

Association between mutation of interleukin 36 receptor antagonist and generalized pustular psoriasis

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Generalized pustular psoriasis (GPP) is a systemic inflammatory disease with poor outcomes, and several studies have suggested that the mutation of the interleukin 36 receptor antagonist gene (IL36RN) is related to GPP, where the polymorphism c.115+6T>C is reported to be the most common mutation of IL36RN. This study was performed to clarify and comprehensively evaluate the relationship between IL36RN gene polymorphism and the susceptibility of GPP subtypes.

Methods: To conduct a thorough literature review, studies were obtained using databases such as Pubmed, EMBASE, Cochrane, China National Knowledge Infrastructure, and the Wanfang database. Only studies published up to December 2019 were included. The quality of the research studies was estimated using the Newcastle–Ottawa scale. The total odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were pooled and analysed using STATA 14. The publication bias was evaluated through the Egger test, performed using the aforementioned software. Five common gene models were built and analysed to assess the association between the polymorphism c.115+6T>C and subtypes of GPP.

Results: A total of 10 studies were selected, including 683 cases of GPP patients. Meta-analyses showed that there was a significant statistical correlation of IL36RN mutation between GPP with or without psoriasis vulgaris (OR=3.82, 95%CI 2.63–5.56) and between adult GPP and paediatric GPP (OR=0.42, 95%CI 0.23–0.77). No obvious discrepancy between European patients (OR=4.03, 95%CI 2.23–7.26) and Asian patients was found. The gene models showed clear associations between the polymorphism c.115+6T>C and GPP through the dominant model (CC+ TC vs TT, OR 2.74, 95%CI 2.06–3.64), recessive model (CC vs CT + TT, OR 4.33, 95%CI 2.84–6.60), homozygote model (CC vs TT, OR 4.37, 95%CI 2.88–6.62), heterozygote model (CT vs TT, OR 2.26, 95%CI 1.32–3.85) and allelic model (C vs T, OR 3.35, 95%CI 2.63–4.27).

Conclusion: The IL36RN mutation is strongly related to GPP without psoriasis vulgaris and the early onset of GPP. Furthermore, the single-nucleotide polymorphism c.115+6T>C of the IL36RN gene plays a significant role in GPP vulnerability, especially in homozygous mutation. GPP could be a different inflammatory disease, independent of psoriasis.

Abbreviations: GPP = generalized pustular psoriasis, GPP alone = patients with generalized pustular psoriasis without a history of psoriasis vulgaris, IL-36RN = interleukin 36 receptor antagonist, NF-κB = nuclear factor κB, PV = psoriasis vulgaris.

Keywords: c.115+6T>C, generalized pustular psoriasis, interleukin 36 receptor antagonist, meta-analysis, mutation

1. Introduction

Generalized pustular psoriasis (GPP; OMIM 614204) is viewed as an uncommon subtype of psoriasis. GPP is a systemic

inflammatory disease that not only manifests as generalized pustulosis in the skin but also leads to systemic symptoms.^[1–4] An epidemiological survey in China found that about 0.69% of

Editor: Muhammad Tarek Abdel Ghafar.

Systematic review registration number: CRD42020149114 (PROSPERO)

Authors have no conflict of interest to declare.

The datasets generated during and/or analyzed during the current study are publicly available.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Liu ZJ, Tian YT, Shi BY, Zhou Y, Jia XS. Association between mutation of interleukin 36 receptor antagonist and generalized pustular psoriasis: a PRISMA-compliant systematic review and meta-analysis. *Medicine* 2020;99:45(e23068).

Received: 20 March 2020 / Received in final form: 18 September 2020 / Accepted: 30 September 2020

<http://dx.doi.org/10.1097/MD.00000000000023068>

psoriasis patients had GPP.^[5] Another study, conducted in France, showed that the mortality rate was as high as 2%.^[6]

The pathogenesis of GPP is unclear, and factors like sudden withdrawal from glucocorticoids, infections, trauma, and pregnancy could lead to progression of the disease.^[7] Recently, some studies have demonstrated that GPP is highly dependent on genetics. Marrakchi^[8] found that the pathogenesis of GPP is related to the homozygous missense mutation of the IL-36 receptor antagonistic gene (IL36RN). Subsequently, several studies have been conducted to identify the association between the IL36RN gene mutation and GPP susceptibility. Through these studies, in addition to c.115+6T>C (rs:148755083), more than 20 mutations were detected in patients with GPP from all over the world.^[3] These studies indicate a strong relationship between GPP and the IL36RN mutation. However, the differences between IL36RN mutations and the subtypes of GPP have not been verified, particularly those involving patients with GPP with existing or prior psoriasis vulgaris (PV) and patients with generalized pustular psoriasis without a history of PV (GPP alone). Moreover, some differences between adult patients and paediatric patients have been demonstrated in some studies.^[8] This meta-analysis was performed to clarify and evaluate the relationship between IL36RN gene polymorphism and the susceptibility of GPP subtypes.

2. Method

This study conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^[9] Because the study did not obtain private patient data, the meta-analysis does not require ethical approval.

2.1. Literature screening

Using ‘IL36RN,’ ‘psoriasis,’ ‘pustular psoriasis,’ ‘generalized pustular psoriasis,’ ‘GPP,’ ‘mutation,’ ‘gene polymorphism’ and ‘single nucleotide polymorphism’ as keywords, the Pubmed, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure, the Wanfang database, and other databases were searched, and studies published up to December 2019 were included.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria. Studies that meet the following criteria will be included in this research:

- (1) Case-control or observation studies on GPP patients;
- (2) All patients have a clinical diagnosis of the GPP;
- (3) An investigation into the relationship between the estimated IL36RN mutation and the GPP susceptibility;
- (4) The study should be available for full-text use, including sufficient genotype distribution;
- (5) The study must be a peer-reviewed academic paper;
- (6) In the case of a duplicate study, the most recent literature is selected.

2.2.2. Exclusion criteria. Studies that meet the following criteria will be excluded from this research:

- (1) Review, duplicate literature and animal studies;
- (2) Duplicate data included in the study.

Two independent researchers extracted studies according to the inclusion and exclusion criteria above. If the 2 authors

disagreed, the conflict was addressed by the third, independent researcher.

2.3. Data extraction

The data extracted from each article included the following: the first author, year of publication, the study design, the country of the study, the sample size, the main single nucleotide polymorphisms of IL36RN, the total number of the patients (including patients suffering from GPP alone, adult GPP and paediatric GPP), and the frequency of IL36RN gene mutation.

2.4. Literature quality evaluation

Using the Newcastle–Ottawa scale (NOS),^[10] the methodological quality of the included studies was systematically assessed by 2 independent researchers. The NOS criteria describe 3 aspects of quality: the selection of subjects in case groups (0 to 4 stars), comparability between groups (0 to 2 stars) and determination of exposure or outcomes in case-control studies (0 to 3 stars). If the aggregate score equals 9, the literature is deemed to be of the best quality, and a score of 0 indicates the worst quality. Observational studies with scores of 6 and above can be considered to be of high quality.

2.5. Statistical methods

A meta-analysis of the data was carried out using the systematic evaluation software Stata 14. Heterogeneity was calculated using the Q test and I^2 test,^[11] where $P < .1$ and $I^2 > 50\%$ refer to obvious heterogeneity between the included studies – the source of heterogeneity will be determined through subgroup analysis. If statistical heterogeneity existed between the 2 groups without clinical heterogeneity or differences, the random-effect model was used. When $P > .1$ and $I^2 < 50\%$, the heterogeneity is deemed as acceptable, and the fixed-effect model was used to pool the statistic variables.^[9] The 95% confidence interval (95% CI), the P -value and the odds ratios (ORs) of the mutation were used to assess the association between the IL36RN and the GPP. In this study, $P \leq .05$ is considered to be statistically significant. The confidence interval of each study is determined or approximated according to existing data. The analysis and reporting of these data are carried out and explained in accordance with the PRISMA declaration guidelines.^[9] The Egger test was performed to evaluate publication bias.^[12] Five gene models were built, including the dominant model (CC + CT vs TT), recessive model (CC vs CT+ TT), homozygote model (CC vs TT), heterozygote model (CT vs TT) and allelic model (C vs T). The OR and 95% CI were used to analyse all the indexes. The Hardy–Weinberg equilibrium (HWE) was calculated to assess the bias of inheritance.

3. Results

3.1. Search for studies

The study-retrieval process is shown in Figure 1. In the first step, the keyword search, a total of 284 relevant articles were retrieved. Eighty-four studies were found in Pubmed, 178 articles were retrieved from EMBASE, 9 articles were retrieved from China National Knowledge Infrastructure and 13 articles were retrieved from the Wanfang database. In the subsequent literature screening, a total of 155 duplicate articles were excluded first. After reviewing the title and summary, 109 irrelevant articles

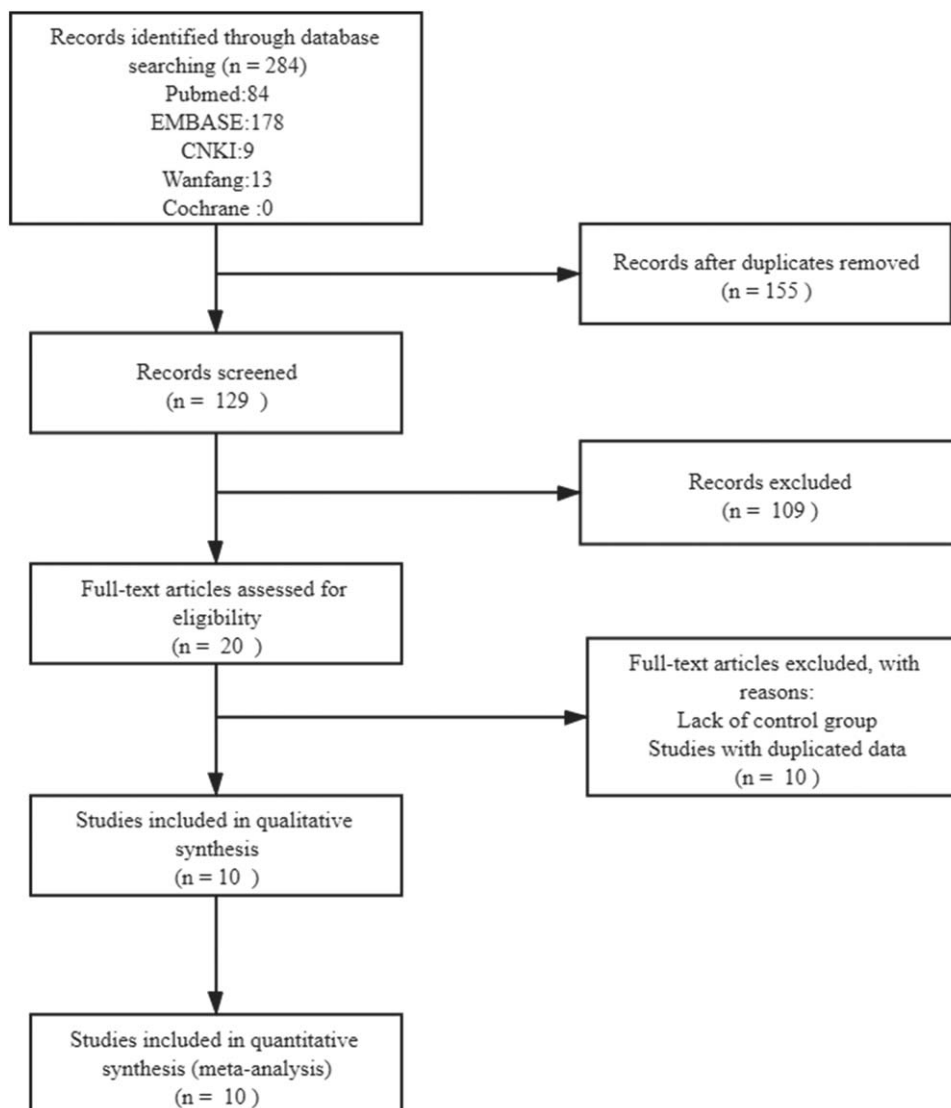


Figure 1. Process of searching for studies. CNKI=China National Knowledge Infrastructure database, Wanfang=Wanfang database.

were subsequently excluded. The remaining 20 studies were read in detail and, using the inclusion criteria and exclusion criteria, 10 articles of literature were excluded. The remaining 10 articles^[13–22] were included in this study for quality evaluation and meta-analysis.

3.2. Characteristics of the studies included

Finally, 10 articles were included, with a total of 683 GPP patients. Seven of the 10 studies were on the Chinese Han population, 1 was from Japan and 2 came from Europe. The earliest was published in 2013, and the latest in 2018. The studies focused on the genotyping method, the number of patients with different subtypes and the main polymorphisms of IL36RN (Table 1).

3.3. Quality assessment of the studies

As mentioned before, a total of 10 articles were included in the quality evaluation. They were evaluated according to

the NOS evaluation scale. The average score for NOS evaluation was 6.3, and the score of each study was greater than 6, indicating that all studies included were of high quality.

3.4. Difference in IL36RN mutation between GPP alone and GPP+ PV

In total, our study involved 683 GPP patients. Extracted from 8 studies, 332 cases of GPP alone and 351 cases of GPP+PV were collected. Among these patients, 171 patients with GPP and 84 patients with GPP+PV were from Europe, and the rest were from Asia. A heterogeneity test was conducted ($I^2=0.0\%$, $P=.448$), where the heterogeneity was found to be acceptable. The pooled statistic $OR=3.82$ (95%CI, 2.63–5.56) was obtained by using the fixed-effect model (Fig. 2). Moreover, no obvious discrepancies were found between European patients ($OR=4.03$ 95% CI, 2.23–7.26) and Asian patients ($OR=3.69$ 95%CI, 2.27–6.00) (Fig. 2).

Table 1
Characteristics of the studies included.

Study (yr)	Country	Ethnicity	Genotyping method	No. of patients				Detected Polymorphism Of IL36RN Mutation
				GPP alone	GPP+PV	Adult GPP	Pediatric GPP	
XiuYan Li (2014)	China	Chinese Han	Sanger Sequence	17	45	16	46	c.115+6T>C;c.140A>G; 169G>A; c.227C>T; c.245C>T
XiaoHua Wang (2017)	China	Chinese	RFLP-PCR	17	24		NA	c.115+6T>C;c.227C>T;c.140A>G; c.28C>T; c.368C>T
ZhongTao Li (2018)	China	Chinese Han	RFLP-PCR	24	19	6	18	c.115+6T>C;c.140A>G; c.227C>T
Wang (2015)	China	Chinese Han	Sanger Sequence	29	54		NA	c.115+6T>C;c.227C>T;c.140A>G;c.334G>A;
Sugiura (2013)	Japan	Japanese	RFLP-PCR	11	20	23	8	c.28C>T;c.115+6T>C
R. Mössner (2018)	Germany	European and Iraq mainly	Sanger Sequence	47	28		NA	c.333>C>T;c.227C>T;.338C>A c.130G>A; c.308G>A
Sophie (2018)	Britain	European	Sanger Sequence	124	56		NA	NA
L Li (2018)	China	Chinese Han	RFLP-PCR	31	76	31	76	c.115+6T>C;c.29G>A;c.140A>G;c.227C>T;c.142C>T;c.233T>C;c.267T>A;c.304C>T
M Li (2013)	China	Chinese	RFLP-PCR		NA	30	38	c.115+6T>C; c.227C>T
Teng Zhu (2018)	China	Chinese Han	RFLP-PCR		NA		NA	c.115+6T>C;c.227C>T

RFLP-PCR=restriction fragment length polymorphism polymerase chain reaction technique.

3.5. IL36RN mutation and age of GPP onset

Extracted from 6 studies,^[13,15,16,18,19,22] the number of adult and paediatric GPP cases were 146 and 83, respectively (patients who were 18 or above at the time of onset of GPP are defined as adult

GPP; those who were less than 18 years old at the time of onset are defined as paediatric GPP^[23]). The heterogeneity test was conducted ($I^2=0.0\%$, $P=.592$), and it was found that the heterogeneity was acceptable. The pooled statistic $OR=0.42$

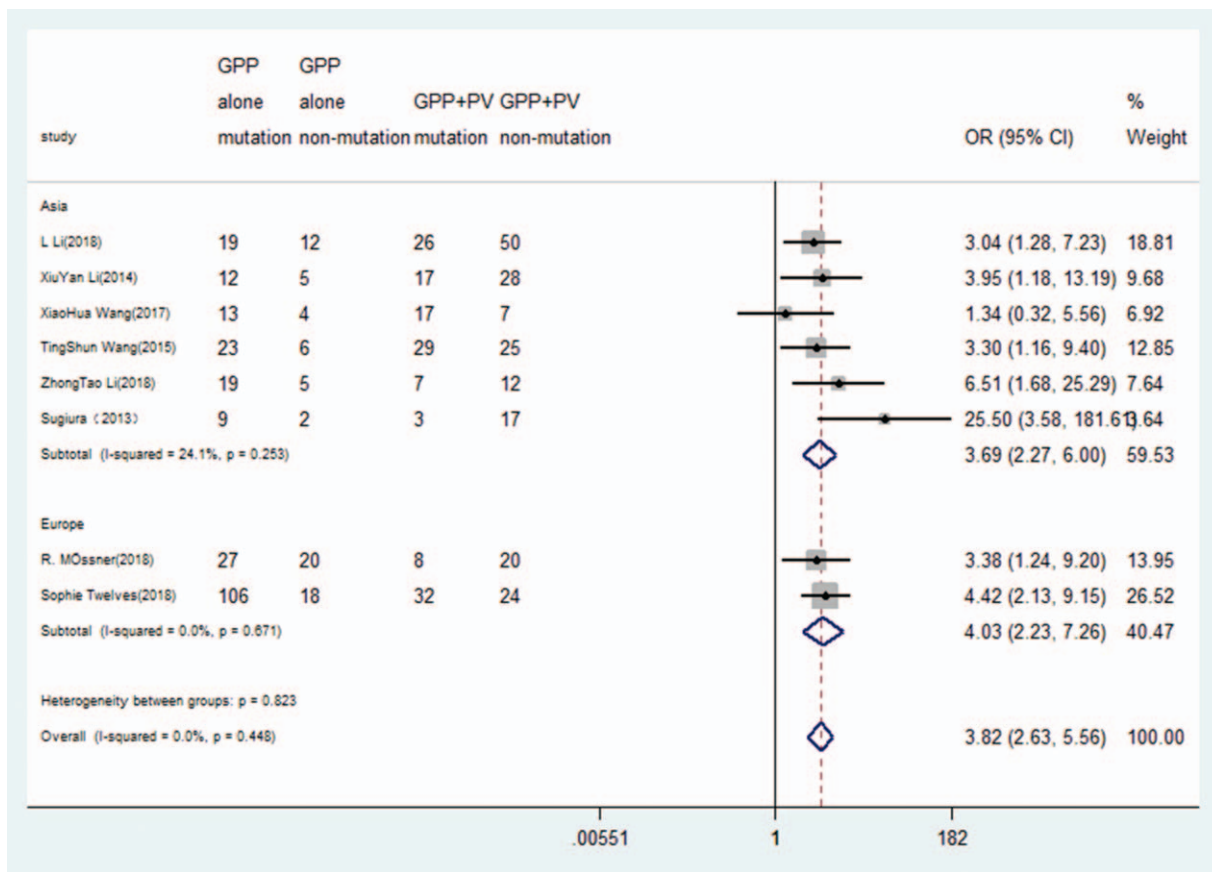


Figure 2. Forest plot of the association between IL36RN mutation and GPP: GPP alone vs GPP+PV. [Footnote]GPP alone=patients with generalized pustular psoriasis without a history of psoriasis vulgaris, GPP + PV=patients with generalized pustular psoriasis with a history of psoriasis vulgaris.

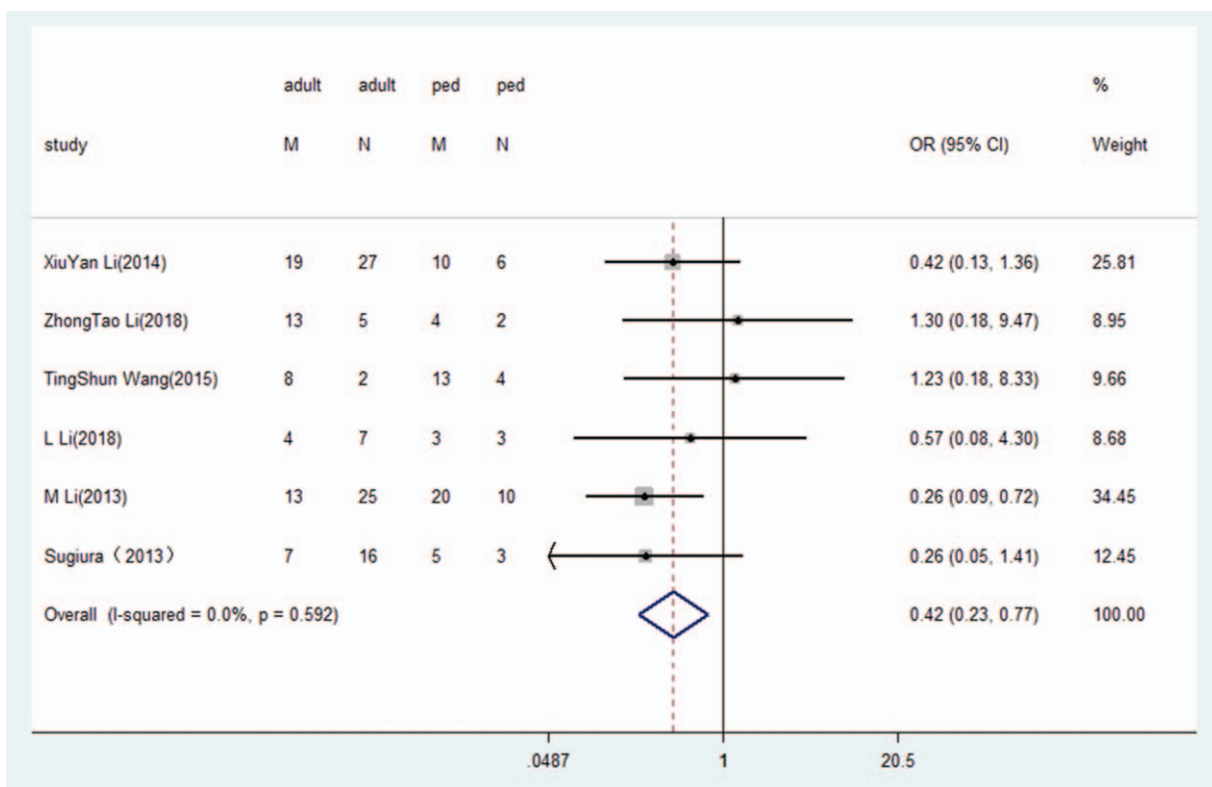


Figure 3. Forest plot of the association between IL36RN mutation and GPP: Adult GPP vs Paediatric GPP. Adult GPP = patients with generalized pustular psoriasis diagnosed when they were 18 years of age or older, Paediatric GPP = patients with generalized pustular psoriasis diagnosed when they were below 18 years of age.

(95% CI, 0.23–0.77) was obtained using the fixed-effect model (Fig. 3).

3.6. Polymorphism c.115+6T>C and GPP

Extracted from 6 studies,^[13,14–18] a total of 393 cases of polymorphism of c.115+6T>C led to IL36RN mutation, including 193 cases of GPP patients and 200 cases of the control group. Five gene models were built: the dominant model (CC+TC vs TT, OR 2.74, 95% CI 2.06–3.64), recessive model (CC vs CT + TT, OR 4.33, 95% CI 2.84–6.60), homozygote model (CC vs TT, OR 4.37, 95% CI 2.88–6.62); heterozygote model (CT vs TT, OR 2.26, 95% CI 1.32–3.85) and allelic model (C vs T, OR 3.35, 95% CI 2.63–4.27). Heterogeneity was calculated for each model and no heterogeneity was found in all 5 models (Table 2). The pooled statistics were obtained using the fixed-effect model (Table 2). However, the control group in 3 of the studies are not in HWE.

3.7. Publication bias

The Egger test was used to assess publication bias in the included studies. No distinct publication bias was found ($P = .833$).

4. Discussion

Although von Zumbusch^[24] reported the first clinical case of GPP in 1910, its etiology still remains unclear. Recent studies have shown that GPP is a disease with a genetic tendency. Blumberg^[25] found that the IL1F6 of mice was directly homologous to human

IL36RN. When the IL1F5 gene of mice was knocked out, pustules occurred on the skin – along with inflammation – in mice, which is similar to skin lesions occurring in humans with GPP.

IL-36 – including IL36 α , IL36 β and IL-36 γ – is 1 of the main members of the interleukin-1 (IL-1) family.^[26,27] The 3 aforementioned cytokines all belong to the interleukin family and play the role of binding to the IL36 receptor antagonist interleukin-1 receptor-like 2 (IL1RL2), which, after binding, can recruit the IL1 receptor coprotein to inhibit the nuclear factor- κ B (NF- κ B) signalling pathway and mitogen-activated protein kinase signalling pathway, effectively inhibiting inflammatory response.^[28] IL36Ra can also bind to the IL36 receptor; however, this binding cannot recruit auxiliary proteins. Therefore, IL 36Ra cannot produce the abovementioned biological activity. IL36Ra can antagonize the activity of IL36 α , β and γ , so the downstream NF- κ B and MAP kinase signalling pathways can be inhibited to avoid aggravating the inflammatory response.^[29]

Marrakchi^[9] found that the occurrence of GPP was related to the homozygous missense mutation (p.Leu27Pro) of IL36RN. Proline replaced leucine at amino acid 27 in this mutation, which changed the IL-36 receptor antagonist (interleukin-36) through homozygous localization and direct sequencing of GPP in 9 Tunisian families. The change in the structure and function of the receptor antagonist of IL-36Ra plays a role in the pathogenesis of GPP. Therefore, when non-functional IL-36Ra does not have an anti-inflammatory effect (such as IL36RN gene mutation), IL-36 loses its ability to increase the production of inflammatory mediators. Therefore, IL-36Ra cannot antagonize the activation of the NF- κ B and mitogen-activated protein kinase signalling pathways, causing an inflammatory response.^[30] The mutation

Table 2
Five gene models of c.115+6T>C polymorphism.

Gene Models	Gene Type	Case	Control	OR	P	95%CI	I ²	P [*]
Dominant	CC + CT vs TT	193	200	2.74	<.01	2.06–3.64	0.0%	.757
Recessive	CC vs CT+ TT	193	200	4.33	<.01	2.84–6.60	0.0%	.653
Homozygote model	CC vs TT	167	174	4.37	<.01	2.88–6.62	0.0%	.685
Heterozygote model	CT vs TT	78	176	2.26	<.01	1.32–3.85	0.0%	.950
Allelic model	C vs T	366	374	3.35	<.01	2.63–4.27	15.6%	.313

P. P value of pooled statistic.

* P. P value of heterogeneity chi-square.

of the IL36RN gene can lead to IL36Ra deficiency – also referred to as deficiency of interleukin 36 receptor antagonist (DITRA) – aggravating the inflammatory response of patients and triggering GPP. After Marrakchi, a series of studies was conducted to verify the association between IL36RN mutation and GPP. Sugiura^[31] reported the first case of GPP patients with IL36RN mutations in Asian populations in 2012. To date, IL36RN mutation has been verified as an essential factor in the pathogenesis of GPP.

However, more in-depth research into the association between IL36RN mutation and the subtypes of GPP is still required. In terms of the presence of lesions, GPP was thought to be divided into GPP alone (patients without PV) and patients with GPP with existing or prior PV. Given this information, Sugiura et al^[31] compared and analysed the gene mutation frequency of IL36RN; they found that most GPP-alone patients carry the IL36RN gene mutation, and that the mutation rate is significantly higher than that found in GPP + PV patients. As a result, Sugiura suggested that patients with GPP alone and the GPP + PV have genetic heterogeneity, and he proposed a viewpoint that the single-type GPP is an independent inflammatory disease that differs from psoriasis. In our study, we pooled statistics of patients with GPP alone and GPP + PV separately. A meta-analysis of the pooled statistics had the same outcome as that found by Sugiura, suggesting that GPP alone may be a different disease than psoriasis with pustular dermatitis.

In addition, in our study, we extracted data from 10 studies, where GPP patients were separated into adult GPP and paediatric GPP groups according to the age of onset of GPP. The results show that the mutation rate of IL36RN in paediatric GPP was significantly higher than that in adult GPP, similar to the findings of Li et al.^[22] This indicates that the expression of IL36RN mutation may present differently at various ages. Research should be conducted in the future to assess the early prognosis of GPP emergence in infants who carry the IL36RN mutation.

On the other hand, several scholars have proposed that the mutant genotype of the IL36RN gene is associated with the severity of the clinical manifestation phenotype of GPP.^[32–34] Hussain et al^[32] analysed the relationship between the clinical phenotype and IL36RN genotype in 233 GPP patients in 2015, confirming the above 2 conclusions. In addition, it was found that GPP patients with IL36RN gene mutation had more serious conditions and were more prone to systemic inflammation than GPP patients without IL36RN gene mutations.

Moreover, according to recent research, more than 20 polymorphisms of IL36RN exist in GPP patients, such as c.80T>C (p.Leu27Pro), c.338C>T (p.Ser113Leu) and c.115+6T>C (p.Arg10ArgfsX1).^[3,30,36,37,38] Among them, c.115+6T>C is most often present in Asian populations.^[13,16–18] Located beyond the critical 2 bp of the splice junction, the c.115+6T>C mutation caused skipping of exon 3, resulting in a

frameshift with premature transcription termination, leading the emergence of insufficient IL36Ra.^[35] To verify the association between c.115+6T>C and GPP, 6 studies were selected to build 5 commonly used gene models. Given this data, it can be concluded that all 5 gene models exhibited statistical differences between GPP alone and GPP+PV. Further, the polymorphism c.115+6T>C is related to the susceptibility of GPP-alone patients. Wang et al^[17] also found that c.227C>T variants are always present, accompanying the c.115+6T>C. In our meta-analysis, the homozygote model is stronger in correlation than the heterozygote model, which may indicate that some mutations had negative regulation, helping refine the IL36RN mutation.

Although this study combines existing studies on the relationship between IL36RN and GPP susceptibility, it has a few limitations. First, the number of studies included and the total number of cases are few, which affects the applicability of the results to the general population. Second, the included studies mostly focus on the Chinese Han population, so the results are more suitable for Asians. Third, in the gene models, the control group in 3 studies did not conform to HWE, which affects the reliability of the results.

5. Conclusion

Existing studies have shown that there is a significant correlation between IL36RN gene mutation and the different subtypes of GPP. IL36RN mutation is strongly associated with GPP without PV and the early onset of GPP. Therefore, GPP may be a different inflammatory disease, independent of psoriasis. Further, polymorphism c.115+6T>C of IL36RN plays a significant role in the pathogenesis of GPP, especially in homozygous mutation. To verify the findings of this study, large sample, multi-centre, multi-area and multi-ethnicity research is needed.

Author contributions

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