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 undertaken 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^{1–3}. As with other dermatoses, the patients who suffered from it also have to face the huge psychological burden because of visible disfigurement. Considerable comorbid disease occur more often in psoriasis patients, including psoriatic arthritis, metabolic syndrome, cardiovascular disorders, gastrointestinal diseases, mood disorders as well as other emerging comorbid diseases⁴. Psoriasis affects approximately 2%–3% of the population world-wide, and its prevalence is much higher in western countries^{5,6}. To date, five types of psoriasis have been identified: psoriasis vulgaris, guttate, flexural psoriasis, pustular psoriasis, pustular psoriasis³.

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 for psoriasis occurrence and aggravation have been identified, such as Mild localized trauma, drugs, HIV infection, Streptococcal pharyngitis and exposure to natural sun light⁷. 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 psoriasis⁸. 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 2009⁹.

TNFAIP3 gene is located on human chromosome 6q23.3, while TNIP1 is located on 5q33.1. They are all Protein Coding gene encoding 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^{10,11}. 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^{12–14}. 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 BD 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-analysis¹⁵. 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 studies¹⁶. 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 and funnel plots.

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 UK¹⁹, Egypt²⁰, India²¹, China^{22–25}, Pakistani²⁶, USA²⁷, Sweden²⁸, México²⁹. 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 UK¹⁹, Europe³⁰, China^{22,23,31}, India²¹, Pakistani²⁶, USA²⁷, México²⁹. 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. The funnel plots of rs610604 and rs17728338 were visually symmetrical (Figs. 5 and 6), suggesting no statistically significant publication bias.

Functional analysis

The results of functional analysis conducted using HaploReg are shown in Figure 7.

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 years 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 1990³⁴. After that, in the year of 2004, Dixit and co-workers discovered that A20 was involved in TNF-induced NF- κ B 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 study³⁷ 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 samples⁴⁰. The molecular mechanism of A20 functions underlying these biological processes is generally characterized as inhibitory effect of NF- κ B 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^{41,42}. Apart from NF- κ B 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^{43,44}. There were also studies focusing on blocking autophagy and anti-apoptotic activities by deubiquitination⁴⁵. 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- κ B signaling pathway^{46,47}. 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)^{19,27,48–50}. 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 study number and sample size is concerned, although we have gathered all the currently available evidences, false negatives of our study still exist. Second, the genetic factor for psoriasis be 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. Finally, only studies published in English was 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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None

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

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 sclerosis

RA

Rheumatoid arthritis

Tables

Table 1. Main characteristics of included studies

Study	Year	Country	Ethnicity	Case/Control	Case		Control		HWE
					M	W	M	W	
<i>Rs610604 (T/G)</i>									
Bowes (1) ¹⁹	2011	UK	UK	742/5198	520	844	3286	7110	0.04
Bowes (2) ¹⁹	2011	UK	Ireland	161/334	102	220	235	433	1
Haase ²⁰	2014	Egypt	Egyptian	132/175	123	141	118	232	0.016
Indhumathi ²¹	2015	India	Indian	360/360	260	460	202	518	0.223
Li ²²	2014	China	Chinese	201/300	20	382	58	542	0.754
Munir ²⁶	2015	Pakistani	Asian	533/373	354	712	320	746	> 0.05
Nair (1) ²⁷	2009	USA	Caucasian	1359/1400	1017	1701	890	1510	NA
Nair (2) ²⁷	2009	USA	Caucasian	5048/5051	3635	6461	3233	6869	NA
Nikamo ²⁸	2015	Sweden	Caucasian	1411/1529	1040	1782	979	2079	NA
Villarreal-Martínez ²⁹	2016	México	México	46/103	38	54	91	115	1
Yang ²³	2012	China	Chinese	974/1181	187	1761	189	2173	0.05
Zhang, Z ²⁴	2015	China	Chinese	238/420	62	414	84	756	0.914
Zhang, C ²⁵	2015	China	Chinese	351/296	105	597	61	531	0.928

M, mutant allele; W, wild allele; HWE, Hardy-Weinberg Equilibrium

Table 2. Main characteristics of included studies

Study	Year	Country	Ethnicity	Case/Control	Case		Control		HWE
					M	W	M	W	
<i>Rs17728338 (G/A)</i>									
Bowes (1) ¹⁹	2011	UK	UK	742/5198	114	1370	572	9824	0.42
Bowes (2) ¹⁹	2011	UK	Ireland	161/334	29	293	33	635	0.04
Das ³⁰	2015	Europe	European	2212/2855	398	4026	286	5424	NA
Han ³¹	2016	China	Han population	140/476	54	226	85	867	> 0.05
Indhumathi ²¹	2015	India	Indian	360/360	202	518	147	573	0.747
Li ²²	2014	China	Chinese	201/300	56	544	40	560	0.754
Munir ²⁶	2015	Pakistani	Asian	533/373	142	924	67	679	> 0,05
Nair (1) ²⁷	2009	USA	Caucasian	1359/1400	253	2465	157	2643	NA
Nair (2) ²⁷	2009	USA	Caucasian	5048/5051	878	9218	546	9556	NA
Villarreal-Martínez ²⁹	2016	México	México	46/103	11	81	11	195	0.245
Yang ²³	2012	China	Chinese	974/1181	276	1672	213	2149	1

M, mutant allele; W, wild allele; HWE, Hardy-Weinberg Equilibrium;

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

n/Study	Adequate definition of cases	Representativeness of cases	Selection of control subjects	Definition of control subjects	Control for important factor or additional factor	Exposure assessment	Same method of ascertainment for all subjects	Non- response rate	Total score
wes ¹⁹	1	0	1	1	1	1	1	1	7
1									
s ³⁰ 2015	1	0	1	1	1	1	1	1	7
ase ²⁰	1	0	1	1	1	1	1	1	7
4									
n ³¹ 2016	1	0	1	1	1	1	1	1	7
humathi ²¹	1	0	1	1	1	1	1	1	7
5									
² 2014	1	0	0	1	1	1	1	1	6
nir ²⁶	1	0	1	1	1	1	1	1	7
5									
ir ²⁷ 2009	1	0	1	1	1	1	1	1	7
amo ²⁸	1	0	0	1	1	1	1	1	6
5									
arreal- rtínez ²⁹	1	0	1	1	1	1	1	1	7
6									
ng ²³ 2011	1	0	1	1	1	1	1	1	7
ng, Z ²⁴	1	0	1	1	1	1	1	1	7
5									
ng, C ²⁵	1	0	0	1	1	1	1	1	6
5									

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 6

Funnel plot of rs17728338 in TNIP1 gene and risk of psoriasis

A

Query SNP: rs610604 and variants with $r^2 \geq 0.8$

chr	pos (hg38)	LD (r ²)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNase	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
6	137873904	0.9	1	rs629953	A	G	0.11	0.55	0.83	0.65		5 tissues	15 tissues	BLD, LNG		5 altered motifs				TNFAIP3	intronic
6	137874824	0.86	1	rs71670547	TCTC	T	0.11	0.55	0.83	0.64			15 tissues	8 tissues		5 altered motifs				TNFAIP3	intronic
6	137876194	0.9	1	rs661561	A	C	0.11	0.55	0.83	0.65			BLD, THYM	BLD		Mef2				TNFAIP3	intronic
6	137878280	1	1	rs610604	G	T	0.30	0.59	0.91	0.67			5 tissues	15 tissues	PU1	TBX5	2 hits			TNFAIP3	intronic
6	137885905	0.95	0.99	rs622091	C	T	0.28	0.63	0.90	0.67				BLD		Trf				2.6kb 3' of

Figure 7

Haplotype view of rs610604 and rs17728338 in IL-23R gene using HaploReg version 4.1. (A) rs610604; (B) rs17728338.