------|-------------------------------|----------------------------------|
| Bowes 2011 | 1                          | 0                           | 1                           | 1                             | 1                                |
| Das 2015   | 1                          | 0                           | 1                           | 1                             | 1                                |
| Haase 2014 | 1                          | 0                           | 1                           | 1                             | 1                                |
| Han 2016   | 1                          | 0                           | 1                           | 1                             | 1                                |
| Indhumathi 2015 | 1                     | 0                           | 1                           | 1                             | 1                                |
| Li 2014    | 1                          | 0                           | 0                           | 1                             | 1                                |
| Munir 2015 | 1                          | 0                           | 1                           | 1                             | 1                                |
| Nair 2009  | 1                          | 0                           | 1                           | 1                             | 1                                |
| Nikamo 2015 | 1                       | 0                           | 0                           | 1                             | 1                                |
| Villarreal-Martínez 2016 | 1                     | 0                           | 1                           | 1                             | 1                                |
| Yang 2011  | 1                          | 0                           | 1                           | 1                             | 1                                |
| Zhang, Z 2015 | 1                   | 0                           | 1                           | 1                             | 1                                |
| Zhang, C 2015 | 1                    | 0                           | 0                           | 1                             | 1                                |
Figures

Figure 1

Network of TNFAIP3, TNIP1 and their closest functional partners. These data were from the Search Tool for the Retrieval of Interacting Genes (STRING) database (http://string-db.org/)
Figure 2

Flow diagram of literature search and screen
Figure 3
Forest plot of rs610604 in TNFAIP3 gene and risk of psoriasis

Figure 4
Forest plot of rs17728338 in TNIP1 gene and risk of psoriasis
Figure 5

Sensitivity analysis of rs610604 in TNFAIP3 gene and risk of psoriasis
Figure 6

Sensitivity analysis of rs17728338 in TNIP1 gene and risk of psoriasis
Egger’s test for rs610604 in TNFAIP3 gene and risk of psoriasis

Figure 7
Egger’s test for rs17728338 in TNIP1 gene and risk of psoriasis
Figure 9

Haploreg view of rs610604 in TNFAIP3 and rs17728338 in TNIP1 gene using HaploReg version 4.1. (A) rs610604; (B) rs17728338.