Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.399690.4032 Volume 31, Issue 9 September. 2025
Manuscript ID:ZUMJ-2507-4032
DOI:10.21608/zumj.2025.399690.4032

ORIGINAL ARTICLE

Association between Transforming Growth Factor β1 Gene Polymorphism and Chronic Spontaneous Urticaria

Amal Hassan Atta[1], Esraa Ahmed Mahmoud Ahmed[1], Manal Mohamed Fawzy[2], Eman Salah Elgharabawy[1]

[1]Medical Microbiology and Immunology, Faculty of Medicine - Zagazig University.
[2]Dermatology, Venereology and Andrology, Faculty of Medicine - Zagazig University.

Corresponding author: Esraa Ahmed Mahmoud Ahmed
Email: m.mahrus95@gmail.com

Submit Date 01-07-2025
Revise Date 28-07-2025
Accept Date 05-08-2025

ABSTRACT

Background: Chronic spontaneous urticaria (CSU) is a prevalent skin disease with an unclear pathogenesis. Transforming growth factor beta 1 (TGF-β1) is an immunoregulatory cytokine potentially incorporated into autoimmune and inflammatory diseases. This study assessed the association of TGF-β1 gene polymorphisms (codon 10 and codon 25) with CSU susceptibility and clinical characteristics.

Methods: This case-control study involved 24 CSU patients and 24 age- and sex-matched healthy controls. All subjects were genotyped for the detection of TGF-β1 codon 10 (rs1982073) and codon 25 (rs1800471) polymorphisms using Amplification Refractory Mutation System PCR (ARMS-PCR). Clinical data included urticaria activity score (UAS7), angioedema, and autologous serum skin test (ASST) results.

Results: The incidence of the G/C genotype at codon 25 was significantly higher amongst CSU patients than controls (87.5% vs. 37.5%, p = 0.005), having an odds ratio (OR) of 10.9 (95% CI: 2.5–47.1). The C allele was also more common among patients (p = 0.031; OR =2.62 (95% CI: 1.08–6.32). Non-significant correlations was found in distribution of genotypes for TGF-β1 codon 10 between patients and controls (p = 0.53), also between TGF-β1 gene polymorphisms (at codon 10 and codon 25) and age (p = 0.5, >0.999), gender (p >0.999), ASST reactivity (p =0.4, 0.2), angioedema (p = 0.5, >0.999), or UAS7 scores (p = 0.1).

Conclusion: TGF-β1 gene polymorphism at codon 25 is associated with a higher risk of CSU, with carriers of the G/C genotype showing almost 10.5-fold increased risk. However, these polymorphisms did not affect clinical severity or other features.

Keywords: Transforming Growth Factor β, Gene Polymorphism, Chronic Spontaneous Urticaria.

NTRODUCTION

Urticaria is a widespread inflammatory skin disease affecting up to one in five people during their lifetime. Common symptoms, such as itching, hives, and, in rare cases, angioedema, could occur due to the release of histamine and other mediators by activated and degranulating cutaneous mast cells. This process causes vasodilation, increased permeability of blood vessels, nerve stimulation, and the recruitment of immune cells, resulting in the characteristic swelling and discomfort seen in urticaria [1].

Urticaria can be classified by its duration; acute urticaria lasts six weeks or less, while chronic urticaria continues for over six weeks. Chronic urticaria is categorized into two main types: spontaneous (CSU), which occurs without an

apparent external trigger, and inducible, which is set off by specific factors such as cold or pressure. Chronic spontaneous urticaria is more common, and some individuals can experience both types at the same time [2].

Although CSU often resolves on its own within two to five years, it can persist in about 20–50% of patients for even more extended periods, making it a challenging and sometimes distressing condition. Many people with CSU suffer moderate to severe symptoms that interfere with their daily life and sleep, which could lead to a significant decrease in their quality of life [3].

Current evidence indicates that at least half of CSU cases could be linked to autoimmune mechanisms, though the details are still being investigated. Autoimmunity in CSU may involve IgE antibodies against the body's own proteins (type I hypersensitivity) or IgG autoantibodies targeting IgE or its high-affinity receptor on mast cells (type II hypersensitivity). One frequent way to identify patients with these autoantibodies is by the autologous serum skin test (ASST) [4].

The TGF-β1 is a multifunctional cytokine with a central function in immune regulation, controlling cell growth, differentiation, programmed cell death, and immune cell behavior [5]. The gene for TGF-β1 is located on chromosome 19, and several genetic variants, including polymorphisms at positions −869 (T/C) and −915 (G/C), have been described. These gene variations may impact how TGF-β1 is produced or functions [6,7].

Research suggests that changes in the TGF-β1 gene may be correlated with allergic diseases and autoimmune disorders. TGF-β1 helps maintain the balance of mast cells, encouraging their programmed cell death and dampening the expression of their high-affinity IgE receptor (FcεRI) and the release of inflammatory substances [8]. When the gene for this cytokine has specific promoter polymorphisms, its expression can be altered, potentially reducing its anti-inflammatory actions and contributing to chronic inflammation seen in CSU [9].

Few studies have examined how the −869 T/C and −915 G/C polymorphisms in TGF-β1 relate to CSU's likelihood or intensity, especially in the Egyptian population. The current study aim was to assess whether there is a connection between two frequent polymorphisms in the TGF-β1 gene codon 10 at position −869 (T/C), as well as the codon 25 at position −915 (G/C), and the likelihood of developing CSU. We also explored possible links between these genetic variations and clinical parameters like associated angioedema, disease severity, and ASST results.

METHODS

This case-control study was performed at Zagazig University Hospitals from September 2023 to December 2024. Patients were collected from the Allergy and Immunology Unit and the Dermatology Outpatient Clinic. All molecular procedures were performed at the Molecular Biology Unit, Scientific and Medical Research Center, Zagazig University.

Institutional Review Board (IRB#10862-7-6-2023) clearance was attained, and informed consent was collected from all patients who participated in the study. The research followed the World Medical Association's Code of Ethics (Helsinki Declaration) for studies involving human subjects.

The study population was categorized into two groups. The case group comprised 24 patients diagnosed with chronic spontaneous urticaria (CSU), all recruited from the Allergy and Immunology Unit or the Dermatology Outpatient Clinic. The control group included 24 healthy volunteers carefully matched to the cases by age and sex. These controls had no personal history of urticaria or any autoimmune diseases.

Participants were eligible for the study if they had chronic urticaria, as the presence of wheals with or without angioedema persisting for more than six weeks, regardless of their age or sex [2].

Exclusion criteria included persons having an identified cause for urticaria, such as reactions to drugs, foods, infections, or physical triggers like pressure, temperature changes, or

ultraviolet exposure. Individuals were excluded if they had other pruritic skin diseases, such as atopic dermatitis, senile pruritus, bullous pemphigoid, or dermatitis herpetiformis. Additional exclusion criteria were recent use (within the previous 30 days) of immune-modifying medications, including systemic or topical corticosteroids, methotrexate, cyclosporine, hydroxychloroquine, intravenous immunoglobulin, cyclophosphamide, or plasmapheresis. Patients with significant medical conditions that could interfere with the study and those who declined to participate were also excluded.

Clinical data were collected using a combination of patient interviews, physical examination, and review of medical records. Personal history encompassed demographic information. Present history focused on the onset and duration of urticaria, the sites affected, presence of angioedema, potential relationship to stress or specific triggers, accompanying symptoms, any comorbidities such as diabetes, thyroid disorders, hypertension, or other autoimmune diseases, as well as details of previous treatments. Past history involved documentation of prior urticaria episodes, previous infections, atopic conditions, and, in women, the use of hormonal medications. Family history was taken to identify any occurrence of urticaria, atopic diseases, or autoimmune disorders among relatives.

Disease severity was assessed utilizing the Urticaria Activity Score (UAS7), which rates the number of wheals and the intensity of itching on a daily scale from 0 to 6, summed over seven days for a maximum score of 42. UAS7 scores ≤6 indicate well-controlled disease, 7–15 mild, 16–27 moderate, and 28–42 severe urticaria [10].

Peripheral blood samples totaling three milliliters were collected from each participant using aseptic technique. Two milliliters of the total volume were placed into EDTA tubes for subsequent DNA extraction and genotyping. The remaining one milliliter was transferred into a serum separator tube and reserved for autologous skin testing (ASST).

Autologous Serum Skin Test (ASST)

For the ASST, the patient's serum (0.05 mL) was intradermally injected into the forearm. Normal saline and histamine served as negative and positive controls, respectively. The test was deemed positive compared to the negative control if the mean wheal diameter was 1.5 mm or larger [11] **(**Supplementary Figure 1).

Detection of TGF-β1 Codon 10 and 25 Gene Polymorphisms

Genomic DNA Extraction

Genomic DNA was isolated from peripheral blood samples collected in EDTA tubes utilizing a commercially available extraction kit (gSYNCTM DNA Extraction Kit), following the manufacturer's guidelines. The purified DNA was stored at -25°C until further analysis. To detect polymorphisms in the TGF-β1 gene at codon 10 (T869C, rs1982073) and codon 25 (G915C, rs1800471), allele-specific polymerase chain reaction employing the amplification refractory mutation system (ARMS-PCR) was performed, using previously established primer sets [12] (Supplementary Table 1).

Each PCR reaction was prepared at a total volume of 20 µL, and negative controls were included to check for contamination.

PCR amplification was initiated with a single cycle of denaturation at 95°C for 5 minutes. This was followed by 40 cycles comprising denaturation at 95°C for 30 seconds, primer annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds. The process concluded with a final extension step at 72°C for 5 seconds. Amplified products corresponding to codon 10 (241 bp) (Supplementary Figure 2) and codon 25 (233 bp) (Supplementary Figure 3) were separated by electrophoresis on a 1.5% agarose gel stained with ethidium bromide, and DNA bands were visualized using ultraviolet transillumination.

Statistical analysis

Data analysis was performed using SPSS software, version 27. Categorical variables were assessed by Fisher's exact or chi-square

tests, depending on group frequencies. At the same time, trends in ordinal data were evaluated using the chi-square test for trend. Crude odds ratios were calculated to estimate event likelihoods. The Shapiro-Wilk test was applied to assess the normality of quantitative data. Results for continuous variables were expressed as mean ± standard deviation, and comparisons between normally distributed groups were made using the independent samples t-test. Statistical significance was set at $P<0.05$, with a P value of 0.001 considered highly significant.

RESULTS

Non-statistically significant differences were revealed as regards gender or age between the case and control groups, with females representing 75% and 58.4%, respectively, and mean ages of 32.08 ± 11.17 and 32.21 ± 6.61 years, respectively **(Table 1)**.

CSU patients achieved an average UAS7 of 26.71 ± 9.84, ranging from 8 to 42. Half of the CSU patients had severe urticaria, while 33.3% had moderate urticaria. Eleven patients (44%) had a positive ASST while only nine patients (37.5%) had angioedema **(Table 2)**.

No significant association between age or gender and ASST results, angioedema, or disease severity **(Table 3)**.

The TGF-β1 codon 10 genotypes and allele distribution did not show significant variations between CSU patients and controls. However, for codon 25, the CG genotype and C allele were significantly more common among CSU patients compared to controls ($P = 0.005$ and $P = 0.031$, respectively). The risk of CSU is 10.9 times higher among those with the CG genotype. The C allele significantly increases the risk of CSU by 2.62-fold **(Table 4)**.

No significant associations were revealed between TGF-β1 codon 10 or codon 25 genotypes and either age or sex among CSU patients **(Table 5)**, and no significant associations were found between TGF-β1 codon 10 or codon 25 genotypes and angioedema or ASST positivity in CSU patients **(Table 6).**

No significant associations were revealed between TGF-β1 codon 10 or codon 25 genotypes and CSU severity, as genotype distributions did not differ significantly among patients with mild, moderate, or severe urticaria ($P > 0.05$) **(Table 7).**

Genotyping of the Codon 10 Polymorphism of TGF-β1 (T869C) by ARMS–PCR: each two successive lanes correspond to one sample. The C or T allele-specific band is at 241bp. Lanes 1 is the molecular marker. All lanes 2 & 3, 4 & 5, and 6 & 7 are (TT homozygote) (Supplementary Figure 2).

Genotyping of the Codon 25 Polymorphism of TGF-β1 (G915C) by ARMS–PCR: each two successive lanes correspond to one sample. The C or G allele-specific band is at 233bp.

Lane 1 is the molecular marker. Lanes 2 and 3, 4 and 5, and 6 and 7 are CG (heterozygotes) (Supplementary Figure 3).

Table 1: Comparison between the studied groups regarding demographic data (n=48)

	Case group N=24 (%)	**Control group N=24 (%)**	χ^2	***P-value***
Gender **Female** **Male**	 18 (75%) 6 (25%)	 14 (58.4%) 10 (41.6%)	1.5	0.221
	Mean ± SD **Range**	**Mean ± SD** **Range**	**T**	***P-value***
Age (year)	32.08 ± 11.17 18-50	32.21 ± 6.61 20 - 50	-0.047	0.963

χ^2Chi square test t independent sample t tes

Table 2: Clinical characteristics of CSU patients (n=24)

Variable	CSU patients (*n*=24)
UAS7 ***Mean ± SD*** ***Range***	 **26.71 ± 9.84** **8 – 42**
Classification: ***Mild*** ***Moderate*** ***Severe***	 **4 (16.7%)** **8 (33.3%)** **12 (50%)**
ASST **Negative** **Positive**	 **13 (56%)** **11 (44%)**
Angioedema **Positive** **Negative**	 **9 (37.5%)** **15 (62.5%)**

Table 3: Relation between Demographic Characteristics (Age and Gender) and Disease-Specific Data (n=24)

Disease-Specific Data	Age <35 years n=17	Age ≥35 years n=7	Test of significance	P-value	Female n=18	Male n=6	Test of significance	P-value
ASST								
Negative	9 (52.9%)	4 (57.1%)	$\chi^2 = 0.035$	0.851	10(55.6%)	3 (50%)	Fisher exact test	>0.999
Positive	8 (47.1%)	3 (42.9%)			8 (44.4%)	3 (50%)		
Angioedema								
Negative	11 (64.7%)	4 (57.1%)	Fisher exact test	>0.999	10(55.6%)	5(83.3%)	Fisher exact test	0.351
Positive	6 (35.3%)	3 (42.9%)			8(44.4%)	1(16.7%)		
Severity								
Mild	3 (17.7%)	1 (14.2%)			4(22.2%)	0 (0%)		
Moderate	5 (29.4%)	3 (42.9%)	$\chi^2 = 0.039$	0.844	5(27.8%)	3 (50%)	$\chi^2 = 0.383$	0.536
Severe	9 (52.9%)	3 (42.9%)			9 (50%)	3 (50%)		

ASST: Autologous Serum Skin Test; χ^2: Chi square test; n: number of subjects; %: percentage; Severity: Disease severity graded as Mild, Moderate, or Severe.

Table 4: Distribution of TGF-β1 Codon 10 (T/C869) and Codon 25 (G/C915) Genotypes in CSU Patients and Controls

Genetic Marker	Genotype / Allele	CSU Patients (n=24)	Controls (n=24)	χ^2	P-value	COR (95% CI)
Codon 10 (T/C869)						
	CC Genotype	0 (0%)	4 (16.7%)	0.395	0.53	0
	CT Genotype	22 (91.7%)	16 (66.6%)			2.75 (0.45–16.9)
	TT Genotype	2 (8.3%)	4 (16.7%)			1 (reference)
	C allele	22 (45.8%)	24 (50%)	0.167	0.683	0.85 (0.38–1.89)
	T allele	26 (54.2%)	24 (50%)			
Codon 25 (G/C915)						
	CC	0 (0%)	1 (4.2%)	7.73	0.005*	0

Genetic Marker	Genotype / Allele	CSU Patients (n=24)	Controls (n=24)	χ^2	P-value	COR (95% CI)
	Genotype					
	CG Genotype	21 (87.5%)	9 (37.5%)			10.9 (2.5–47.1)
	GG Genotype	3 (12.5%)	14 (58.3%)			1 (reference)
	C allele	21 (43.8%)	11 (22.9%)	4.688	0.031*	2.62 (1.08–6.32)
	G allele	27 (56.2%)	37 (77.1%)			

TGF-β1: Transforming Growth Factor Beta 1; CSU: Chronic Spontaneous Urticaria; χ^2: Chi square test; COR: Crude Odds Ratio; CI: Confidence Interval; *: Significant P value (P < 0.05

Table 5: Relation between demographic data of CSU patients and TGF-β1 (T/C869 and G/C915) genotypes

Genotypes	**Age**		**Sex**	
	<35 years N=17 (%)	**≥35 years N=7 (%)**	**Female N=18 (%)**	**Male N=6 (%)**
CODON 10				
CC	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CT	16 (94.1%)	6 (85.7%)	16 (88.9%)	6 (100%)
TT	1 (5.9%)	1 (14.3%)	2 (11.1%)	0 (0%)
Test of significance	Fisher exact test		Fisher exact test	
P-value	0.507		>0.999	
CODON 25				
CC	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CG	15 (88.2%)	6 (85.7%)	16 (88.9%)	5 (83.3%)
GG	2 (11.8%)	1 (14.3%)	2 (11.1%)	1 (16.7%)
Test of significance	Fisher exact test		Fisher exact test	
P-value	>0.999		>0.999	

Table 6: Association of TGF-β1 (T/C869 and G/C915) Genotypes with Angioedema and ASST in CSU Patients

Polymorphism	Genotype	CSU with Angioedema N=9(%)	CSU without Angioedema N=15(%)	ASST Negative N=13(%)	ASST Positive N=11(%)
Codon 10 (T/C869)	CC	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	CT	9 (100%)	13 (86.7%)	11 (84.6%)	11 (100%)
	TT	0 (0%)	2 (13.3%)	2 (15.4%)	0 (0%)
Test of significance		**Fisher exact test**		**Fisher exact test**	
P-value		**0.511**		**0.482**	
Codon 25 (G/C915)	CC	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Polymorphism	Genotype	CSU with Angioedema N=9(%)	CSU without Angioedema N=15(%)	ASST Negative N=13(%)	ASST Positive N=11(%)
	CG	8 (88.9%)	13 (86.7%)	10 (76.9%)	11(100%)
	GG	1 (11.1%)	2 (13.3%)	3 (23.1%)	0 (0%)
Test of significance		**Fisher exact test**		**Fisher exact test**	
P-value		**>0.999**		**0.223**	

TGF-β1: Transforming Growth Factor Beta 1; CSU: Chronic Spontaneous Urticaria; ASST: Autologous Serum Skin Test; χ^2: Chi square test; COR: Crude Odds Ratio; CI: Confidence Interval; *: Significant P value (P < 0.05).. n: number of subjects; %: percentage.

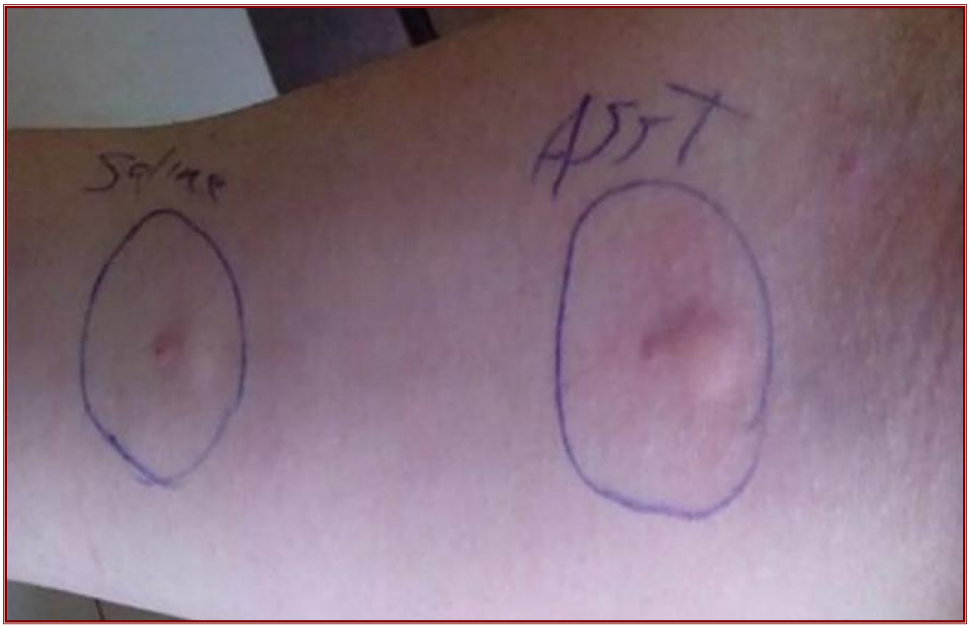
Table 7: Association between TGF-β1 (T/C869 and G/C915) genotypes and severity of CSU patients

Genotype	**Mild Urticaria N=4 (%)**	**Moderate Urticaria N=8 (%)**	**Severe Urticaria N=12 (%)**
CODON 10			
CC	0 (0%)	0 (0%)	0 (0%)
CT	3 (75%)	7 (87.5%)	12 (100%)
TT	1 (25%)	1 (12.5%)	0 (0%)
χ^2	2.614		
P-value	0.106		
CODON 25			
CC	0 (0%)	0 (0%)	0 (0%)
CG	3 (75%)	6 (75%)	12 (100%)
GG	1 (25%)	2 (25%)	0 (0%)
χ^2	2.629		
P-value	0.105		

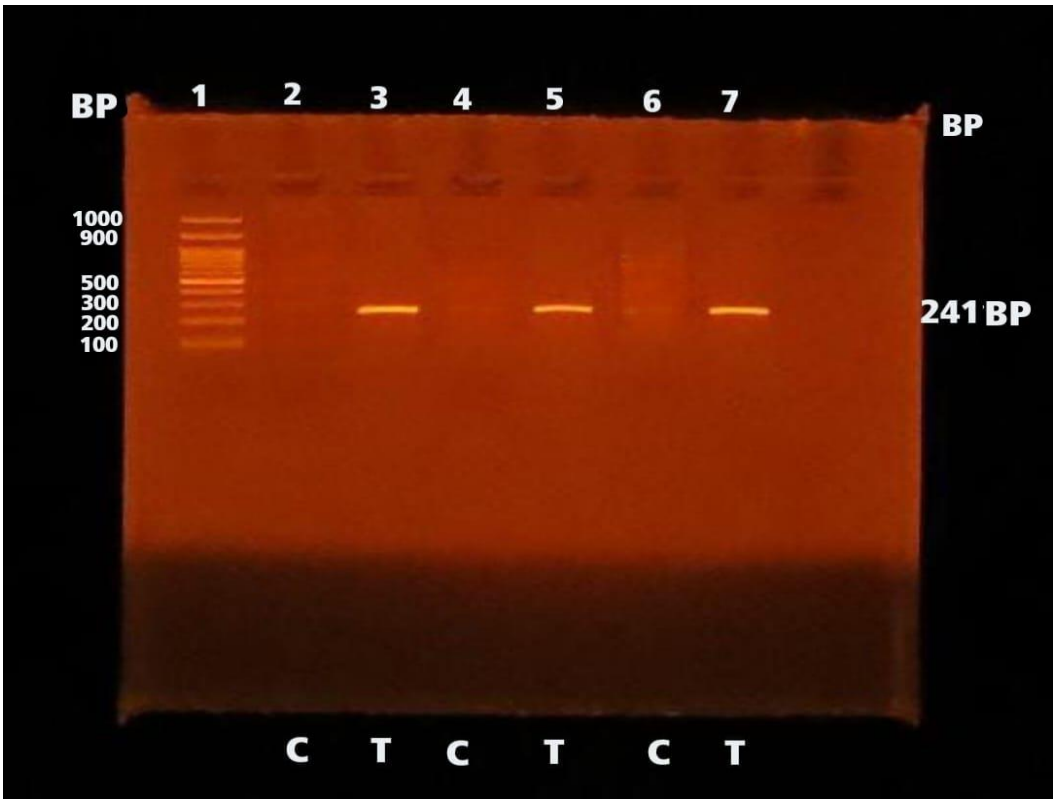
χ^2Chi square test

Supplementary Table 1: Primer sequences for codon-10 polymorphism (T869C) and for codon-25 polymorphism (G915C)

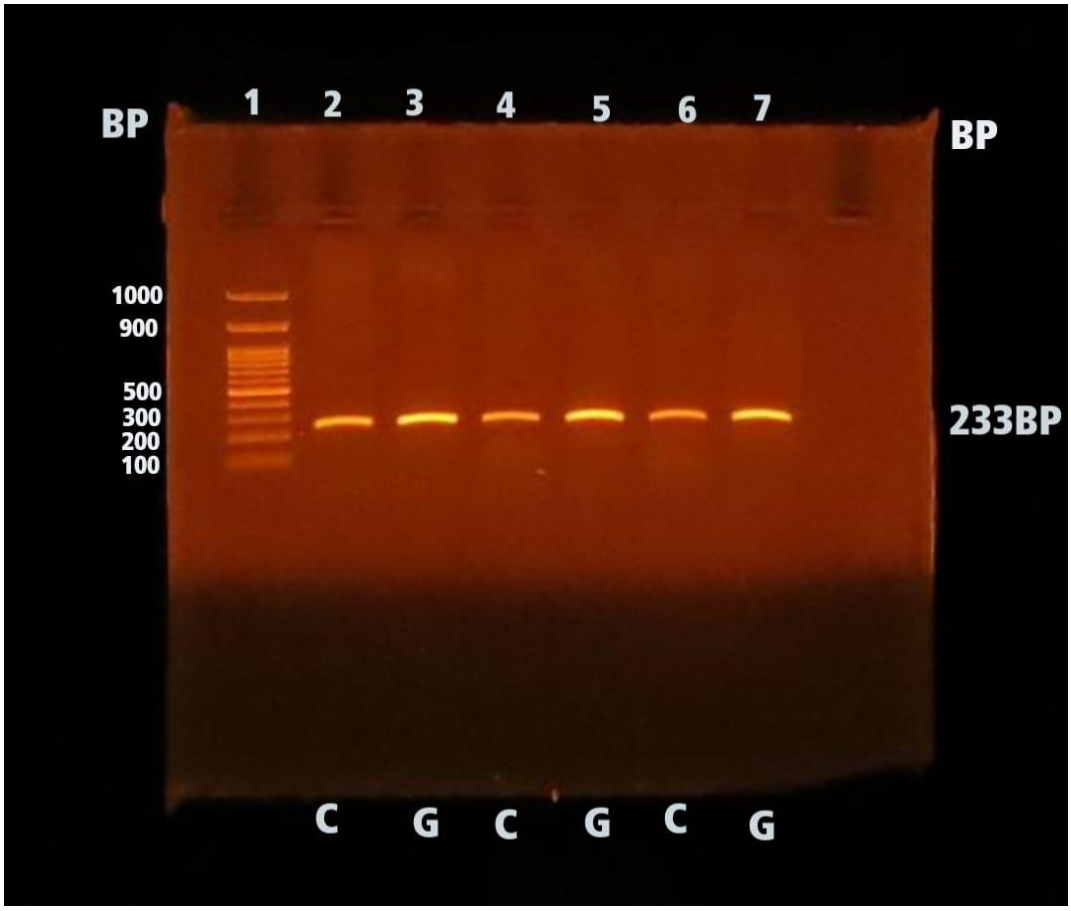
Polymorphism (Codon/Allele)	**Primer Type**	**Primer Sequence (5' → 3')**	**Predicted Product Size (bp)**
Codon-10 (T869C)			241
Codon-10 (T869C), C allele	Allele-specific	GCAGCGGTAGCAGCAGCG	
Codon-10 (T869C), T allele	Allele-specific	AGCAGCGGTAGCAGCAGCA	
Codon-10 (T869C)	Generic	TCCGTGGGATACTGAGACAC	—
Codon-25 (G915C)			233
Codon-25 (G915C), C allele	Allele-specific	GTGCTGACGCCTGGCCC	—
Codon-25 (G915C), G allele	Allele-specific	GTGCTGACGCCTGGCCG	—
Codon-25 (G915C)	Generic	GGCTCCGGTTCTGCACTC	—



Supplementary Figure 1: Autologous serum skin test Positive ASST elicited by intradermal injection of patient's undiluted autologous serum and normal saline, as negative control.



Supplementary Figure 2: Polymorphism at codon 10 of the TGF-β1 gene produces fluorescent PCR bands of 241 base pairs (bp).



Supplementary Figure 3: Polymorphism at codon 25 of the TGF-β1 gene produces fluorescent PCR bands of 233 base pairs (bp).

DISCUSSION

The latest international urticaria guidelines emphasize the importance of a structured diagnostic approach known as the 7C concept. This strategy aims to help clinicians systematically evaluate patients with chronic spontaneous urticaria (CSU) by confirming the diagnosis, identifying causes or cofactors, checking for autoimmune markers and comorbidities, assessing the impact on daily life, and monitoring disease course and possible biomarkers to guide therapy [2].

TGF-β1, encoded by the TGF-β gene, is recognized as a key regulator of various cellular processes, including growth, apoptosis, differentiation, and immune function [5]. This study examined the potential impact of TGF-β1 gene polymorphisms at codon 10 (−869 T/C) and codon 25 (−915 G/C) on CSU susceptibility and their relation to clinical characteristics. We evaluated each patient's urticaria activity score (UAS7), autoreactivity by ASST, the presence of angioedema, and TGF-β1 genotyping.

The current study included 48 participants—24 CSU patients and 24 healthy controls matched for gender and age. The average age was just over 32 years, which is consistent with the known higher prevalence of CSU among adults, with a peak onset in the third and fourth

decades of life. This observation aligns with previous studies that reported CSU typically presents between 20 and 45 years of age, often leading to substantial morbidity and negative effects on quality of life, including sleep disruption and impaired work or school performance [3,13,14].

The ASST is widely used as an in vivo test to evaluate autoreactivity in urticaria. However, a positive ASST does not necessarily define autoimmune urticaria, but may reflect the presence of mast cell-activating autoantibodies. In different studies, reported rates of ASST positivity in chronic urticaria vary significantly, ranging from 4% to over 75% [15]. In the current study, 44% of CSU patients displayed ASST positivity. Other reports have found higher rates; for example, Bajaj *et al*. [16] and El-Korashi *et al*. [17] documented ASST positivity in 55% and 52.2% of patients, respectively. These variations likely reflect differences in study design, patient selection, and technical aspects of the test.

UAS7 is considered the gold standard for evaluating CSU disease activity by tracking the wheals and severity of itching over seven days [18]. The current study findings revealed UAS7 scores ranging from 8 to 42, with a mean of 26.7, comparable to other studies reporting mean scores around 28 to 30 [19,20]. Regarding disease severity, half of our CSU patients had severe symptoms, a third had moderate disease, and about 17% had mild disease. This pattern differs from findings by El-Korashi *et al*. [17] and Abdel Latif *et al.* [21], who noted higher rates of mild or moderate disease in their cohorts. Such differences may stem from variations in patient characteristics, assessment methods, and the timing of symptom evaluation. It is essential to consider these factors when interpreting UAS7 results across studies.

Angioedema, which presents deeper, sometimes painful swelling, was observed in over a third of our patients. This is similar to earlier reports indicating that angioedema occurs in 40–50% of individuals with CSU [22].

The present study showed no statistically significant difference in the relationship between ASST positivity and age or gender among CSU patients. These findings are in line with previous reports by Vikramkumar *et al*. [23], Kumaran *et al.* [24], and El Mahdi *et al*. [25], who also found no statistical association between ASST results and demographic variables in chronic urticaria.

Furthermore, we did not find a significant correlation between ASST results and UAS7 scores in CSU patients, echoing findings from Kasperska-Zając *et al.* [26], Kumaran *et al.* [24], and El Mahdi *et al*. [25], who reported that ASST status was not correlated with disease activity or symptom severity. In contrast, several studies, including those by Sabroe *et al*. [27], Godse [28], Song *et al*. [29], Niu *et al*. [30], and El-Korashi *et al*. [17], reported that patients with positive ASST tended to have higher UAS scores, indicating more active disease and possibly more pronounced autoimmune features. The discrepancy between studies could be related to differences in sample size, disease duration, or how ASST reactivity was defined.

We also found no significant association between ASST reactivity and the presence of angioedema. This observation aligns with Kasperska-Zając *et al*. [26], who found no consistent correlation between ASST positivity and angioedema. However, Nettis *et al*. [31] reported a higher frequency of angioedema episodes among ASST-positive patients, suggesting that methodological and population differences can impact the strength of observed associations.

Genetic predisposition is believed to play a significant role in CSU development. To our knowledge, this is the first study in Egypt to investigate the association between TGF-β coding region polymorphisms and CSU. We examined two well-studied polymorphic sites in the first exon of the TGF-β1 gene, at codon 10 (C/T, rs1982073) and codon 25 (G/C, rs1800471). These changes result in the substitution of leucine for proline at codon 10 and arginine for proline at codon 25. The

current study findings showed no significant difference in the distribution of TGF-β1 T/C869 genotypes or allele frequencies between CSU patients and controls. The CT genotype at codon 10 was found in 91.7% of CSU patients versus 66.6% of controls, while the TT genotype appeared in 8.3% of patients and 16.7% of controls.

By contrast, the most significant association was seen at codon 25. Carriers of the GC genotype and the C allele were significantly more frequent among CSU patients, with odds ratios of 10.9 (95% CI, 2.5–47.1) and 2.62 (95% CI, 1.08–6.32), respectively. The GG genotype was observed in 12.5% of patients and 58.3% of controls, while the CG genotype appeared in 87.5% of patients compared to 37.5% of controls. These results are similar to those of Tavakol *et al*. [32] in the Iranian population, who also reported a higher frequency of the C allele and GC genotype among CSU patients, though their odds ratios and confidence intervals differed. Differences among studies may be explained by population genetics, study design, and the complex multifactorial nature of urticaria, which involves genetic and environmental components.

Previous findings in atopic and autoimmune conditions support the current study results. For example, Arkwright *et al*. [33] demonstrated that 40% of patients with atopic dermatitis carried the GC genotype at TGF-β codon 25 compared to only 12% of controls, highlighting a potential genetic association. Similar increased GC genotype frequency observations have been reported in asthma and common variable immunodeficiency by Movahedi *et al.* [34] and Rezaei *et al.* [35], respectively.

Conversely, Behniafard *et al*. [36] reported a strong association between TGF-β1 polymorphisms at codon 10 and 25 and atopic dermatitis. Park *et al.* [37] showed that a promoter polymorphism (−509C/T) of the TGF-β gene was associated with aspirin-intolerant chronic urticaria. These findings support that cytokine gene polymorphisms can influence susceptibility to various inflammatory diseases. As an immunoregulatory cytokine, TGF-β1 inhibits T-helper 2 cytokines and downregulates FCεR1 expression on mast cells, suppressing inflammatory mediator release [13].

In the current study, there was no statistically significant association between patient age or gender and TGF-β1 genotypes in CSU. This is consistent with Kasperska-Zajac *et al.* [26], who reported no significant influence of demographic factors on this relationship. However, other autoimmune diseases such as systemic lupus erythematosus have shown demographic associations with TGF-β1 genotypes, including higher frequencies of specific female genotypes, possibly related to hormonal factors [26]. These findings indicate that the relationship between TGF-β1 polymorphisms and demographic variables may differ among immune-mediated diseases, warranting further research.

The current study findings also showed no significant associations between TGF-β1 polymorphisms and angioedema, ASST reactivity, or UAS7 scores. This agrees with Tavakol *et al*. [32], who found a significant association between the codon 25 polymorphism and CSU risk but did not demonstrate clear links with ASST, UAS7, or angioedema. Likewise, Kasperska-Zajac *et al*. [26] and Shahrokhi *et al*. [38] found no significant correlations between TGF-β1 genotypes and these clinical markers in CSU.

To our knowledge, few studies have explored these specific associations in CSU, and future work with larger, ethnically diverse samples is needed to clarify these relationships. Our findings suggest that while TGF-β1 genetic variants—particularly at codon 25—may predispose individuals to CSU, their role in determining disease severity or clinical presentation is limited. This highlights the complex interplay between genetics, environment, and other factors in CSU pathogenesis.

Despite the insights provided, this study has limitations, including its case-control design and relatively small sample size. These factors

limit the ability to draw definitive conclusions regarding causality or the broader generalizability of our results. Although we identified an association between TGF-β1 codon 25 G/C polymorphism and CSU, this does not establish a direct effect on disease severity or functional cytokine levels. Ideally, additional research, including functional studies and detailed phenotype subdivisions, is needed to better understand how these genetic variants interact with other factors to influence CSU risk and presentation.

CONCLUSION

This study found that individuals with the G/C genotype at codon 25 (rs1800471) of the TGF-β1 gene and carriers of the C allele have a higher risk of developing CSU. However, TGF-β1 polymorphisms were not associated with clinical features such as age, gender, ASST reactivity, angioedema, or disease severity. These results suggest a genetic predisposition linked to TGF-β1, but not CSU clinical expression. Further research with larger samples is needed to clarify these findings.

Conflict of Interest or financial disclosure: No potential conflict of interest to be reported by the authors.

REFERENCES

1. Kolkhir P, Giménez Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. Nat Rev Dis Primers. 2022;8(1):61.
2. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Baker D, Ballmer Weber B, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734–66.
3. Terhorst Molawi D, Fox L, Siebenhaar F, Metz M, Maurer M. Stepping down treatment in chronic spontaneous urticaria: what we know and what we don't know. Am J Clin Dermatol. 2023;24(4):483–91.
4. Bracken SJ, Abraham S, MacLeod AS. Autoimmune theories of chronic spontaneous urticaria. Front Immunol. 2019;10:627.
5. Rich JN, Borton AJ, Wang X. Transforming growth factor beta signaling in cancer. Microsc Res Tech. 2001;52(4):363–73.
6. Kim SY, Han SW, Kim GW, Lee JM, Kang YM. TGF beta1 polymorphism determines the progression of joint damage in rheumatoid arthritis. Scand J Rheumatol. 2004;33(6):389–94.
7. Awad MR, El Gamel A, Hasleton P, Turner DM, Sinnott PJ, Hutchinson IV. Genotypic variation in the transforming growth factor beta1 gene: association with transforming growth factor beta1 production, fibrotic lung disease, and graft fibrosis after lung transplantation. Transplantation. 1998;66(8):1014–20.
8. Su W, Fan H, Chen M, Wang J, Brand D, He X, et al. Induced CD4+ forkhead box protein positive T cells inhibit mast cell function and established contact hypersensitivity through TGF beta1. J Allergy Clin Immunol. 2012;130(2):444–52.
9. Shah R, Rahaman B, Hurley CK, Posch PE. Allelic diversity in the TGFB1 regulatory region: characterization of novel functional single nucleotide polymorphisms. Hum Genet. 2006;119(1–2):61–74.
10. Jáuregui I, Ortiz de Frutos FJ, Ferrer M, Giménez Arnau A, Sastre J, Bartra J, et al. Assessment of severity and quality of life in chronic urticaria. J Investig Allergol Clin Immunol. 2014;24(2):80–6.
11. Palladino A, Villani F, Pinter E, Visentini M, Asero R. The autologous serum skin test predicts the response to anti-IgE treatment in chronic spontaneous urticaria patients: a prospective study. Eur Ann Allergy Clin Immunol. 2025;57(3):115–9.
12. Ahmed BT, Saeed MY, Noori SH, Amin DM. TGF beta1 gene polymorphism and its correlation with serum level of TGF beta1 in psoriasis vulgaris among Iraqi people. Clin Cosmet Investig Dermatol. 2020;13:889–96.
13. Beck LA, Bernstein J, Maurer M. A review of international recommendations for the diagnosis and management of chronic urticaria. Acta Derm Venereol. 2017;97(2):149–58.
14. Gonçalo M, Giménez Arnau A, Al Ahmad M, Ben Shoshan M, Bernstein JA, Ensina LF, et al. The global burden of chronic urticaria for the patient and society. Br J Dermatol. 2021;184(2):226–36.
15. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA (2) LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy*. 2009;64(9):1256-68.
16. Bajaj AK, Saraswat A, Upadhyay A. Autologous serum skin test in chronic urticaria: a study of 100 patients. Indian J Dermatol Venereol Leprol. 2008;74(2):109–13.
17. El Korashi LA. Interleukin 23/Interleukin 17 axis in chronic spontaneous urticaria: a case control study. Egypt J Med Microbiol. 2021;30(1):169–74.
18. Młynek A, Zalewska Janowska A, Martus P, Staubach P, Siebenhaar F, Church MK, et al. How to assess disease activity in patients with chronic urticaria? Allergy. 2008;63(6):777–80.
19. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the Urticaria Activity Score (UAS): a simple measure of disease activity for use in clinical trials and routine practice. J Allergy Clin Immunol. 2014;133(5):1365–73.
20. Maurer M, Metz M, Anderson J, Talreja N, Young D, Crowley E, et al. Anti KIT Barzolvolimab for chronic

spontaneous urticaria. Allergy. 2025;Advance online publication.
21. Abdel Latif OM, Ashour ZA, Moneer M, Zakaraya DN, El Sayed HM. Evaluation of interleukin 13 versus transforming growth factor beta as a prognostic factor in the management of chronic spontaneous urticaria. Egypt J Immunol. 2025;32(2):119–28.
22. Maurer M, Costa C, Gimenez Arnau A, Guillet G, Labrador Horrillo M, Lapeere H, et al. Antihistamine resistant chronic spontaneous urticaria remains undertreated: 2 year data from the AWARE study. Clin Exp Allergy. 2020;50(10):1166–73.
23. Vikramkumar AG, Kiran P, Prabhu S, Nandakumar G, Kanthraj GR. Autologous serum skin test in chronic urticaria: is there any association with age and gender? Indian J Dermatol. 2014;59(2):181–2.
24. Kumaran MS, Kanwar AJ, Parsad D, Mahajan R. Autologous serum skin test in chronic urticaria: comparison of result with disease severity and other clinical parameters. Indian J Dermatol. 2017;62(2):137–40.
25. El Mahdi AR, Melek N, Abd Allah AM, El Nogoly AM, Abdel Latif OM. Assessment of serum cathelicidin in chronic spontaneous urticaria patients. Egypt J Immunol. 2025;32(2):70–9.
26. Kasperska Zajac A, Brzoza Z, Rogala B, Jura Szołtys E. Plasma levels of interleukin 6 (IL 6), IL 18 and C reactive protein (CRP) in patients with chronic urticaria and angioedema. Eur Cytokine Netw. 2008;19(4):206–12.
27. Sabroe RA, Greaves MW, Francis DM. The autologous serum skin test in chronic idiopathic urticaria: histological findings and clinical relevance. Br J Dermatol. 2002;146(3):434–40.
28. Godse K. Assessment of disease activity in chronic urticaria. Indian J Dermatol. 2012;57(6):475–6.
29. Song Z, Zhai Z, Zhong H, Zhou Z, Chen W, Hao F. Evaluation of autologous serum skin test and skin prick test reactivity to house dust mite in patients with chronic spontaneous urticaria. PLoS One. 2013;8(5):e64142.
30. Niu XL, Zhu LL, Shi MH, Zhang YJ, Gao XH, Qi RQ. Association of positive and negative autologous serum skin test responses with clinical features of chronic spontaneous urticaria in Asian patients: a systematic review and meta-analysis. Exp Ther Med. 2019;17(4):2603–11.
31. Nettis E, Colanardi MC, Ferrannini A, Tursi A. Autoantibodies in chronic idiopathic urticaria: clinical and immunological features. Clin Exp Allergy. 2003;33(9):1100–5.
32. Tavakol M, Movahedi M, Amirzargar AA, Aryan Z, Bidoki AZ, Heidari K, et al. Association of interleukin 10 and transforming growth factor β gene polymorphisms with chronic idiopathic urticaria. Acta Dermatovenerol Croat. 2014;22(4):239–45.
33. Arkwright PD, Chase JM, Babbage S, Pravica V, David TJ, Hutchinson IV. Atopic dermatitis is associated with a low producer transforming growth factor beta(1) cytokine genotype. J Allergy Clin Immunol. 2001;108(2):281–4.
34. Movahedi M, Mahdaviani SA, Rezaei N, Moradi B, Dorkhosh S, Amirzargar AA. IL 10, TGF beta, IL 2, IL 12, and IFN gamma cytokine gene polymorphisms in asthma. J Asthma. 2008;45(9):790–4.
35. Rezaei N, Aghamohammadi A, Shakiba Y, Mahmoudi M, Jalali A, Moradi B, et al. Cytokine gene polymorphisms in common variable immunodeficiency. Int Arch Allergy Immunol. 2009;150(1):1–7.
36. Behniafard N, Amirzargar AA, Gharagozlou M, Delavari F, Hosseinverdi S, Sotoudeh S, et al. Single nucleotide polymorphisms of the genes encoding IL 10 and TGF β1 in Iranian children with atopic dermatitis. Allergol Immunopathol (Madr). 2018;46(2):155–9.
37. Park HJ, Ye YM, Hur GY, Kim SH, Park HS. Association between a TGF beta1 promoter polymorphism and the phenotype of aspirin intolerant chronic urticaria in a Korean population. J Clin Pharm Ther. 2008;33(6):691–8.
38. Shahrokhi S, Pourpak Z, Moin M, Haj Kashani A, Hojati V, Kalantari T, et al. Association between TGF β1 gene polymorphisms and chronic urticaria in Iranian patients. Iran J Allergy Asthma Immunol. 2014;13(5):314–20.

Citation

Atta, A., Ahmed, E., Fawzy, M., Elgharabawy, E. Association between Transforming Growth Factor β1 Gene Polymorphism and Chronic Spontaneous Urticaria. ***Zagazig University Medical Journal*****, 2025; (4747-4759): -. doi: 10.21608/zumj.2025.399690.4032**