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Exploring *C5AR1* gene variants (rs11673309) and their impact on clinical features of chronic spontaneous urticaria

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Abstract

This study evaluated the genotype frequency of the rs11673309 single-nucleotide polymorphism (SNP) in the *C5AR1* gene and its association with clinical features in Vietnamese chronic spontaneous urticaria (CSU) patients. A cross-sectional study was conducted on 102 patients at Ho Chi Minh City Hospital of Dermato-Venereology (Vietnam) from May to October 2023. Clinical data and 2 mL blood samples were collected, and SNP analysis was performed at Pham Ngoc Thach University's Biomedical Research Center (Vietnam). Among 102 patients (29 males, 73 females; mean age: 37.6±12.5 years), three genotypes were identified: TT (32.4%), TG (49.0%), and GG (18.6%). The TT genotype showed the earliest disease onset (31.2±11.9 years, p=0.017). No significant association was observed between genotypes and Urticaria Activity Score (UAS; p=0.144), but a significant difference was found in Dermatology Life Quality Index (DLQI) scores (p=0.003). Furthermore, patients with the TG genotype required a higher dose of desloratadine (p<0.001). Patients with the TG genotype experienced lower quality of life, emphasizing the need for proactive management. These findings contribute to understanding the genetic basis of CSU in Vietnamese patients.

Introduction

Chronic spontaneous urticaria (CSU) is a prevalent condition, affecting approximately 15-30% of the global population. For chronic urticaria specifically, the prevalence is reported to be around 0.5-5% worldwide, though this figure may not be entirely accurate due to variations in diagnostic criteria and underreporting in different regions.[1] The annual incidence rate of chronic urticaria is estimated at 1.4%, and CSU is known to significantly impair patients' quality of life, leading to both physical discomfort and psychological distress.[2] Despite its prevalence, the pathogenesis of CSU remains poorly understood, with mast cell activation recognized as the central mechanism driving disease symptoms. Mast cells are multifunctional immune cells involved in allergic and inflammatory reactions. They can be activated by both immune and non-immune stimuli, leading to the release of histamine and other inflammatory mediators.[3]

Two primary endotypes of CSU pathogenesis have been identified. Autoallergic CSU (Type I), also referred to as immunoglobuline (Ig)E-mediated CSU, involves the binding of IgE to its high-affinity FcεRIα receptor on mast cells. Dysregulated intracellular signaling pathways, such as overactivation of spleen tyrosine kinase (SYK) and reduced activity of inositol phosphatases, result in spontaneous granule release. In contrast, Type IIb autoimmune CSU is characterized by the presence of autoantibodies, including IgG, IgM, and IgA, that activate FcεRIα directly or indirectly, leading to excessive degranulation of mast cells.[1,4]

In addition to these pathways, the complement system, particularly component C5a, plays a crucial role in mast cell activation. The interaction between C5a and its receptor, C5aR1, expressed on mast cells and other immune cells, drives inflammatory responses by promoting granule release and the production of pro-inflammatory cytokines. C5aR1, a G-protein-coupled receptor encoded by the *C5AR1* gene, is involved in intracellular signaling pathways, including calcium mobilization, MAPKs, and PI3K-Akt, all of which contribute to inflammation.[5]

Emerging evidence suggests that genetic variations, particularly single-nucleotide polymorphisms (SNPs) in the *C5AR1* gene, may influence susceptibility to CSU and its clinical manifestations. For instance, the rs11673309 SNP has been implicated in the regulation of C5aR1 expression and activity, potentially altering the inflammatory response in CSU patients. Studies have also hinted at its role in modulating treatment outcomes, including responsiveness to antihistamines and other therapeutic agents.[6]

To address the gap in understanding the genetic basis of CSU, this study aims to investigate the genotype frequency of the rs11673309 SNP in the C5AR1 gene among Vietnamese patients with CSU. Additionally, we examine its association with clinical characteristics, such as disease severity, duration, and response to treatment, thereby contributing to the growing body of knowledge on CSU pathogenesis and individualized therapy.

Materials and Methods

Patients with CSU who sought examination and treatment at the Ho Chi Minh City Hospital of Dermato-Venereology (Vietnam) between May 2023 and October 2023 were included in this study. Inclusion criteria required that patients be Vietnamese with at least three generations residing in Vietnam, and be aged 18 years or older. Additionally, patients or their guardians had to agree to participate in the study by providing informed consent. Exclusion criteria disqualified patients who were pregnant, breastfeeding, or suffering from neurological disorders. Research steps included recruiting patients who met the inclusion criteria and providing them with a thorough explanation of the study objectives. Upon agreement, participants signed a consent form and underwent interviews, clinical examinations, and evaluations for Urticaria Activity Score (UAS)[7] and Dermatology Life Quality Index (DLQI).[8] Each participant provided 2 mL of venous blood, collected into specialized tubes containing 1.5 mg/mL ethylenediaminetetraacetic acid (EDTA) anticoagulant.

The SNP variants of the *C5AR1* gene were analyzed at the Biomedical Research Center of Pham Ngoc Thach University of Medicine (Vietnam). DNA extraction was performed using an Eppendorf Minispin Plus VWR machine (Thermo Fisher Scientific, VWR, USA), followed by SNP genotyping with a QuantStudio 5 system (Thermo Fisher Scientific, USA). Genotype determination was based

on the cycle threshold (Ct) values of the polymerase chain reactions (PCRs). For homozygous genotypes, the Ct value of the present allele was at least five cycles lower than that of the absent allele ($\Delta Ct \geq 5$), or the absent allele reaction was negative. For heterozygous genotypes, the Ct values of the two PCR reactions were equivalent.

Data processing was conducted using SPSS 26.0 software. Qualitative variables were summarized as frequencies and percentages, while quantitative variables were expressed as mean ± standard deviation (SD) for normally distributed data or as median and interquartile range for non-normally distributed data. Statistical analyses included the chi-square test (χ^2) or Fisher's exact test for relationships between qualitative variables and the Mann-Whitney U test or Kruskal-Wallis test for comparing dependent variables with non-normal distributions against independent variables. Results were considered statistically significant at $p<0.05$ with a 95% confidence interval.

The study received approval from the Ethics Board of Pham Ngoc Thach University of Medicine, Vietnam (867/TĐHYKPNT-HĐĐĐ). Informed consent was acquired from all participants. The procedures adhered to the ethical guidelines set by the institutional committee overseeing human experimentation, as well as the 1975 Helsinki Declaration, revised in 2013.

Results

From May to October 2023, a total of 102 patients meeting the inclusion criteria participated in the study. Among them, individuals with the rs11673309 TG genotype represented the largest proportion at 49%, followed by those with the TT genotype at 32.4%, and the GG genotype at 18.6%. The average age of participants was 37.6±12.5 years, ranging from 18 to 70 years. A statistically significant difference in age was observed among the rs11673309 genotypes (p=0.015).

The majority of participants were female, accounting for 73 cases (71.6%), compared to 29 males (28.4%), with a female-to-male ratio of 2.5:1. However, no statistically significant difference in gender distribution was found among the rs11673309 genotypes.

The age of onset ranged from 7 to 70 years, with an average of 35.8±13.3 years. A statistically significant difference in onset age was noted among the rs11673309 genotypes (p=0.017), with patients carrying the TT genotype experiencing the earliest onset at an average age of 31.2±11.9 years.

Most participants (70.6%) had an onset age below 40 years. A statistically significant association was identified between the onset age group (<40 or ≥40 years) and the rs11673309 SNP (p=0.030).

Regarding disease duration, 81.4% of participants had a duration of less than one year. There was no statistically significant relationship between disease duration and the rs11673309 genotypes or alleles ($p>0.05$).

The majority of CSU patients also had concurrent chronic inducible urticaria (CIndU), accounting for 64.7%. The TG genotype was associated with the highest comorbidity rate (45.5%), but no statistically significant differences were observed between genotypes and the presence of concomitant CIndU ($p>0.05$).

No statistically significant association was found between the rs11673309 SNP and UAS scores ($p=0.144$). However, the DLQI score had a median of 13.0 [9.0-19.0], and there was a statistically significant difference between rs11673309 genotypes and DLQI scores ($p=0.003$; Table 1).

The majority of participants (81.8%) had a disease duration of less than one year. No statistically significant differences were found between disease duration and the rs11673309 genotypes or alleles ($p>0.05$; Table 2). Similarly, most participants (73.5%) had no history of food allergies, and no statistically significant associations were observed between rs11673309 genotypes or alleles and food allergy history ($p>0.05$; Table 3).

The majority of participants in this study did not report a family history of CSU (81.4%). Statistical analysis revealed no significant differences in the genotypes or alleles of the rs11673309 polymorphism concerning family history ($p>0.05$).

A statistically significant difference was identified between rs11673309 genotypes and desloratadine dosage at week 8 of treatment ($p<0.05$; Table 4). The TG genotype required the highest average dose of desloratadine (14.0±4.2 mg).

The distribution of desloratadine dosages at week 8 also varied significantly among rs11673309 genotypes ($p<0.05$; Table 5). Most patients required either 10 mg or 15 mg doses, with the 10 mg dose being the most common (60.8%). The 5 mg dose was the least frequently used, predominantly among GG genotype patients. For the higher doses of 15 mg and 20 mg, the TG genotype had the highest proportion of patients requiring these doses (78.4%).

Discussion

In our study of 102 CSU patients, the rs11673309 genotype distribution was predominantly TG (49%), followed by TT (32.4%) and GG (18.6%). Significant associations were found between this genotype and patient age ($p=0.015$), age of disease onset ($p=0.017$, with TT showing earlier onset), early onset (<40 years, $p=0.030$), DLQI scores ($p=0.003$), and the desloratadine dosage required at week 8 ($p<0.05$, with TG needing higher doses). No significant association was observed between the rs11673309 genotype and gender, disease duration, concomitant CIndU, UAS scores, food allergy history, or family history of CSU (all $p>0.05$).

CSU is an inflammatory skin condition in which the complement component C5a plays a pivotal role in disease pathogenesis. By binding to its receptor C5aR1, C5a stimulates various immune cells,

including neutrophils, eosinophils, and monocytes, enhancing vascular permeability and triggering the release of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF).[4,9] Importantly, mast cells in the skin highly express C5aR1, particularly in tryptase- and chymase-positive subsets, facilitating degranulation and further inflammation. This is relevant to our study, which investigated the rs11673309 polymorphism in the *C5AR1* gene and its relationship with clinical characteristics of CSU.

Our study observed the distribution of rs11673309 genotypes, with TT accounting for 32.4%, TG for 49.0%, and GG for 18.6%. These findings align closely with those of Yan *et al.* (2014), who reported similar distributions of 30.2%, 50.5%, and 19.3% in the Chinese population.[6] In our study, the average age of disease onset was 35.8±13.3 years, which is on the higher end compared to literature reports suggesting that CSU typically begins between the ages of 20 and 40.[10] Regarding disease duration, our study found an average duration of 1.8±4.6 years (21.6±55.2 months), aligning with the results of Yan *et al.*, who reported an average duration of 22.8±37.8 months.[6] Approximately 47.1% of patients recovered within one year, a proportion comparable to the 50% reported by Kozel *et al.* (2001).[11] A small subset of patients (8.8%) had a disease duration of 5 years or more, consistent with the approximately 10% reported by Wertenteil *et al.*[10] and Stepaniuk *et al.*[12] However, this figure is significantly lower than the 20% reported by Nebiolo *et al.* (2009).[13]

Chronic urticaria is estimated to have a prevalence of 0.5-5% globally, with an annual incidence of 1.4%, and around 20% of acute urticaria cases progress to CSU.[1,14] Most CSU cases resolve spontaneously within 2-5 years, although approximately 20% persist beyond five years.[10] Variability in disease duration data may stem from reliance on patients' recall of their disease history, differing awareness levels about CSU, and limited access to specialized healthcare facilities, which could delay diagnosis.

Concurrent CIndU was observed in 64.7% of CSU patients in our study, a figure considerably higher than the 20% reported by Curto-Barredo *et al.* (2018).[14] This discrepancy could be attributed to the study being conducted at a specialized dermatology center in Ho Chi Minh City, where more severe and refractory cases are referred. Patients with resistant forms of CSU may also be more likely to develop concurrent CIndU, necessitating more complex treatment protocols.

In assessing disease severity, our study found no statistically significant relationship between UAS scores and rs11673309 genotypes, a finding consistent with the results of Yan *et al.*[6] However, there was a significant association between DLQI scores and rs11673309 genotypes in our study (p=0.003). Patients with the TG genotype had the highest median DLQI score (16.0 [10.0; 20.0]), indicating a poorer quality of life compared to other genotypes. This suggests that the TG genotype may be

associated with more severe disease impact, highlighting the need for targeted evaluation and more aggressive treatment in these patients. Interestingly, this finding contrasts with the results of Yan *et al*., who did not observe a significant association between DLQI scores and rs11673309 genotypes.[14] This suggests that variations in the *C5AR1* gene may not influence disease severity directly but might modulate disease burden via inflammatory mechanisms, possibly through altered receptor expression or responsiveness to C5a. Additionally, the higher prevalence of CIndU comorbidity in this genotype group may further exacerbate disease burden, necessitating integrated management approaches. Future research should explore whether these genetic differences influence treatment response or prognosis.

Regarding food allergy history, 26.5% of participants reported having food allergies, which is notably higher than the 3.3% reported by Alen Coutinho *et al.* (2020).[15] Food intolerance and allergies are recognized as factors that may exacerbate CSU severity. While low-histamine diets and avoiding allergenic foods may benefit some patients, robust evidence supporting these interventions remains limited and contentious. Eliminating specific foods should be done cautiously and only for short periods (3-4 weeks) to avoid unnecessary dietary restrictions. Furthermore, patients often struggle to recall precise food triggers, which can complicate treatment strategies. The variability in food allergy prevalence across studies may result from differences in dietary habits, cultural practices, and individual immune responses in different populations.

The link between genetic polymorphisms such as rs11673309 and treatment responses has been increasingly studied. Genotype TG's association with higher dose requirements of desloratadine may indicate a role in predicting treatment resistance. Kaplan (2004) suggested that genetic differences in inflammatory pathways could affect antihistamine responsiveness.[5] Furthermore, Maurer *et al.* (2013) demonstrated that therapies targeting IgE pathways, such as omalizumab, offer effective alternatives for severe cases, raising questions about whether specific genotypes also influence outcomes with biologics.[16] These findings underscore the potential for personalized treatment strategies based on genetic profiling.

Desloratadine, a second-generation H1-antihistamine, has demonstrated efficacy in inhibiting histamine release and reducing pro-inflammatory cytokines, such as IL-3, IL-6, IL-8, TNF-α, and GM-CSF.[17] It is recommended as a first-line treatment for CSU by the EAACI/GA^{2}LEN/EDF/WAO guidelines.[18] According to Choonhakarn *et al.*,[19] 94.4% of patients required variable desloratadine doses for symptom control, indicating that standard doses (5 mg) are often insufficient. Patients with concurrent antithyroid antibodies or elevated erythrocyte sedimentation rates (>20 mm/h) were less likely to respond to higher doses of desloratadine ($p<0.05$). Among patients achieving complete symptom control, 94% relapsed after treatment discontinuation. However, extending treatment with

effective doses for 8 weeks before tapering reduced the relapse rate to 4.9%, suggesting that prolonged maintenance therapy is beneficial for sustained disease control.[19]

Analysis of desloratadine dosing patterns revealed that the TG genotype group had the highest dose requirements, with an average dose of 14.0±4.2 mg by week 8 of treatment. These findings align with research by Choonhakarn *et al.* (2018) and Staevska *et al.* (2010), where higher doses (10-20 mg) were commonly required for effective CSU management.[19,20] Notably, 97.1% of patients in this study needed doses exceeding 5 mg, reflecting the severity of cases typically seen at a specialized dermatology center in Vietnam. The TG genotype was associated with higher dose requirements, suggesting it may be a risk factor for treatment resistance. Given that C5aR1 activation triggers downstream signaling via intracellular calcium mobilization, MAPKs, PI3K, and Akt pathways,[9] all contributing to inflammation, it is plausible that rs11673309 variants may affect the sensitivity of these pathways to inhibition, thereby influencing antihistamine responsiveness. This potential mechanistic connection highlights the importance of understanding the genetic basis of inflammation in CSU and supports the idea of personalized treatment strategies based on genetic profiles.

Our study has some strengths and weaknesses. Regarding the strengths, this study has a clear focus, investigating the association between the rs11673309 genetic variants and various aspects of CSU. It gathered diverse and relevant clinical data, including disease characteristics, quality of life, and treatment response. However, a key limitation is the relatively small sample size of 102 patients, which may limit the statistical power to detect all associations and increase the potential for findings due to chance. The study was conducted in a single specific population, meaning the results may not be generalized to other ethnic groups. Furthermore, focusing solely on one SNP might not fully capture the complex genetic influences on CSU and its treatment response.

Conclusions

In summary, our findings underscore the heterogeneity of CSU concerning disease duration, food allergy prevalence, and treatment response. Further research with larger sample sizes and control groups is needed to better understand genetic influences on CSU and develop tailored treatment approaches that optimize patient outcomes.

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Table 1. UAS and DLQI of the study participants (n=102).

	Total	**TT (n=33)**	**TG (n=50)**	**GG (n=19)**	**p-value**
UAS (mean±SD)	3.7±1.0	3.4±0.9	3.8±1.1	3.9±1.0	0.144*
DLQI (median [quartile])	13.0 [9.0-19]	10.0 [9.0-13.5]	16.0 [10.0-20.0]	14.0 [11.0-16.5]	0.003#

UAS, Urticaria Activity Score; DLQI, Dermatology Life Quality Index; *one-way analysis of variance (ANOVA) test; #Kruskal-Wallis test.

Table 2. Correlation between rs11673309 genotypes and disease duration groups (n=102).

Disease duration	**Genotypes**			**p-value**
	TT n (%)	**TG n (%)**	**GG n (%)**	
≤1 year	27 (81.8)	41 (82.0)	15 (78.9)	0.737*
1≤5 years	3 (9.1)	5 (10.0)	2 (10.5)	
≥5 years	3 (9.1)	4 (8.0)	2 (10.5)	

*Fisher's exact test.

Table 3. Correlation between rs11673309 genotypes and food allergy history.

rs11673309 genotypes	**Food allergy history**		**p-value**
	No n (%)	**Yes (%)**	
TT (n=33)	25 (75.8)	8 (24.2)	0.823*
TG (n=50)	36 (72.0)	14 (28.0)	
GG (n=19)	14 (73.7)	5 (26.3)	

*Chi square test.

Table 4. Correlation between rs11673309 genotypes and desloratadine dose (mg) at week 8 of observation (n=102).

Dosage	**Total**	**TT (n=33)**	**TG (n=50)**	**GG (n=19)**	**p-value**
Desloratadine (mg) (mean±SD)	12.4±3.8	11.4±2.9	14.0±4.2	9.7±2.0	<0.001*

*One-way ANOVA test.

Table 5. Correlation between rs11673309 genotypes and desloratadine dose groups (mg) at week 8 of observation (n=102).

Dosage	**Total n (%)**	**TT (n=33)**	**TG (n=50)**	**GG (n=19)**	**p-value**
5 mg	3 (2.9)	0 (0)	1 (2.0)	2 (10.5)	<0.001*
10 mg	62 (60.8)	26 (78.8)	20 (40.0)	16 (84.2)	
15 mg	23 (22.6)	5 (15.2)	17 (34.0)	1 (5.3)	
20 mg	14 (13.7)	2 (6.1)	12 (24.0)	0 (0)	
Total	102 (100)	33 (100)	50 (100)	19 (100)	

*Fisher's exact test.