

Genetic variations in the *ST18* gene and their association with pemphigus vulgaris in Vietnamese patients: insights from a case series

Thi Xuan Tam Huynh, Long Phan Son

Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam

Abstract

This study explores the single nucleotide polymorphism (SNP) variants rs2304365 and rs4074067 in the *ST18* gene and their relationship with clinical manifestations of pemphigus vulgaris (PV) in Vietnamese patients. A case series was conducted with PV patients treated from March to October 2023 at the Ho

Chi Minh City Hospital of Dermato-Venereology (Vietnam). Clinical data and patient histories were documented. Blood samples (2 mL) were analyzed for SNP variants rs2304365 and rs4074067 using Sanger sequencing at the Biomedical Research Center, Pham Ngoc Thach University of Medicine. Among 34 patients, two alleles, C and T, were identified in both SNPs. For rs2304365, allele C accounted for 91.2% and T for 8.8%. In rs4074067, allele C constituted 88.2% and T 11.8%. Patients carrying the T allele in rs2304365 exhibited moderate to severe disease. Additionally, the T allele in either SNP was associated with higher Pemphigus Disease Area Index (PDAI) scores compared to the C allele. SNP variants rs2304365 and rs4074067 in the *ST18* gene may influence disease severity in PV among Vietnamese patients, underscoring the need for further research into their role in personalized treatment strategies.

Correspondence: Thi Xuan Tam Huynh, MD, PhD, Pham Ngoc Thach University of Medicine, No. 2, Duong Quang Trung Str., District 10, Ho Chi Minh City, Vietnam.
E-mail: tamhtx@pnt.edu.vn

Key words: pemphigus vulgaris; rs2304365; rs4074067; *ST18*; single nucleotide polymorphism.

Contributions: TXTH, conceptualization, manuscript writing, and revision; LPS, conceptualization, data collection and analysis. All authors read and approved the final version of the manuscript.

Conflict of interest: the authors have no conflict of interest to declare.

Ethics approval and consent to participate: the study was approved by the Ethics Committee of Pham Ngoc Thach University of Medicine (approval No: 742/TĐHYKPNT-HĐĐĐ, 15 November, 2022). Informed consent was obtained from all participants included in the study.

Consent for publication: not applicable.

Availability of data and materials: due to privacy and ethical concerns, neither the data nor its source can be made available.

Acknowledgments: we thank all the patients for their participation in the study.

Received: 18 January 2025.

Accepted: 11 April 2025.

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

©Copyright: the Author(s), 2025

Licensee PAGEPress, Italy

Dermatology Reports 2025; 17:10265

doi:10.4081/dr.2025.10265

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Introduction

Pemphigus vulgaris (PV) is a rare, potentially life-threatening autoimmune disorder characterized by blistering lesions on the skin and mucous membranes.¹ Extensive epidemiological and candidate gene studies focusing on the major histocompatibility complex (MHC) region have identified genetic susceptibility as a critical factor in the pathogenesis of PV.² Recent research has highlighted the role of *ST18* gene polymorphisms in apoptosis and inflammation, key processes implicated in PV pathogenesis.³ Variants in the *ST18* gene have been associated with an increased risk of PV in specific populations, such as Iranians,⁴ Egyptians, and Jews,⁵ but no similar associations have been observed in Chinese⁶ or German populations.⁵ Because the *ST18* gene exhibits population-specific characteristics and there is currently no genetic data on this gene in Vietnamese patients with PV, this study aims to investigate two single nucleotide polymorphisms (SNPs), rs2304365 and rs4074067, within the *ST18* gene and assess their potential association with clinical features of PV in a Vietnamese cohort.

Materials and Methods

Patient recruitment

This study was conducted between March 2023 and October 2023 at the Department of Dermatology and Venereology, Ho Chi Minh City Hospital, Vietnam. Ethical approval was granted by the Pham Ngoc Thach University of Medicine Ethics Committee. Patients were included if they met the pemphigus diagnostic criteria of the Japanese Dermatological Association (JAD) and were ≥18 years old. Exclusion criteria included non-Vietnamese ancestry (up to three generations; the patients were asked to provide their family history to determine whether their ancestors were of Vietnamese origin), disorders affecting healing mechanisms (e.g., coagulation or bleeding disorders, uncontrolled diabetes, or

HIV/AIDS), prior or ongoing use of immunosuppressants during the active phase of pemphigus, or blood/DNA samples failing to meet the Biomedical Research Center's quality standards.

Patients received detailed counseling about the study's benefits and risks and provided written informed consent before participating. A total of 34 patients were included based on clinical manifestations, histological findings, and direct immunofluorescence results. None of the patients had received prior treatment. Disease severity was assessed using the Pemphigus Disease Activity Index (PDAI)⁷ and categorized as mild (PDAI score ≤ 15), moderate ($15 < \text{PDAI score} \leq 45$), or severe (PDAI score > 45). Glucocorticoid response was evaluated by assessing disease control (defined as no new lesions and 80% healing of existing lesions) achieved solely with glucocorticoids during treatment. Patients requiring additional immunomodulatory therapy were classified as non-responders.

ST18 SNP genotyping

Venous blood samples (2 mL) were collected into tubes coated with Ethylenediaminetetraacetic acid (EDTA) (Medisafe, Vietnam) for subsequent DNA extraction. The silica membrane (spin column) method (Wizard[®] Genomic DNA Purification Kit, A1120, Promega) was employed to isolate DNA from blood samples. This is a widely used technique for nucleic acid purification, relying on the selective binding of DNA or RNA to a silica membrane in high-salt conditions. This method offers a fast, efficient, and reliable way to isolate pure nucleic acids for downstream applications such as PCR, sequencing, and cloning. The SNP variants rs2304365 and rs4074067 in the *ST18* gene were analyzed using Sanger sequencing with the primer set shown in Table 1.

Table 1. The primer set and location of SNPs.

SNP	Location	Sequence (5'-3')
rs2304365	Chr8:52217653 (GRCh38.p14)	primer: TTCGTCATGTTACTCCTTC
rs4074067	Chr8:52224769 (GRCh38.p14)	primer: TTGTA AAAAGCGAAGGGGCT

SNP, single nucleotide polymorphism.

Table 2. Distribution of SNP rs2304365 genotype, allele types with clinical characteristics of PV.

rs2304365 Features (n, %)	Genotypes (n=34)			p*	Allele types (n=68)		p*
	CC (n=29)	CT (n=4)	TT (n=1)		C (n=62)	T (n=6)	
Pain							
Yes	25 (86.2)	3 (75)	1 (100)	0.573	53 (85.5)	5 (83.3)	1
No	4 (13.8)	1 (25)	0		9 (14.5)	1 (16.7)	
Itchy							
Yes	9 (31)	1 (25)	0	0.510	19 (30.6)	3 (50)	0.380
No	20 (69)	3 (75)	1 (100)		43 (69.4)	3 (50)	
Bullous types							
Flaccid	26 (89.7)	3 (75)	1 (100)	0.488	55 (88.7)	5 (83.3)	0.543
Tense	3 (10.3)	1 (25)	0		7 (11.3)	1 (16.7)	
Mucosal involvement							
Yes	25 (86.2)	4 (100)	1 (100)	1	54 (87.1)	6 (100)	1
No	4 (13.8)	0	0		8 (12.9)	0	
Nikolsky sign							
Positive	16 (55.2)	4 (100)	1 (100)	0.188	36 (61.3)	6 (100)	0.075
Negative	13 (44.8)	0	0		26 (38.7)	0	

*Fisher's exact test.

Results

Characteristics of the subjects

A total of 34 PV patients who met the study criteria were included, with a mean age of 48.9 ± 13.9 years. Among them, 10 (29.4%) were male, and 24 (70.6%) were female. The average PDAI score was 30.5 ± 27 , with severity levels classified as mild (6 patients, 17.6%), moderate (20 patients, 58.8%), and severe (8 patients, 23.5%).

Frequencies of ST18 SNPs

The SNP rs2304365 displayed two types of alleles and three genotypes, while SNP rs4074067 exhibited two types of alleles but only two genotypes. For SNP rs2304365, the CC homozygous genotype was the most common (85.3%), while the TT homozygous genotype was the least frequent (2.9%). The frequency of the C allele was approximately 10 times higher than that of the T allele (91.2% and 8.8%, respectively). For SNP rs4074067, the CC genotype was the most prevalent (76.5%), and the TT genotype was not observed in the study population (0%).

Correlation between ST18 SNPs and disease triggers

We examined the correlation between *ST18* SNPs and disease triggers, including medications, food, trauma, and idiopathic causes. For SNP rs2304365, individuals carrying the T allele had a significantly higher risk of trauma-induced disease onset compared to those carrying the C allele ($p=0.007$, odds ratio [OR]=19.7, 95% confidence interval [CI]: 2.7-141.9). No other statistically significant correlations were identified.

Association between *ST18* SNPs and clinical manifestations

We analyzed genotypes and allele groups in relation to clinical manifestations of PV, such as pain, itching, bullous features, mucosal involvement, and Nikolsky sign. These results are detailed in Tables 2 and 3. No statistically significant differences were found between the genotypes or alleles of SNP rs2304365 and the clinical symptoms of PV. However, for SNP rs4074067, patients with the CT genotype showed a higher prevalence of a positive Nikolsky sign compared to those with the CC genotype ($p=0.013$, OR=1.6, 95% CI: 1.2-2.3). Similarly, patients carrying the T allele had a higher likelihood of a positive Nikolsky sign compared to those carrying the C allele ($p=0.02$, OR=1.2, 95% CI: 1.1-1.4).

Association between *ST18* SNPs and disease severity

The association between the SNPs rs2304365 and rs4074067 with disease severity was assessed using PDAI scores (Figure 1) and severity classifications (Table 4). For SNP rs2304365, patients carrying the T allele had significantly higher PDAI scores compared to those with the C allele ($p=0.015$; Figure 1B). Additionally, patients with the CC genotype had lower PDAI scores than those with the combined CT and TT genotypes ($p=0.036$; Figure 1C). For SNP rs4074067, no significant differences were observed.

Correlation between *ST18* SNPs and treatment response

We noted that patients carrying the risk allele T in SNP rs4074067 had a lower glucocorticoid response rate compared to

those carrying the C allele (50% vs. 66.7%), although this difference was not statistically significant ($p>0.05$, Fisher's exact test). For SNP rs2304365, patients with the heterozygous or homozygous T genotypes (CT and TT) and those carrying the T allele required higher doses of glucocorticoids compared to individuals with the C allele. However, this difference also lacked statistical significance ($p>0.05$, Mann-Whitney U test).

Discussion

Frequencies of *ST18* SNPs

SNP rs2304365

Our analysis identified two alleles for SNP rs2304365: the common allele C (91.2%) and the rare allele T (8.8%). These findings contrast sharply with those reported in larger Middle Eastern and European populations. For example, Etesami *et al.*⁸ observed A (rare allele) and G (common allele) in an Iranian population, with frequencies of 18.6% and 81.4%, respectively. Similarly, Sarig *et al.*⁹ identified A and G alleles in Jewish, Egyptian, and German populations, with frequencies of 22.9% and 77.1%, respectively. However, our findings are consistent with those of Yue *et al.*,⁴ who analyzed a Chinese population and reported alleles C and T with similar frequencies (91.6% and 8.4%, respectively). Comparing our results to the NCBI dataset¹⁰ for SNP rs2304365, the rare T allele frequency in our study (8.8%) is lower than the global average (20%) and averages for Europe (19%), Africa (35%), and Latin America (23%), but slightly higher than the Asian average (7.1%). Interestingly, the 1000 Genomes Project¹¹ reported a higher frequency of the T allele (18.2%)

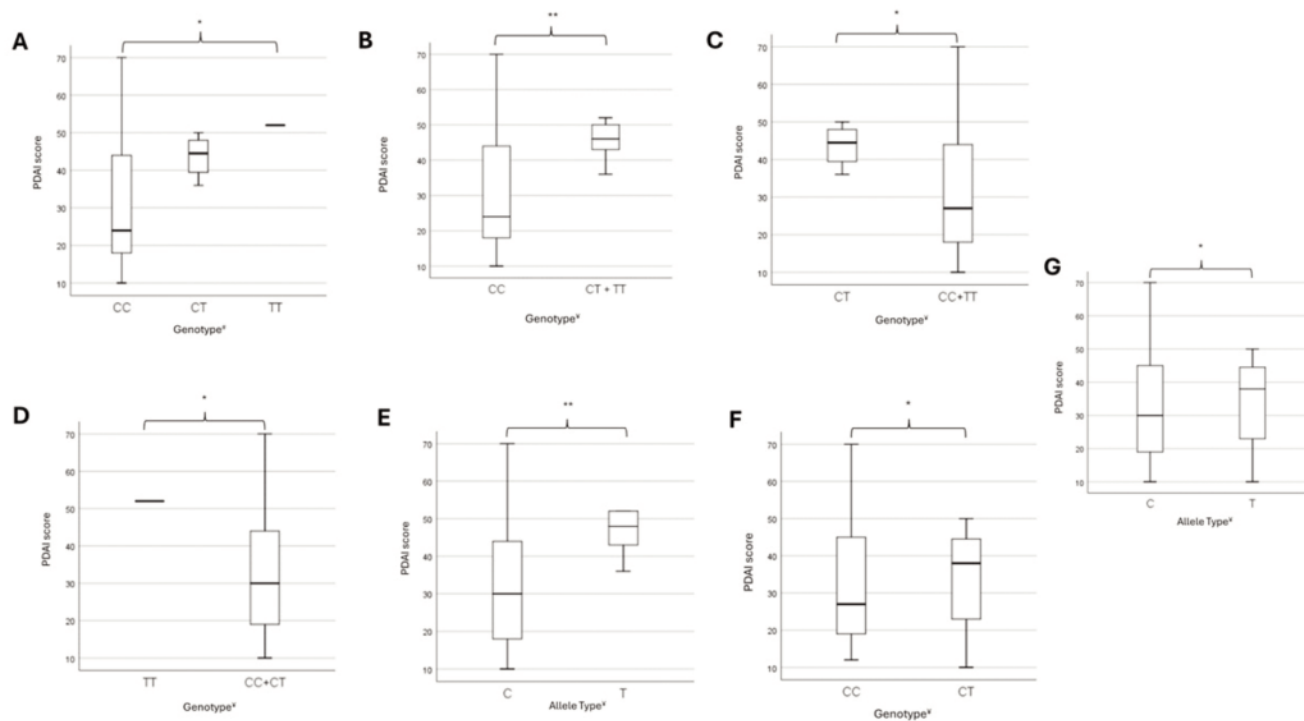


Figure 1. SNP rs2304365 (A-E) and rs4074067 (F-G) correlation with PDAI scores. * $p < 0.05$; ** $p < 0.005$; #Kruskal-Wallis H test; §Mann-Whitney U test.

among healthy Vietnamese individuals of Kinh ethnicity compared to our study on PV patients. This discrepancy might be due to differences in the study populations, as the 1000 Genomes Project focused on healthy individuals, while our study involved PV patients. This raises the research question of whether there is a genuine difference in T allele frequency between healthy individuals and PV patients. Future case-control studies can help address this question.

Regarding genotype distribution, three genotypes were observed: CC (85.3%), CT (11.8%), and TT (2.9%), with CC being the most prevalent. These findings align with those of Yue *et al.*,¹² who reported similar distributions in a Chinese population. In contrast, studies by Sarig *et al.*⁹ and Etesami *et al.*⁸ in Middle Eastern and European populations identified three different genotypes (AA, AG, and GG), with a higher frequency of the rare homozygous genotype in Middle Eastern populations (6.8%) compared to our study (2.9%).

The 1000 Genomes Project¹¹ data for healthy Kinh individuals reported a rare homozygous genotype (TT) frequency similar to ours (3% vs. 2.9%) but showed a lower frequency for the common homozygous genotype (CC: 66.7% vs. 85.3%) and a higher frequency for the heterozygous genotype (CT: 30% vs. 11.8%). Compared to East Asian populations such as Japan and China,¹¹ our results are more consistent with their findings (CC: 81%, CT: 17.7%, TT: 1.4%), suggesting a closer genetic similarity among populations within this region.

SNP rs4074067

For SNP rs4074067, we identified two alleles, C and T, with the C allele being 7.5 times more frequent than the T allele (88.2% vs. 11.8%). These findings differ from those in Middle Eastern populations. For instance, Etesami *et al.*⁸ and Sarig *et al.*⁹ reported A and G alleles instead of C and T. Additionally, the rare allele frequency in Middle Eastern populations (22.7%) was higher than in our study (11.8%). It is noteworthy that no East Asian studies have yet reported allele frequencies for SNP rs4074067 in PV patients. However, research on healthy Kinh individuals in Vietnam recorded a higher rare allele frequency (T: 16%) compared to our find-

ings.¹¹ The global average frequency of the T allele, as reported in the NCBI dataset,¹⁰ is also higher (20%) than in our study, suggesting a potential difference between PV patients and healthy individuals. Larger case-control studies are needed to confirm this association.

In terms of genotype distribution, two genotypes were observed in our study: CC (76.5%) and CT (23.5%). Notably, no individuals with the TT genotype were identified. Studies in Middle Eastern populations by Etesami *et al.*⁸ reported three genotypes (AA, AG, and GG) with frequencies of 5.5%, 34.5%, and 60%, respectively, differing both in genotype type and frequency from our findings.

Our results align more closely with data from the 1000 Genomes Project¹¹ for healthy Vietnamese individuals, which also reported only CC and CT genotypes but with different proportions (67.7% CC and 32.3% CT). Similarly, the Chinese Han population¹¹ displayed the same genotypes (CC and CT) but with slightly different frequencies (87.6% and 12.4%, respectively). Notably, the TT genotype was absent in both Vietnamese and Chinese populations, which is consistent with our study. Globally, the frequency of the CC genotype in our study (76.5%) was significantly higher than the global average (38.3%), while the CT genotype frequency was lower (23.5% vs. 46.9%). These differences highlight genetic diversity across populations, with our findings more closely resembling East Asian populations and differing from other regions. The observed differences in allele and genotype frequencies for SNPs rs2304365 and rs4074067 between PV patients and healthy individuals raise intriguing questions. These findings suggest potential genetic markers for PV in East Asian populations and highlight the need for further investigation into the roles of these SNPs in disease susceptibility and progression. Future studies should include larger and more diverse populations to validate these results and explore their clinical implications. Case-control studies are particularly necessary to assess whether the rare alleles or genotypes are associated with increased PV risk. Additionally, the absence of the TT genotype in East Asian populations may reflect unique genetic or biological factors that warrant further exploration.

Table 3. Distribution of SNP rs4074067 genotype, allele types with clinical characteristics of PV.

rs4074067 Features (n, %)	Genotypes (n=34)			p*	Allele types (n=68)		p*
	CC (n=26)	CT (n=8)	TT (n=1)		C (n=60)	T (n=8)	
Pain							
Yes	22 (84.6)	7 (87.5)	1		44 (84.6)	14 (87.5)	1
No	4 (15.4)	1 (12.5)			8 (15.4)	2 (12.5)	
Itchy							
Yes	5 (19.2)	1 (12.5)	1		10 (30.6)	2 (12.5)	0.380
No	21 (80.8)	7 (87.5)			42 (69.4)	14 (87.5)	
Bullous types							
Flaccid	23 (88.5)	7 (87.5)	1		53 (88.3)	7 (87.5)	1
Tense	3 (11.5)	1 (12.5)			7 (11.7)	1 (12.5)	
Mucosal involvement							
Yes	22 (84.6)	8 (100)	1		52 (86.7)	8 (100)	0.582
No	4 (15.4)	0			8 (13.3)	0	
Nikolsky sign							
Positive	13 (50)	8 (100)	0.013		34 (61.3)	8 (100)	0.020
Negative	13 (50)	0			26 (38.7)	0	

*Fisher's exact test

Association between two SNPs and pemphigus vulgaris triggers

Our study identified a significant association between the alleles (C, T) of SNP rs2304365 and trauma-induced PV. Individuals carrying the T allele of SNP rs2304365 had a 19.6-fold higher likelihood of developing trauma-induced PV compared to those with the C allele. The mechanism of trauma-induced PV remains poorly understood. Daneshpazhooch *et al.*¹³ hypothesized that trauma exposes intercellular adhesion molecules, particularly desmogleins, in the epidermis, which triggers two sequential inflammatory phases. In the first phase, non-specific inflammation occurs, where immune cells such as neutrophils and monocytes release pro-inflammatory cytokines, including IL-1, IL-6, and TNF- α . In the second phase, a specific immune response develops, characterized by antigen presentation and the activation of B and T lymphocytes, resulting in the production of autoantibodies against desmoglein 1 and/or desmoglein 3. These autoantibodies cause clinical manifestations of PV. However, this hypothesis leaves critical questions unanswered, such as why some PV patients with trauma do not experience disease onset or why healthy individuals do not develop PV despite desmoglein exposure following trauma.

Our findings offer insights into these questions. First, Vodo *et al.*¹⁴ demonstrated that individuals with abnormalities in the *ST18* gene exhibit significantly heightened inflammatory responses *in vitro*, with notable increases in IL-1, IL-6, and TNF- α levels ($p < 0.001$). This excessive inflammation likely enhances the activation of B and T lymphocytes, leading to increased production of circulating anti-desmoglein (anti-Dsg) autoantibodies. Combining this evidence with Daneshpazhooch *et al.*'s trauma-related inflammation hypothesis,¹³ we propose that individuals with *ST18* gene abnormalities may produce higher levels of circulating anti-Dsg autoantibodies following trauma, predisposing them to PV onset. Second, Vodo *et al.*¹⁴ also found that desmogleins in individuals with *ST18* gene abnormalities are more sensitive to anti-Dsg autoantibodies. Specifically, epidermal samples from individuals with these abnormalities exhibited a twofold increase in acantholysis compared to samples from individuals without abnormalities when exposed to equivalent levels of anti-Dsg antibodies ($p < 0.05$). This suggests that individuals carrying the T allele of SNP rs2304365 are not only more likely to produce higher levels of anti-Dsg antibodies but also exhibit heightened sensitivity to

these autoantibodies, resulting in more severe acantholysis and PV manifestation, even when anti-Dsg levels are relatively low.

In conclusion, trauma-induced PV onset appears to result from two interrelated mechanisms: i) elevated levels of circulating anti-Dsg antibodies driven by excessive inflammatory responses, and ii) increased sensitivity of desmogleins to these autoantibodies. Both mechanisms are likely attributable to abnormalities in the *ST18* gene, particularly the T allele of SNP rs2304365. These findings suggest that individuals with *ST18* gene abnormalities are at higher risk of developing PV following trauma than those with normal *ST18* expression. However, larger-scale studies are needed to validate this hypothesis.

Association of two *ST18* SNPs with pemphigus vulgaris clinical features

The Nikolsky sign is an important clinical indicator used to assess epidermal acantholysis in PV patients and monitor treatment responses. Our study identified a higher prevalence of positive Nikolsky signs in individuals with the CT genotype of SNP rs4074067 and those with the T allele. According to the literature, there are two types of Nikolsky signs: direct (performed on clinically unaffected skin) and indirect (performed at the periphery of blisters). Furthermore, Nikolsky signs can be classified as macroscopic (visible to the naked eye) or microscopic (observable only under a microscope).¹⁵ Thus, not all PV patients exhibit a macroscopic Nikolsky sign, although microscopic Nikolsky signs may be present. *In vitro* studies have shown that abnormalities in the *ST18* gene significantly increase acantholysis by twofold compared to non-mutated controls.¹⁴ This may explain the more pronounced macroscopic Nikolsky signs observed in our study among individuals carrying the T allele of SNP rs4074067. Moreover, Lopez-Robles *et al.*¹⁶ found elevated levels of pro-inflammatory cytokines (IL-6 and TNF- α) in PV blisters, while these levels remained normal in unaffected skin, suggesting that acantholysis may also be influenced by heightened inflammatory cytokines. These cytokines are more pronounced in individuals with *ST18* gene abnormalities. Our findings provide a novel perspective on the clinical variability of PV patients and mark a significant step forward in understanding the molecular mechanisms underlying these differences. Nevertheless, larger studies are required to confirm these results and further elucidate the complex interactions between genetic abnormalities and clinical manifestations of PV.

Table 4. Relationship between two SNPs of *ST18* gene and PV severity classification.

rs2304365 Severity	Genotypes (n=34)			p*	Allele types (n=68)		p*
	CC (n=29)	CT (n=4)	TT (n=1)		C (n=62)	T (n=6)	
Mild	6 (20.7)	0	0	0.191	12 (19.4)	0	0.042 ^a
Moderate	18 (61.1)	2 (50)	0		38 (61.3)	2 (33.3)	0.581 ^b
Severe	5 (17.2)	2 (50)	1 (100)		12 (19.4)	4 (66.7)	0.024 ^c

rs4074067 Severity	Genotypes (n=34)		p*	Allele types (n=68)		p*
	CC (n=26)	CT (n=8)		C (n=60)	T (n=8)	
Mild	4 (15.4)	2 (25)	0.875	10 (16.7)	2 (25)	0.772
Moderate	16 (61.5)	4 (50)		36 (60)	4 (50)	
Severe	6 (23.1)	2 (25)		14 (23.3)	2 (25)	

*Fisher's exact test; ^acomparison between mild group, moderate group, and severe group; ^bcomparison between mild group and moderate-severe group; ^ccomparison between mild-moderate group and severe group.

Association between *ST18* SNPs and Pemphigus Disease Activity Index, disease severity, and treatment response

Correlation with PDAI

Global studies examining the relationship between SNPs and PDAI scores are limited. The *ST18* gene has been shown to increase acantholysis and pro-inflammatory cytokines, which could influence PDAI scores in individuals carrying risk alleles or genotypes.¹⁴ In our study, individuals with the T allele of SNP rs2304365 had significantly higher PDAI scores compared to those with the C allele ($p=0.015$). Similarly, individuals with the CT or TT genotypes exhibited higher PDAI scores than those with the CC genotype ($p=0.036$).

Based on these findings, we concluded that individuals carrying the T allele are associated with higher PDAI scores compared to non-carriers, and the genetic phenotype of SNP rs2304365 demonstrates a dominant influence on PDAI. Similarly, Etesami *et al.*⁸ reported an increased PDAI score in carriers of the rare A allele ($p=0.019$), although their findings differed in terms of allele type. Conversely, Yue *et al.*¹² did not find any correlation between *ST18* SNPs and PDAI in the Chinese population, while Zhang *et al.*¹⁷ also reported no association between *ST18* SNPs and PV in East Asian populations. Zhang hypothesized that the A risk allele found in Middle Eastern populations may be absent in East Asians.

Although our study did not identify the Middle Eastern A risk allele, the observed PDAI differences between groups suggest that the T allele of SNP rs2304365 may still act as a risk allele in East Asian populations. Larger and more robust studies are needed to confirm the role of the T allele in PV pathogenesis within these populations.

Association with disease severity

Abnormalities in the *ST18* gene disrupt apoptosis and inflammation regulation, as evidenced by increased pro-inflammatory cytokines and heightened keratinocyte apoptosis when exposed to anti-Dsg antibodies.¹⁴ This suggests that individuals carrying risk alleles or genotypes may experience more severe disease. Our results supported this hypothesis, demonstrating a statistically significant association between the T allele of SNP rs2304365 and PV severity ($p=0.042$). Specifically, individuals with the T allele had an 8.3-fold higher risk of severe PV compared to those with the C allele ($p=0.024$, OR=8.3, 95% CI: 1.4-50.9). Etesami *et al.*⁸ also found that carriers of the rare A allele had a higher likelihood of severe PV than those with the common G allele ($p<0.05$). Further supporting evidence comes from Assaf *et al.* (2022),¹⁸ who proposed the “p53-dependent self-amplifying loop” hypothesis, suggesting that *ST18* abnormalities create a pathological cycle, reducing desmoglein expression and exacerbating PV severity. Our clinical findings align with these *in vitro* studies, providing additional evidence for the role of *ST18* abnormalities in PV severity.

Association with treatment response

Glucocorticoid resistance in PV has been reported in several studies worldwide.¹⁹ Chriguier *et al.*²⁰ identified three possible mechanisms of GC resistance in PV patients: i) excessive pro-inflammatory cytokine production (IL-1, IL-6, TNF- α); ii) impaired GC-receptor binding; and iii) reduced GC receptor expression, all of which hinder GC's anti-inflammatory and immunomodulatory effects. We hypothesized that *ST18* abnormalities, which increase pro-inflammatory cytokine levels, might con-

tribute to GC resistance in PV. Although our findings indicated a lower response rate to GC monotherapy among T allele carriers of SNP rs4074067 compared to C allele carriers (50% vs. 66.7%), the difference was not statistically significant ($p>0.05$). This may be due to the limited sample size in our study.

Systemic GC therapy remains a cost-effective treatment for PV.²¹ However, high-dose GC therapy poses significant challenges due to its adverse effects.²² In SNP rs2304365, individuals with CT or TT genotypes and T allele carriers required higher GC doses compared to C allele carriers, although the difference was not statistically significant. This suggests that the T allele of SNP rs2304365 might be a risk allele associated with increased GC dosage requirements in PV patients. While SNPs such as rs17209237 and rs11745958 of the NR3C1 gene have been linked to lower GC dosage requirements for PV treatment,^{19,23} there is limited data on the *ST18* gene. Given that *ST18* abnormalities contribute to increased inflammation and acantholysis, higher GC doses may be necessary to address both pathophysiological mechanisms. However, our study's small sample size may have limited our ability to detect significant differences.

Conclusions

Our findings highlight the critical role of *ST18* gene abnormalities, particularly SNP rs2304365, in influencing disease activity, severity, and treatment responses in PV. However, one notable limitation of our study is the small sample size, with only 34 patients included. This limited sample may reduce the statistical power of our analysis and restrict the generalizability of our findings to larger populations. While the T allele appears to be a potential risk allele in East Asian populations, larger studies with improved designs are essential to validate its role in PV pathogenesis and clinical management. Future research should focus on elucidating the molecular mechanisms underlying *ST18*-related PV and exploring targeted therapies to optimize treatment outcomes.

References

- Alshami ML, Aswad F, Abdullah B. A clinical and demographic analysis of oral pemphigus vulgaris: A retrospective cross-sectional study from 2001 to 2021. *Health Sci Rep* 2022;5:e832.
- Vodo D, Sarig O, Sprecher E. The Genetics of Pemphigus Vulgaris. *Front Med (Lausanne)* 2018;5:226.
- Hashimoto T. Pathogenic role of ST18 in pemphigus vulgaris. *Br J Dermatol* 2021;184:1001-2.
- Etesami I, Seirafi H, Ghandi N, et al. The association between ST18 gene polymorphism and severe pemphigus disease among Iranian population. *Exp Dermatol* 2018;27:1395-8.
- Sarig O, Bercovici S, Zoller L, et al. Population-specific association between a polymorphic variant in ST18, encoding a pro-apoptotic molecule, and pemphigus vulgaris. *J Invest Dermatol* 2012;132:1798-805.
- Yue Z, Fu X, Chen M, et al. Lack of association between the single nucleotide polymorphism of ST18 and pemphigus in Chinese population. *J Dermatol* 2014;41:353-4.
- Rahbar Z, Daneshpazhooh M, Mirshams-Shahshahani M, et al. Pemphigus disease activity measurements: pemphigus disease area index, autoimmune bullous skin disorder intensity score, and pemphigus vulgaris activity score. *JAMA Dermatol*

- 2014;150:266-72.
8. Etesami I, Seirafi H, Ghandi N, et al. The association between ST 18 gene polymorphism and severe pemphigus disease among Iranian population. *Exp Dermatol* 2018;27:1395-8.
 9. Sarig O, Bercovici S, Zoller L, et al. Population-specific association between a polymorphic variant in ST18, encoding a pro-apoptotic molecule, and pemphigus vulgaris. *J Invest Dermatol* 2012;132:1798-805.
 10. National Center for Biotechnology Information. Single Nucleotide Polymorphism rs4074067.
 11. Ensembl. Population frequencies & genotypes: allele-frequency data from the 1000 Genomes Project (Phase 3). Available from: <https://www.ensembl.org/info/genome/variation/species/populations.html>
 12. Yue Z, Chen M, Wang Z, et al. Lack of association between the single nucleotide polymorphism of ST18 and pemphigus in Chinese population. *J Dermatol* 2014;41:353-4.
 13. Daneshpazhooh M, Fatehnejad M, Rahbar Z, et al. Trauma-induzierter Pemphigus: eine Fallserie von 36 Patienten. *J Dtsch Dermatol Ges* 2016;14:166-72.
 14. Vodo D, Sarig O, Geller S, et al. Identification of a functional risk variant for pemphigus vulgaris in the ST18 gene. *PLoS Genet* 2016;12:e1006008.
 15. Maity S, Banerjee I, Sinha R, et al. Nikolsky's sign: A pathogenic boon. *J Family Med Prim Care* 2020;9:526-30.
 16. López-Robles E, Avalos-Díaz E, Vega-Memije E, et al. TNF α and IL-6 are mediators in the blistering process of pemphigus. *Int J Dermatol* 2001;40:185-8.
 17. Zhang SY, Zhou XY, Zhou XL, et al. Subtype-specific inherited predisposition to pemphigus in the Chinese population. *Br J Dermatol* 2019;180:828-35.
 18. Assaf S, Vodo D, Malovitski K, et al. Up-regulation of ST18 in pemphigus vulgaris drives a self-amplifying p53-dependent pathomechanism resulting in decreased desmoglein 3 expression. *Sci Rep* 2022;12:5958.
 19. Fang S-Y, Li C-L, Liu X-S, et al. Correlation between polymorphisms of the NR3C1 gene and glucocorticoid effectiveness in patients with pemphigus vulgaris. *Sci Rep* 2017;7:11890.
 20. Chriguer RS, Roselino AM, de Castro M. Glucocorticoid sensitivity and proinflammatory cytokines pattern in pemphigus. *J Clin Immunol* 2012;32:786-93.
 21. Kang S, Amagai M, Bruckner AL, et al. *Fitzpatrick's Dermatology*. 9th ed. New York (NY): McGraw-Hill Education; 2019.
 22. Joly P, Horvath B, Patsatsi A, et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). *J Eur Acad Dermatol Venereol* 2020;34:1900-13.
 23. Le TVT, Nguyen DQ, Tran ND, Trinh HKT. Association of single nucleotide NR3C1 gene polymorphisms with glucocorticosteroid responsiveness in patients with pemphigus vulgaris. *Dermatol Rep* 2021;14:9190.