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# Nuclear Factor- kappa B (NF-κB) Activation Gene Single Nucleotide Polymorphisms (SNP) Associated with the Risk of Psoriasis in Chinese Han People of Wuhan, Hubei Province

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author MM came up with the concept, design, definition of intellectual content. Author WX involved with investigation, methodology, project administration, resources and data interpretation however, all the authors had significant contributions under the supervision of author SJQ. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Psoriasis is a chronic, life-long inflammatory disorder that primarily affects the skin. The etiopathogenesis of psoriasis remains elusive. The activation of the NF-κB/Rel transcription family, by nuclear translocation of cytoplasmic complexes, plays a critical role in inflammation through its ability to induce transcription of pro-inflammatory genes. This pathway is activated upon appropriate cellular stimulation, most often by signals related to pathogens or stress.
**Objective:** To study TRAF3IP2 (rs33980500), TNFAIP3 (rs610604) and NFKBIA (rs12586317) gene activation single nucleotide polymorphisms are associated with risk of psoriasis in Chinese Han population of Wuhan city, Hubei Province.
**Materials and Methods:** The genetic analysis included samples from 44 patients and 50 controls

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was analyzed by Amplified Fragment Length Polymorphisms (AFLP System) using Applied Biosystems Gene Mapper 4.0.

**Results:** The average age of clients was 47 years with an age range of 9–86 years and an average age of onset of 37 years. 38 were male (86.36%) and 6 (13.64%) were female, of which six patients (13.64%) had a family history of psoriasis. The psoriasis area severity index (PASI) was about 10.7 (range 3.5-24), this scale evaluates the severity of three clinical signs (erythema, induration and desquamation) on a scale from 0 to 4 (from none to maximum). However, our research on the Chinese community yielded lack of association for the SNP rs12586317, rs33980500, and rs610604 with P-values of 0.9177, 0.3482, and 0.2009, respectively.

**Conclusion:** Genetic polymorphisms of NFKB1A (rs12586317), TRAF3IP2 (rs33980500) and TNFAIP3 (rs610604) were not associated with the susceptibility of psoriasis vulgaris in Chinese Han patients of Wuhan, Hubei province. However, the authors recommend a larger scale study.NF-kB is a key regulatory element in a variety of immune and inflammatory pathways, in cellular proliferation and differentiation and in apoptosis, thus, orchestrates inflammation and other complex biological processes in cells. Drugs that act on NF-kB will be key in the treatment of most chronic dermatoses.

*Keywords: Psoriasis; NF-kB; SNP; NFKB1A (rs12586317); TRAF3IP2 (rs33980500); TNFAIP3 (rs610604); Wuhan; Chinese population.*

## 1. INTRODUCTION

Psoriasis is a chronic, life-long inflammatory disorder that primarily affects the skin [1]. It is a group of common chronic inflammatory and proliferative disorder of the skin which are associated with systemic manifestations involving many organ systems. Morphological variants are common like Guttate, plaque, erythrodermic, seborrheic, arthritic, pustular and others [2]. The systemic manifestation of the disease results in co-morbid conditions, including, but not limited to, metabolic syndrome, cardiovascular disease (CVD), diabetes, depression, and cancer [3,4].

Nestle et al. indicates that psoriasis affects up to 2% of people worldwide, with affected individuals suffering high social and economic costs and increased morbidity and mortality [5,6] Ding et al. estimate the prevalence at 0.47% of psoriasis in China, [7] however, the report by the global psoriasis report in 2009 estimated it at 0.59%. Psoriasis is associated with an increased degree of morbidity; most clients are markedly bothered about their skin appearance, and there are side effects of medications. Also, it has been observed that individuals with psoriasis, as with patients with other major medical disorders, have reduced chances of employment and income as well as a decreased quality of life. The combined long-term therapy and social costs of the disease have a significant impact on health care systems and society in general [8,9].

It is proposed that both genetic and environmental influences have a critical role in the etiology and pathogenesis. The etiopathogenesis of psoriasis remains elusive. However, it is assumed that there is an interplay between genetic factors and environmental factors. Disease initiation of complex diseases, such as psoriasis, takes place in genetically predisposed individuals in which a dysregulated immune response occurs following exposure to specific environmental triggers. Although mechanistic associations linking distinct environmental factors with specific genetic determinants and dysregulated immune processes are still scarce, critical determinants of this pathogenic interplay have been identified. The commonly attributed environmental factors are; infections (viral and bacterial especially), some medicines, alcohol misuse, sunshine exposure, cigarette smoking, psychological stress, physical trauma. These factors inter-playing with some genetic polymorphisms give rise to the disease [10].

Faber and Nall conducted population studies of nearly 6000 psoriatic patients and did show that the incidence of psoriasis is higher in first-degree and second-degree relatives of patients than among the general population. That a genetic component may be responsible for this finding is backed by studies of disease concordance in twins that show a risk of psoriasis that is two to three-fold higher among monozygotic twins as among dizygotic twin [11]. There is complexity in the mode of inheritance of psoriasis [10].

Classic genome-wide linkage analysis has reviewed at least nine chromosomal loci with statistically appreciable links to psoriasis; these loci are referred to as Psoriasis Susceptibility 1 through 9 (*PSORS1* through *PSORS*9) [5]. By far, the significant psoriasis genetic determinant is PSORS1, which probably accounts for 35–50% of the known heritability of the disease, and has been replicated in virtually all linkage studies [12]. PSORS1 is situated within the major histocompatibility complex (MHC) on chromosome 6p, with an approximately 300-kb segment within the class I region [12,13]. Isolation of the causative gene at this locus is hampered by the extensive linkage disequilibrium observed within the MHC. The consensus major risk allele at this site is HLA-C: 06:02, but there may be additional independent associations within the MHC, for instance with MHC class I chain –related gene A(MICA) and MHC class I chain –related gene B(MICB) [14]. Phenotypic variants of psoriasis are genetically heterogeneous at the level of PSORS1. Thus, Guttate psoriasis is strongly associated with PSORS1, [6] whereas late-onset (over 50 years of age) plaque psoriasis is not [7].

The Genome-wide association scans have linked variants in the gene encoding the receptor Interleukin-23 (IL23R) and also the untranslated region of the interleukin-12B (IL12B) (p40) Gene as being the measure of risk for psoriasis [15,16]. The gene IL23R variants are also associated with ankylosing spondylitis and psoriatic arthritis. Another gene, CDKAL1, is associated with psoriasis as well as Crohn's disease and type 2 diabetes mellitus [17,18]. There is an intriguing association of Crohn's disease and type 2 diabetes with moderate-to-severe psoriasis and also the increased prevalence of cardiovascular disease among patients with psoriasis.

Currently, too small a proportion of the heritability is accounted for by known loci for geno-typing to contribute to the diagnosis, but rare genetic mutations of major effect (e.g., in CARD14 or IL36RN) are being identified that may be useful in sub-classifying psoriatic diseases [19,20]. Currently, there is suggestive evidence that polymorphisms in TNFAIP3 may be associated with response to tumor necrosis factor (TNF)-α inhibitors [21] and that patients who have the HLA-C risk allele may respond better to ustekinumab [22] than those who are HLA-C:06:02 negative [23] The presence of HLA-C∗0602 allele is a risk factor for psoriasis [24]. Ustekinumab is a human monoclonal antibody which exerts ifs action against interleukin 12 and 23, which are naturally occurring proteins that are involved in the regulation of the immune system and immune-mediated inflammatory disorders like psoriasis [25].

The activation of the NF-kB/Rel transcription family, by nuclear translocation of cytoplasmic Complexes, plays a critical role in inflammation through its ability to induce transcription of pro-inflammatory genes [26]. This pathway is activated upon appropriate cellular stimulation, most often by signals related to pathogens [27] or stress [28].

In this study, we shall study NF-kB signaling. At least five psoriasis associated genomic regions contain genes involved with control controlling signaling through transcription factor NF-kB [29]: Tumor necrosis factor alpha-induced protein 3 (TNFAIP3), TNIP1, Nuclear factor kappa B 1A (NFKBIA), FBXL19 [30] and Tumor necrosis factor receptor-associated factor 3, Induced Protein 2(TRAF3IP2).

We hypothesized that variations in these genes alter Psoriasis risk; thus, we shall study the likely association of TRAF3IP2 (rs33980500), TNFAIP3 (rs610604) and NFKBIA (rs12586317) gene polymorphisms with risk of psoriasis in Chinese Han population of Wuhan city, Hubei Province. We intend to also review the possibility of Nuclear Factor-single nucleotide polymorphism in psoriasis among the Chinese Han people of Wuchang district of Wuhan city, Hubei province is associated with favorable treatment outcome using biologics agents. The gene has not been fully studied in the Chinese Han population in this place mentioned above.

## 2. PATIENTS AND METHODS

### 2.1 Study Population

According to the following formula below, the estimated sample size would be 92 patients as the following formula [31–33];

$$N= [Z^2 P (1-P)]/d^2$$

where

N: Sample size, Z: Confidence interval, P: Prevalence, and d: Precision. A total of 94 cases and controls for sequencing and genotyping for the study of NF-κB activation gene polymorphism

were recruited from Zhongnan Hospital of Wuhan University, Wuhan, China during the periods December 2017 to month end of September 2018.

## 2.2 Study Variables

### 2.2.1 Dependent variables

The data of the 44 patients with psoriasis where collected with prior consent and approval by the Ethics Committee of Zhongnan Hospital of Wuhan University, and also abiding by the Helsinki Declaration in the implementation process. All the candidates, both cases and controls, were Han Chinese residing in Wuhan and surrounding towns of Hubei province, China.

### 2.2.2 Independent variable

The independent variables were Age, Gender, Psoriasis Area and Severity Index (PASI), Anti-streptolysin-O titer (ASOT), Erythrocyte Sedimentation Rate (ESR), alcohol consumption, cigarette smoking and co-morbid conditions like diabetes Miletus, hypertension and others.

## 2.3 DNA Extraction and SNP Genotyping

The deoxyribose nucleic acid (DNA) from the cases and controls was extracted from peripheral blood with the Instrument and Reagents 5424 Desktop Centrifuge (Eppendorf) S1000 Thermal Cycler PCR BIO (BIO-AD), DYY-6C electrophoresis instrument (Beijing Liuyi Instrument Factory), Tanon1600 Gel Imaging System (Shanghai Tianneng Technology Co., Ltd.); 2xTsingKe Master Mix (Wuhan Optimus Innovation Biotechnology Co., Ltd.), Blood Genomic DNA Extraction Kit (DP318) according to the standard protocol of the manufacturer.

The subjects' fasting blood was collected in EDTA purple anticoagulant tube about 5ml of it in the morning and preserved at 4°C. The genomic DNA of peripheral blood was extracted by Phenol-protease K method, and the content and concentration of DNA were determined by Ultraviolet spectrophotometer, A 260 /A 280 ＞ 1.8, and was kept at -20°C.

After selecting the target gene, the primers were synthesized by Wuhan Optimus Family Innovational Biotechnology. The PCR amplification conditions were as follows: 3 minutes at 94℃, 30 seconds at 94℃, 30 seconds at 56℃, 30 seconds at 72℃, and 30 seconds at 35°C. The PCR products were analyzed by the Snapshot method by Wuhan Zhengke Innovation Biotechnology Co., Ltd., after the 2-agarose gel electrophoresis, the amplified results were verified as per standard protocol.

The polymorphisms at positions- rs12586317 (NFKB1A), rs33980500 (TRAF3IP2) and rs610604 (TNFAIP3) was analyzed by Amplified Fragment Length Polymorphisms (AFLP System) using Applied Biosystems Gene Mapper 4.0.

## 2.4 Statistical Analysis

Sample files that were generated by running PCR-amplified and fluorescently tagged Microsatellite samples on an ABI PRISM® 3100 Genetic Analyzer using the Gene Scan. 500 LIZ® size standard was analyzed using the Statistical Package-MedCalc. Results acquired was analyzed with reference to Cross tabulation, Frequencies, Descriptive Ratio Statistics, Means, t-test, and Prediction for numerical outcomes (Linear regression).

## 3. RESULTS

We labored to investigate the association between the polymorphisms at positions- rs12586317 (NFKB1A), rs33980500 (TRAF3IP2) andrs610604 (TNFAIP3) in NF-kB signaling with the risk psoriasis. The study included 94 participants with 46.8% with the disease of interest. The main characteristics of the study cohorts are summarized in Table 1.

The genetic analysis included samples from 44 patients and 50 controls with an age range of 9–86 years and an average age of onset of 37 years. Of the patients, 38 were male (86.36%) and 6 (13.64%) were female, of which six patients (13.64%) had a family history of psoriasis.

The SNPs frequencies for the three variants are summarized in Table 2. our allele and genotype were not statistically significant ($P$>0.05) between patients and controls for the three gene variants, as such we postulated that none of these polymorphisms contributed significantly to the risk of psoriasis in the Chinese Han of Wuhan city.

**Table 1. The clinical and laboratory characteristics of the study population for the NF-kB SNP gene activation in psoriatic patients in Wuchang District, Wuhan City Hubei Province in China**

| Characteristic | | n (%) | |
|---|---|---|---|
| **Sex** | Male | 38(86.36) | |
| | Female | 6(13.64) | |
| **Age (years)** | Average | 47.46(9 – 86) | |
| | Age of Onset | 37.27 years | |
| | Adults | 42(95.45) | |
| | Children | 2(4.55) | |
| **PASI** | Average | 10.7(3.5 – 24) | |
| **Genetic Predisposition** | Positive | 6(13.64) | |
| | Negative | 38(86.36) | |
| **Types of Psoriasis** | Articular | 2(4.55) | |
| | Guttate | 7(15.91) | |
| | Vulgaris | 31(70.45) | |
| | Pastular | 3(6.82) | |
| | Erythrodermic | 1(2.27) | |
| **Smoking** | Positive | 19(43.18) | |
| | Negative | 25(56.82) | |
| **Alcohol** | Positive | 21(47.73) | |
| | Negative | 23(52.27) | |
| **Co-morbid conditions** | Cardiovascular | 16(36.36) | |
| | Diabetes Mellitus | 2(4.55) | |
| | Others | 9(20.45) | |
| | Nil | 17(38.64) | |
| **Laboratory Parameters – Inflammatory markers** | Leukocytosis(10 x $10^9$/L) | Raised | 5(11.36) |
| | | Normal | 39(86.64) |
| | ASO-T(<100T odds Units) | Raised | 11(25.00) |
| | | Normal | 33(75.00) |
| | ESR | Raised | 18(40.41) |
| | | Normal | 26(59.10) |

**Table 2. Distribution of genotypes and allele frequency in NF-kB activation SNP at positions rs12586317, rs33980500 and rs610604**

| Site | Genotype/Allele | Casas | Control | P-Value | RR(95% CI) |
|---|---|---|---|---|---|
| | | n (%) | n (%) | | |
| **Rs12586317** | CT | 21(47.73) | 26(52.00) | P =0.9177 | |
| **(NFKB1A)** | TT | 22(50.00) | 23(46.00) | | |
| | CC | 1(2.27) | 1(2.00) | | |
| | C | 23(26.14) | 28(28.00) | P = 0.7746 | 0.9334 |
| | T | 65(73.86) | 72(72.00) | | (0.5826 – 1.4955) |
| **Rs33980500** | GG | 44(100.00) | 49(98.00) | P =0.3482 | |
| **(TRAF3IP2)** | GA | 0(0.00) | 1(2.00) | | |
| | AA | 0(0.00) | 0(0.00) | | |
| | G | 88(100.00) | 99(99.00) | P = 0.3173 | 1.0101 |
| | A | 0(0.00) | 1(1.00) | | (0.9904 – 1.0302) |
| **rs610604** | GT | 13(29.55) | 8(16.OO) | P = 0.2009 | |
| **(TNFAIP3)** | TT | 31(70.45) | 41(82.00) | | |
| | GG | 0(0.00) | 1(2.00) | | |
| | G | 13(14.77) | 10(10.00) | P = 0.3225 | 1.4773 |
| | T | 75(85.23) | 90(90.00) | | (0.6819 – 3.2003) |

## 4. DISCUSSION

Psoriasis is a chronic inflammatory disorder; thus, an understanding of some of the inflammatory pathways like the NF-kB pathway is vital in a quest to find better newer drugs [34]. Our experiment labored to establish an association between NF-kB activation single nucleotide polymorphism in psoriasis at positions rs12586317, rs33980500, and rs610604.

A total of 94 clients were enrolled for the association study, of which 46.81% were those with the disease of interest and of which 86.36% were males. The study only had 2 children subjects. The average age of the clients was 47 years with a range age of 9 to 86. The mean age of onset of disease was slightly above 37 years. The psoriasis area severity index (PASI) was about 10.7 (range 3.5-24). This scale evaluates the severity of three clinical signs (erythema, induration, and desquamation) on a scale from 0 to 4 (from none to maximum).

Cigarette smoking and alcohol consumption had no significant contribution among the subjects of interest, although these factors have a considerable negative impact on the progression of disease [35–38]. Our study showed that about 13.64% of the patients with psoriasis have a positive family history of psoriasis (suspected genetic predisposition). This observed misnomer could be due to the nuclear family set up in the Chinese population, the one child policy hence it was not able to access issues of genetic predisposition among family members-smaller family size. Cardiovascular diseases were the most single commonest comorbid condition at 36.36%. Psoriasis Vulgaris was the most prevalent at 70.45% and erythrodermic psoriasis being least at 2.27%. Guttate type was the second commonest at 15.91%. The majority of the patients had a normal erythrocyte sedimentation rate (ESR), Anti-Strep-O-titers (ASO-T) and leukocyte values representing 59.10%, 75.00%, and 86.64% respectively.

Through this case-control study, we investigated the possible association between NF-kB single nucleotide polymorphisms (SNP) and Psoriasis in Chinese Han population of Wuhan Hubei province, by studying three candidate SNPs. We observed that rs12586317, rs33980500, and rs610604 in NF-kB were not associated with Psoriasis in this study population. Our research on the Chinese community yielded lack of association for the SNP rs12586317, rs33980500 and rs610604 with P-values of 0.9177, 0.3482 and 0.2009 respectively.

This research is an endeavor to reveal an insight into the hereditary foundation of psoriasis among Wuhan subjects which is upheld by the finding of a positive connection and family Ancestry of the illness in about 14 percent of patients. As far as we know, this is the first primary investigation testing for the relationship between polymorphisms in NFKB1A (rs12586317), TRAF3IP2 (rs33980500) and TNFAIP3 (rs610604) genes with psoriasis vulgaris susceptibility and clinical pattern among Chinese Han patients of Wuhan.

This study did not only indicate statistically non-significant association (P-values) only, cases and controls both had comparable frequencies of specific genotypes as in NFKB1A (rs12586317) CT, TT, CC, TRAF3IP2 (rs33980500) GG, GA, AA and TNFAIP3 (rs610604) GT, TT, GG genotypes. This might attract our attention to the potential effect of the relatively small sample size of the study on the power and significance of results. In this respect, we would recommend undertaking another large scale study testing for these genetic polymorphisms along with their expression pattern in the psoriatic skin cells.

Regarding psoriasis, a common and complex immune-mediated inflammatory disease, genetic factors have been shown to play a critical role in its pathogenesis, including numerous genetic variants related to innate immunity. Given the significant part of the NF-kB pathway in the inflammatory regulation pathway, [39] we explored the association between SNPs in NF-kB and psoriasis pathogenesis and progress.

### 4.1 Activation of NF-κB in Inflammation

NF-kB activation is widely implicated in several inflammatory diseases like rheumatoid arthritis, atherosclerosis, chronic obstructive pulmonary disease, asthma, multiple sclerosis, inflammatory bowel disease, and ulcerative colitis [40]. There are at least two separate pathways for NF-kB activation namely the a) The “canonical” pathway which is triggered by microbial products and proinflammatory cytokines such as TNFα and IL-1, usually leading to activation of RelA- or cRel-containing complexes [41] and b) An "alternative" NF-κB pathway is activated by TNF family cytokines—lymphotoxin β (TNFSF3), CD40 ligand (CD40L and TNFSF5), B cell activating factor (BAFF and TNFSF13B), and receptor

activator of NF-κB ligand (RANKL and TNFSF11), resulting in activation of RelB/p52 complexes [42–45].

The activation of the alternative pathway regulates genes required for lymph-organogenesis and B-cell activation. These pathways are characterized by the differential requirement for IκB Kinase (IKK) subunits. The IKKβ regulates activation of the canonical pathway through phosphorylation of IκBs and requires the IKKγ subunit but not IKKα, whereas IKKα is required for activation of the alternative pathway through the phosphorylation and processing of p100, the precursor for p52, but this is independent of both IKKβ and IKKγ as summarized by Toby Lawrence, 2009 in their article [34].

### 4.2 NF-KB Comparative Studies Done

Regarding TRAF3IP2 (rs33980500) SNP gene, according to Ellinghaus et al. 2010, they described that the genetic variants in the locus TRAF3IP2 are implicated in both psoriasis arthritis and vulgaris. Their study yielded statistically significant P-value results for both psoriasis vulgaris and arthritis in the German population with P-value of $2.04\times10^{-6}$ (OR=1.37, CI=1.20–1.57) and P-value of $4.57\times10^{-12}$ for rs33980500 (OR=1.57, CI=1.38–1.78) respectively in a combined sample population of 9956 (1,919 cases and 8,037 controls) [46]. The IL-17mediated T-cell immune responses are due to the positive signaling adaptor activation by the gene derivatives of SNP TRAF3IP2. The TRAF3IP2 protein interacts with tumor necrosis aspect receptor-related element (TRAF) proteins and either I-κB kinase or mitogen-activated protein kinase to activate either NF-κB or Jun kinase. Upon recruitment to CD40 and the BAFF receptor in B-cells, TRAF3IP2 additionally negatively regulates B-cellular survival via its interaction with TRAF3 [47]. In psoriasis vulgaris, a subset of T-cells expressing IL-17 plays a key role.

In epithelial cells, the binding of IL-17A and IL-17F to the heterodimeric IL-17R leads to the recruitment of TRAF3IP2 via homotypic interactions among conserved (SEFIR) domains. This allows the incorporation of TRAF6 into the signaling complex after which downstream activation of the NF-κB and mitogen-activated protein kinase pathways [48]. We hence speculate that dysregulation of TRAF3IP2 may have a primary effect on IL-17 signaling and, as a result, on the activation of NF-kB-pathways, main to the upregulation of pro-inflammatory elements [47].

The NFKB1A (rs12586317) SNP gene, studies have shown associated with psoriasis susceptibility like by Stuart et al. [49].

Indhumathi S et al. [50] in a study he conducted in an ethnic group, South Indian Tamils. They found TNFAIP3 (rs610604) SNP gene associated with the risk of psoriasis in the Indian ethic group.

## 5. CONCLUSION

In conclusion, nuclear factor kappa B (NF-kB) is a key regulatory element in a variety of immune and inflammatory pathways, in cellular proliferation and differentiation and in apoptosis. This transcription factor, orchestrates inflammation and other complex biological processes in cells. It will be key in the treatment of most chronic dermatoses [51]. Therefore NF-κB is a crucial mediator involved in the pathogenesis of psoriasis. Genetic polymorphisms of NFKB1A (rs12586317), TRAF3IP2 (rs33980500) and TNFAIP3 (rs610604) were not associated with the susceptibility of psoriasis vulgaris in Chinese Han patients of Wuhan, Hubei province. However, the authors are of the view that these SNP might have an association with the clinical type and severity of the disease and recommends a larger scale study.

## WHAT IS KNOWN?

Genome-wide association analysis identified NF-kB activation gene Single Nucleotide Polymorphism (SNP):rs33980500 (TRAF3IP2), rs610604 (TNFAIP3) and rs12586317 (NFKBIA) as psoriasis susceptibility loci in the European population.

## WHAT THE STUDY BRINGS

1. The study on nuclear factor kappa B (NF-kB) as a key regulatory element in a variety of immune and inflammatory pathways, in cellular proliferation and differentiation and in apoptosis will be key in the treatment of most chronic dermatoses.
2. Despite our study showing lack of association, NF-kB activation gene Single Nucleotide Polymorphism(SNP) need to be

explored further in other races at a larger scale.

## CONSENT

All patients gave written informed consent and for minors, their next of kin consented for them. Fifty healthy volunteers with no history of psoriasis disease, any autoimmune disorders, and systemic disorders or any family history of psoriasis and other autoimmune-related disorders acted as controls for this case-control study.

## ETHICAL APPROVAL

It is not applicable.

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The study was sponsored by Wuhan University, Research Department via the Department of Dermatology and Venereology; Zhongnan Hospital of Wuhan University.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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