INTRODUCTION

Psoriasis is a common inflammatory disease of the skin affecting 2% of the population (Boehncke & Schon, 2015). Plaque psoriasis, the most common variant of psoriasis, is characterized by inflamed, red skin covered by a silvery white scale (Boehncke & Schon, 2015). Psoriasis is an independent risk factor for mortality and contributes to numerous comorbid conditions, including rheumatological arthritis, depression, cardiovascular disease, and diabetes (Kim, Jerome, & Yeung, 2017). At present, there is no cure for psoriasis and there are no specific markers that can accurately predict the development of psoriasis. Although psoriasis pathogenesis remains poorly understood, it is accepted by most dermatologists that psoriasis arises via the interactions of genetic, immunological, and environmental factors (Mahil, Capon, &
Currently, more than 40 independent loci are associated with the susceptibility to psoriasis.

Interleukin-1 receptor antagonist (IL-1Ra) is a member of the IL-1 family and an important anti-inflammatory cytokine. IL-1Ra competitively blocks the effects of IL-1α and IL-1β by binding to the IL-1 receptor. An imbalance between IL-1 and IL-1Ra is associated with increased production of pro-inflammatory cytokines and the development of inflammatory disorders (Mistry, Savic, & Hilst, 2017). IL-1Ra-deficient mice spontaneously developed a dermatitis that histologically resembled human psoriasis (Nakajima et al., 2010; Shepherd, Little, & Nicklin, 2004). In a human coculture model with keratinocytes and autologous T cells, application of a recombinant human form of IL-1Ra significantly reduced pro-inflammatory cytokine production (Renne, Schafer, Werfel, & Wittmann, 2010). In addition, the levels of pro-inflammatory cytokines were significantly up-regulated in lesional psoriatic epidermis due to decreased formation and secretion of IL-1Ra (Debets et al., 1997; Kristensen et al., 1992). In intron 2 of the IL-1Ra gene (IL-1RN), there is an 86-basepair variable number tandem repeat (VNTR) polymorphism. The IL-1RN allele 2 is thought to result in higher IL-1Ra release (Bid, Manchanda, & Mittal, 2006). Since IL-1Ra is involved in the inflammatory responses within psoriatic plaques, dermatologists have carried out genetic studies to assess the relationship of the IL-1RN VNTR polymorphism with psoriasis risk. A quantitative summary of their findings is needed.

IL-10 is an anti-inflammatory cytokine synthesized by monocytes, macrophages, and lymphocytes as a response to inflammation (Fontoura et al., 2015). It is able to inhibit antigen presentation and suppress the synthesis and function of a number of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), IL-6, and IL-1 (Rutz & Ouyang, 2016). IL-10 mRNA expression was dramatically decreased in the psoriatic lesions compared with the normal skin tissues (Cheng et al., 2001). In addition, levels of IL-10-producing regulatory B cells (B10 cells) were decreased in patients with psoriasis (Hayashi et al., 2017). Given that IL-10 played a protective role in inflammation development, adoptive transfer of B10 cells effectively suppressed imiquimod-induced skin inflammation in a mouse model of psoriasis (Yanaba et al., 2013). Moreover, administration of recombinant IL-10 significantly reduced the severity of psoriasis in humans (Asadullah et al., 1999). Three single-nucleotide polymorphisms (SNPs) at -592A/C (rs1800872), -819C/T (rs3021097), and -1082A/G (rs1800896) in the IL-10 promoter region have recently been evaluated in a number of genetic association studies regarding their relationship with psoriasis susceptibility, but the findings of these studies are contradictory.

Both IL-1Ra and IL-10 are important anti-inflammatory cytokines in psoriasis pathogenesis. Our study seeks to

![FIGURE 1 Process of study selection](image-url)
### TABLE 1  Characteristics of the studies evaluating the relationship between the IL-1RN VNTR polymorphism and psoriasis risk

| Author       | Journal              | Year | Country          | Ethnicity | Controls | Cases | Male in controls (%) | Male in cases (%) | Genotyping method | Controls selection | HWE |
|--------------|----------------------|------|------------------|-----------|----------|-------|----------------------|-------------------|-------------------|--------------------|-----|
| Tarlow       | Br J Dermatol        | 1997 | UK and Germany   | Caucasians| 331      | 271   | Not available        | Not available     | PCR assay         | Not available     | Yes |
| Liu          | Natl Med J China     | 1998 | China            | Asians    | 130      | 82    | Not available        | 56.1              | PCR assay         | Hospital           | Yes |
| Peng         | Immunol J            | 1999 | China            | Asians    | 85       | 38    | Not available        | 63.2              | PCR assay         | Population         | Yes |
| Li           | J Clin Dermatol      | 1999 | China            | Asians    | 30       | 30    | Not available        | 53.3              | PCR assay         | Not available     | Yes |
| Reich        | J Invest Dermatol    | 2002 | Germany          | Caucasians| 345      | 231   | 52.8                 | 65.4              | PCR assay         | Hospital           | Yes |
| Peddle       | Ann Rheum Dis        | 2005 | Canada           | Caucasians| 95       | 226   | Not available        | 52.2              | PCR assay         | Not available     | Yes |
| Chang        | Br J Dermatol        | 2007 | China            | Asians    | 210      | 272   | Not available        | 64.7              | PCR assay         | Hospital           | Yes |
| Moorchung    | Indian J Dermatol    | 2015 | India            | Asians    | 243      | 112   | Not available        | 56.3              | PCR assay         | Hospital           | Yes |

Notes. HWE: Hardy–Weinberg equilibrium; IL-1RN VNTR: interleukin-1 receptor antagonist variable number tandem repeat; PCR: polymerase chain reaction; UK: United Kingdom.

### TABLE 2  Characteristics of the included studies assessing the association between the IL-10 polymorphisms and psoriasis risk

| Author       | Journal              | Year | Country | Ethnicity | Controls | Cases | Male in controls (%) | Male in cases (%) | Genotyping method | Selection of controls | IL-10 polymorphism |
|--------------|----------------------|------|---------|-----------|----------|-------|----------------------|-------------------|---------------------|----------------------|---------------------|
| Reich        | J Invest Dermatol    | 1999 | Germany | Caucasian | 123      | 151   | 54.5                 | 63.6              | Sequencing analysis | Population           | rs1800896           |
| Craven       | Br J Dermatol        | 2001 | UK      | Caucasian | 330      | 78    | Not available        | 41.7              | PCR assay          | Hospital             | rs1800896           |
| Peddle       | Ann Rheum Dis        | 2005 | Canada  | Caucasian | 95       | 226   | Not available        | 52.2              | PCR assay          | Not available        | rs1800896           |
| Chang        | Br J Dermatol        | 2007 | China   | Asian     | 210      | 272   | Not available        | 64.7              | Sequencing analysis | Hospital             | rs1800896, rs3021097, rs1800872 |
| Wongpiyabovorn | Clin Exp Dermatol    | 2008 | Thailand | Asian     | 155      | 139   | 16.1                 | 56.8              | PCR-RFLP           | Population           | rs1800896 and rs1800872 |
| Karam        | Cytokine             | 2014 | Egypt   | Caucasian | 120      | 110   | 35.8                 | 24.5              | PCR-RFLP           | Not available        | rs1800896           |
| Indhumathi   | Hum Immunol          | 2017 | India   | Asian     | 360      | 360   | 80.0                 | 81.1              | TaqMan 5' allele discrimination assay | Not available | rs1800896 and rs3021097 |

Notes. IL-10: interleukin-10; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction–restriction fragment length polymorphism; UK: United Kingdom.
systematically review the literature and meta-analyze the results of case–control studies on the relation of IL‐1RN and IL‐10 polymorphisms with psoriasis risk.

2 | METHODS

2.1 | Ethical compliance

Ethics approval was waived because this study does not involve any human participants or animals.

2.2 | Systematic literature search

On 2nd of November 2017, two reviewers carried out independent electronic searches on the Wanfang, China National Knowledge Infrastructure (CNKI), Medline, and PubMed databases covering the entire period of each database. The following algorithm was applied: “(interleukin-1 OR interleukin-10 OR cytokine) AND (psoriasis OR genetics OR polymorphism).” Results were limited to studies in English or Chinese, featuring human participants and with abstracts available. We supplemented these searches by searching review articles and reference lists of the included studies. We did not contact study authors to request additional data. Disagreements were solved by discussion and consensus.

2.3 | Inclusion/exclusion criteria

Studies were assessed against the following inclusion criteria: (a) assessing the relation of the IL‐1RN polymorphism or the IL‐10 polymorphisms (rs1800896, rs3021097, and rs1800872) with psoriasis risk; (b) used validated measures to determine the presence of psoriasis; (c) the study was case–control designed; (d) all data were original; (e) sufficient information on odds

Table 3 Summary of results for meta-analyses

| Polymorphism       | Dominant modela | p value of the z test | p derived from heterogeneity test | Recessive modelb | p value of the z test | p derived from heterogeneity test |
|--------------------|-----------------|-----------------------|-----------------------------------|------------------|-----------------------|-----------------------------------|
| IL‐1RN VNTR        |                 |                       |                                   |                  |                       |                                   |
| All (n = 8)        | 1.33 (0.76–2.35)| 0.317                 | 0.021                             | 1.77 (0.65–4.82) | 0.262                 |
| Asians (n = 5)     | 1.53 (0.59–3.98)| 0.379                 | 0.019                             | 2.38 (0.63–9.02) | 0.201                 |
| Caucasians (n = 3)| 0.98 (0.70–1.36)| 0.881                 | Not applicable                     | 0.83 (0.45–1.55) | 0.566                 |
| IL‐10 rs1800896    |                 |                       |                                   |                  |                       |                                   |
| All (n = 7)        | 1.05 (0.85–1.29)| 0.672                 | 0.184                             | 1.18 (0.73–1.89) | 0.438                 |
| Asians (n = 3)     | 0.96 (0.73–1.27)| 0.771                 | 0.278                             | 1.13 (0.56–2.28) | 0.733                 |
| Caucasians (n = 4)| 1.17 (0.85–1.61)| 0.331                 | 0.123                             | 1.19 (0.60–2.34) | 0.623                 |
| IL‐10 rs3021097    |                 |                       |                                   |                  |                       |                                   |
| All (n = 2)        | Not applicable  | Not applicable        | Not applicable                     | Not applicable   | Not applicable        | Not applicable                    |
| IL‐10 rs1800872    |                 |                       |                                   |                  |                       |                                   |
| All (n = 2)        | Not applicable  | Not applicable        | Not applicable                     | Not applicable   | Not applicable        | Not applicable                    |

Notes. CI, confidence interval; IL‐1RN VNTR, interleukin-1 receptor antagonist variable number tandem repeat; IL‐10, interleukin-10; OR, odds ratio.

*aDominant model: 22 + 2L versus LL for the IL‐1RN VNTR polymorphism; GG + GA versus AA for rs1800896. bRecessive model: 22 versus 2L + LL for the IL‐1RN VNTR polymorphism; GG versus GA + AA for rs1800896. cAdditive model: 22 versus 2L versus LL for the IL‐1RN VNTR polymorphism; GG versus GA versus AA for rs1800896. dAllelic model: 2 allele versus L allele for the IL‐1RN VNTR polymorphism; G allele versus A allele for rs1800896; C allele versus T allele for rs3021097; C allele versus A allele for rs1800872.

FIGURE 2 (a) Sample sizes of the studies assessing the interleukin-1 receptor antagonist variable number tandem repeat polymorphism and risk of psoriasis from 1997 to 2015; (b) Sample sizes of the studies assessing the interleukin-10 polymorphism rs1800896 from 1999 to 2017.
| Allelic model<sup>d</sup> | p derived from heterogeneity test | OR (95% CI) | p value of the z test | p derived from heterogeneity test | OR (95% CI) | p value of the z test | p derived from heterogeneity test |
|--------------------------|---------------------------------|-------------|----------------------|---------------------------------|-------------|----------------------|---------------------------------|
| 0.001                    | 1.80 (0.64–5.09)                | 0.266       | 0.005                | 1.16 (0.89–1.50)                | 0.279       | 0.003                |
| 0.003                    | 2.65 (0.55–12.87)               | 0.226       | 0.006                | 1.27 (0.73–2.23)                | 0.403       | 0.001                |
| Not applicable           | 0.84 (0.44–1.58)                | 0.583       | Not applicable       | 1.04 (0.88–1.23)                | 0.669       | 0.677                |
| 0.098                    | 1.24 (0.76–2.04)                | 0.395       | 0.147                | 1.03 (0.90–1.18)                | 0.639       | 0.122                |
| 0.494                    | 1.09 (0.54–2.21)                | 0.815       | 0.467                | 0.93 (0.75–1.16)                | 0.513       | 0.276                |
| 0.025                    | 1.30 (0.62–2.71)                | 0.492       | 0.046                | 1.10 (0.93–1.31)                | 0.262       | 0.111                |
| Not applicable           | Not applicable                  | Not applicable | Not applicable       | Not applicable                  | Not applicable | 1.17 (0.88–1.56) | 0.288 | 0.092 |
| Not applicable           | Not applicable                  | Not applicable | Not applicable       | Not applicable                  | Not applicable | 1.01 (0.81–1.25) | 0.951 | 0.895 |

ratios (ORs) with their 95% confidence intervals (95% CIs). Exclusion criteria were as follows: (a) not case–control design; (b) not an original paper; (c) performed on animals or human cell lines; (d) studies based on only cases; (e) not offering essential data. Additionally, studies with potentially overlapping cohorts were excluded from the quantitative synthesis. In such cases, we included the study with the largest sample size.

### 2.4 Data extraction

Data extraction was conducted by two investigators (Ju Qiao and Qian-Nan Jia). The senior author (Hong-Zhong Jin) was involved in consulting for the eligibility of a study if a divergence between the two data-extracting investigators existed. From the finally selected papers, data relating to study characteristics for the following variables were extracted: first author, journal name, publication year, location of study, ethnicity, male percentage, number of study subjects, the frequencies of genotypes or alleles in case and control groups, genotyping method, and Hardy–Weinberg equilibrium (HWE) status.

### 2.5 Statistical analyses

All statistical analyses were conducted using Stata version 10.0. To assess the relation of the IL-1RN VNTR polymorphism and the IL-10 variants with susceptibility to psoriasis, pooled ORs and their corresponding 95% CIs were assessed. Between-study heterogeneity was evaluated using Cochrane’s Q statistic. There are two statistical methods for meta-analysis: the fixed-effects model and the random-effects model. If the Q test was statistically significant (p < 0.10), estimates were pooled using random-effects models (SanGiovanni, Berkey, Dwyer, & Colditz, 2000). When between-study heterogeneity was not significant, the overall effects were calculated using the fixed-effects model (Mantel & Haenszel, 1959). HWE in controls was calculated by chi-square test. Funnel plots were drawn as a check for potential publication bias. We also used Egger’s asymmetry test to evaluate publication bias. The significance level was set at p < 0.05, except for test of heterogeneity.

### 3 RESULTS

#### 3.1 Study characteristics

The execution of the search strategy initially resulted in 129 studies after duplicates were removed. Subsequently, 109 studies were excluded at the title/abstract level, and 20 full-text papers were checked for eligibility. After careful evaluation, a total of 13 studies were included in the review (Chang et al., 2007; Craven et al., 2001; Indhumathi et al., 2017; Karam, Zidan, & Khater, 2014; Li, Dong, Zhu, Yu, & Wang, 1999; Liu, Zhang, Yang, & Xu, 1998; Moor Chung, Vasudevan, Chatterjee, Mani, & Grewal, 2015; Peddle, Butt, Snelgrove, & Rahman, 2005; Peng & Wang, 1999; Reich et al., 2002, 1999; Tarlow et al., 1997; Wongpiyabovorn et al., 2008). We did not find any additional studies by hand-searching the reference lists of the included studies. Figure 1 summarizes the process of study selection. The
qualified publications included in our meta-analysis were published between 1997 and 2017. The sample sizes ranged from 60 to 720 participants. Tables 1 and 2 present the characteristics of the individual studies. Figure 2 shows sample sizes of reports over time. We did not find any studies violating HWE in controls.

3.2 | No association of IL-1RN VNTR polymorphism with psoriasis

Five studies evaluating the IL-1RN VNTR polymorphism was performed in Asians (Chang et al., 2007; Li et al., 1999; Liu et al., 1998; Moorchurch et al., 2015; Peng & Wang, 1999), and three in Caucasians (Peddle et al., 2005; Reich et al., 2002; Tarlow et al., 1997). Five studies provided genotype data for the polymorphism (Li et al., 1999; Liu et al., 1998; Moorchurch et al., 2015; Peng & Wang, 1999; Reich et al., 2002), whereas three studies only contained information on allelic frequency (Chang et al., 2007; Peddle et al., 2005; Tarlow et al., 1997). There was significant between-study heterogeneity (Table 3). Random-effect meta-analyses combining the data did not identify any associations of the IL-1RN VNTR polymorphism with psoriasis under four genetic models (dominant model: OR = 1.33, 95% CI: 0.76–1.35, p = 0.317; recessive
model: OR = 1.77, 95% CI: 0.65–4.82, \( p = 0.262 \); additive model: OR = 1.80, 95% CI: 0.64–5.09, \( p = 0.266 \); allelic model: OR = 1.16, 95% CI: 0.89–1.50, \( p = 0.279 \); Table 3 and Figure 3). Then, subgroups analyses by different ethnicity (Asians and Caucasians) were carried out. The results suggested no significant association between the IL‐1RN VNTR polymorphism and psoriasis risk under any of the four genetic models in each ethnic group (Table 3 and Figure 3).

### 3.3 No association of IL‐10 polymorphisms with psoriasis

Seven studies provided summaries of data on the IL‐10 SNP rs1800896 (Chang et al., 2007; Craven et al., 2001; Indhumathi et al., 2017; Karam et al., 2014; Peddle et al., 2005; Reich et al., 1999; Wongpiyabovorn et al., 2008). No evidence for heterogeneity was observed across all studies (Table 3). Pooled results revealed no significant association of rs1800896 with psoriasis risk under any of the comparison models (dominant model: OR = 1.05, 95% CI: 0.85–1.29, \( p = 0.672 \); recessive model: OR = 1.18, 95% CI: 0.73–1.89, \( p = 0.438 \); additive model: OR = 1.24, 95% CI: 0.76–2.04, \( p = 0.395 \); allelic model: OR = 1.03, 95% CI: 0.90–1.18, \( p = 0.639 \); Table 3 and Figure 4). When studies were subgrouped by ethnicity, the relationship between rs1800896 and psoriasis was not significant in Asian or Caucasian populations (Table 3 and Figure 4).

Two studies investigated the relation between the IL‐10 SNP rs3021097 (Chang et al., 2007; Indhumathi et al., 2017) and psoriasis risk. Under allelic contrast, the summary OR was 1.17 (95% CI: 0.88–1.56, \( p = 0.288 \)), suggesting no significant association with psoriasis (Table 3). Significant heterogeneity was identified (Table 3).

Two studies evaluated the association of the IL‐10 SNP rs1800872 with psoriasis risk using data on allelotype (Chang et al., 2007; Wongpiyabovorn et al., 2008). Meta-analysis of fixed-effects model provided an estimated OR of 1.01 (95% CI: 0.81–1.25, \( p = 0.951 \)) revealing no relationship between this polymorphism and psoriasis (Table 3). We did not identify between-study heterogeneity (Table 3).

### 3.4 Sensitivity analysis and publication bias

We conducted sensitivity analyses to evaluate the stability of the overall effect by removing one study at a time and estimating the summary ORs for the remaining studies. The results remained essentially unchanged for the IL‐10 polymorphism rs1800896 and the IL‐1RN VNTR polymorphism (data not shown). Given that the meta-analyses for the IL‐10 SNPs rs3021097 and rs1800872 were performed on a small number of small studies, sensitivity analysis was not carried out for these two SNPs. Begg’s funnel plots (Figures 5 and 6) and Egger’s test revealed no publication bias (\( p > 0.05 \) for each polymorphism).

### 4 DISCUSSION

Interleukin‐1Ra and IL‐10 are critical negative regulators of the inflammatory response. Numerous studies have shown the effects of IL‐1Ra on blocking the activity of IL‐1α and IL‐1β in various in vitro and in vivo systems (Paolo & Shayakhmetov, 2016). IL‐1Ra knockout mice develop skin inflammation with histopathological features resembling human psoriasis (Nakajima et al., 2010; Shepherd et al., 2004), while administration of recombinant IL‐1Ra shows beneficial effects in patients with psoriasis (Viguier, Guigue, Pages, Smahi, & Bachelez, 2010). IL‐10 has a broader spectrum of anti-inflammatory activities because it inhibits the production of a number of pro-inflammatory cytokines, including interferon-\( \gamma \), IL‐8, IL‐6, IL‐1α, and IL‐1β. IL‐10 also
up-regulates the formation and release of anti-inflammatory molecules. Treatment with recombinant IL-10 has been shown to be effective in reducing the inflammatory reactions and disease severity in psoriasis patients (Asadullah et al., 1999; Reich et al., 2001). Because IL-1ra and IL-10 play an important role in controlling inflammation, it is possible that genetic variants in the IL-1RN and IL-10 genes may contribute to psoriasis susceptibility.

In this meta-analysis, we systematically reviewed case-control studies on the association between psoriasis risk and genetic variants in the IL-1RN and IL-10 genes. The results of our meta-analyses found no significant effect of the four individual polymorphisms (IL-1RN VNTR polymorphism and IL-10 SNPs rs1800896, rs3021097 and rs1800872) on psoriasis risk.

There is no previous meta-analysis assessing the relation of the IL-1RN VNTR polymorphism with psoriasis risk. Among the eight case-control studies on this polymorphism, conflicting results were reported. Three studies reported an association between this polymorphism and psoriasis (Liu et al., 1998; Peng & Wang, 1999; Tarlow et al., 1997), but the others did not find any associations (Chang et al., 2007; Li et al., 1999; Moorchung et al., 2015; Peddle et al., 2005; Reich et al., 2002). It is unclear what factors contribute to the conflicting results reported in these studies. Differences in genetic background, percentage of men, origin of controls, sample size, and environmental factors may be responsible for the inconsistent results. Meta-analysis is a quantitative statistical analysis for synthesizing research results across different studies into an overall summary. Our study would benefit clinician by providing a summary of medical literature on the relationship of the IL-1RN VNTR polymorphism with psoriasis. Based on a combined estimate of data from eight genetic studies involving 1,469 psoriasis patients and 1,262 control subjects, we found no association of the IL-1RN VNTR polymorphism with psoriasis risk.

A previous meta-analysis by Lee, Choi, Ji, and Song, (2012 assessed the IL-10 SNPs and psoriasis risk in 2012. In their paper, Lee et al. did not reveal significant associations of rs1800896 and rs3021097 with psoriasis risk in the overall populations, but they identify a significant association between rs1800896 and psoriasis risk in Asian subjects. The SNP rs1800872 was not evaluated in their meta-analysis. Lee et al. included two case-control studies for evaluating the rs1800896 polymorphism in Asians. In addition to the two studies Lee et al. used, we added a recently published Asian study with a large sample size (720 participants) into the pooled analysis, finding no significant association between rs1800896 and psoriasis in Asians. Given that the meta-analysis by Lee et al. only included a small number of studies with small sample sizes for evaluating the relation of rs1800896 and psoriasis risk in Asians, the positive association they reported may be unreliable and needs to be confirmed by studies using larger sample size.

Finally, the limitations of our study must be discussed. First, haplotype analysis for the IL-10 polymorphisms was not performed because of limited number of studies (n = 2) and discrepancy in study methods (Al-Heresh et al., 2002; Baran, Szepietowski, Mazur, & Baran, 2008). It was noted that the two studies evaluating IL-10 haplotype and psoriasis risk did not report a significant association. Second, owing to low sample size of studies, the association of the IL-1RN VNTR polymorphism and IL-10 SNPs with psoriasis subtypes was not taken into account in our meta-analysis. Third, there were discrepancies in the presentation of published data for the IL-1RN VNTR polymorphism. It is recommended that further studies should provide data for both genotype and allelotype frequencies of the polymorphism.

In conclusion, current published studies fail to support the hypothesis that the IL-1RN VNTR polymorphism and three common IL-10 SNPs rs1800896, rs3021097, and rs1800872 are associated with psoriasis risk.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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