Original Article

Association of *SOCS1* and *SOCS3* Gene Polymorphisms with Vitiligo Phenotypes: A Case-Control Study

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Abstract

Aim: Suppressors of cytokine signaling (SOCS) proteins maintain immune homeostasis and are implicated in autoimmune diseases. This case-control study investigated the role of *SOCS1* (rs33989964) and *SOCS3* (rs4969168, rs4969170) gene polymorphisms in vitiligo susceptibility, and examined their potential associations with distinct clinical features to evaluate their contribution to phenotypic heterogeneity in vitiligo.

Materials and Methods: This study included 100 patients with non-segmental vitiligo and 100 age- and sex-matched healthy controls. Genotyping of *SOCS1* (rs33989964) and *SOCS3* (rs4969168 and rs4969170) polymorphisms was performed using TaqMan probe-based polymerase chain reaction. A post-hoc power analysis yielded an estimated statistical power of 98.9% for allelic analyses and 96.2% for genotypic analyses, indicating adequate power for the overall analyses.

Results: The primary analysis revealed no significant association between SOCS polymorphisms and overall vitiligo susceptibility ($P > 0.05$). However, uncorrected exploratory subgroup analyses indicated potential clinical correlations: The *SOCS1* rs33989964 del/del genotype exhibited a preliminary association with progressive disease [$P = 0.025$; odds ratio (OR) = 5.27, 95% confidence interval (CI): 1.08–25.78]. For *SOCS3* rs4969168, the AA genotype demonstrated a potential, uncorrected association with the absence of triggering factors ($P = 0.031$) and the Koebner phenomenon ($P = 0.049$; OR = 4.75, 95% CI: 1.07–21.01), while the A allele was more frequent among patients with familial autoimmunity ($P = 0.036$; OR = 1.83, 95% CI: 1.03–3.23). Additionally, the *SOCS3* rs4969170 AA genotype showed a potential association with poliosis ($P = 0.024$; OR = 2.77, 95% CI: 1.12–6.85), and its A allele was associated, as an uncorrected exploratory finding, with both poliosis ($P = 0.006$; OR = 1.97, 95% CI: 1.21–3.22) and leukotrichia ($P = 0.048$; OR = 1.65, 95% CI: 1.002–2.72).

Conclusion: *SOCS1* and *SOCS3* polymorphisms do not confer overall vitiligo susceptibility. However, these uncorrected exploratory subgroup analyses suggest that they may be associated with adverse clinical features, including progressive disease, familial autoimmunity, Koebner phenomenon, poliosis, and leukotrichia. These findings suggest that *SOCS* variants may act as modulators of disease phenotype and phenotypic variation rather than susceptibility. These uncorrected associations warrant validation in larger, independent, multivariable cohorts.

Keywords: Genetic polymorphism, JAK-STAT pathway, *SOCS1, SOCS3,* vitiligo

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Introduction

Vitiligo is an acquired, chronic autoimmune disorder characterized by the appearance of depigmented macules resulting from the selective destruction of functional melanocytes. At the core of its immunopathogenesis lies a breakdown in immune tolerance, which permits autoreactive CD8+ cytotoxic T lymphocytes to infiltrate the epidermis. Once at the target tissue, these cells secrete high levels of pro-inflammatory cytokines, most notably interferon-gamma (IFN-γ). This establishes a feedback loop that promotes progressive melanocyte loss, continuously recruits additional autoreactive T cells to the lesion site, and drives disease progression.[1]

At the cellular level, the destructive impact of IFN-γ and other pro-inflammatory cytokines is largely orchestrated through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway.[2] To maintain immunological homeostasis and prevent collateral tissue damage, this robust signaling cascade must be tightly restrained. This essential "braking" function is performed by the Suppressor of cytokine signaling (SOCS) family, particularly *SOCS1* and *SOCS3*.[3] Utilizing their unique kinase inhibitory regions, these proteins directly bind to JAK kinases, suppressing JAK catalytic activity, effectively halting STAT hyperactivation and shielding tissues from cytokine-driven pro-inflammatory cascades.[2,3]

Functional single nucleotide polymorphisms within the *SOCS1* and *SOCS3* genes can alter protein expression or stability, potentially disrupting this negative feedback loop. Furthermore, dysregulation or genetic variants of *SOCS1* and *SOCS3* have been widely implicated in the pathogenesis of systemic and cutaneous autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and atopic dermatitis.[4-7] Despite their central role in immune regulation and the clinical relevance of JAK-STAT modulation, the impact of *SOCS1* and *SOCS3* gene polymorphisms on vitiligo remains unexplored. Therefore, this study aims to evaluate the association of specific polymorphisms in *SOCS1* (rs33989964) and *SOCS3* (rs4969168, rs4969170) with overall susceptibility to vitiligo, and to perform exploratory analyses of their potential associations with distinct clinical features, thereby enhancing our understanding of how these variants may act as modulators of vitiligo's phenotypic heterogeneity.

Materials and Methods

Study Population

This case-control study was conducted at the Dermatology Outpatient Department of Uludağ University Faculty of Medicine between March 2019 and June 2019. Approximately 140 patients with suspected depigmentation disorders were screened for eligibility during the initial recruitment phase. Following clinical evaluation, 40 patients who did not meet the inclusion criteria or who declined to participate were excluded, yielding 100 eligible patients. Concurrently, healthy volunteers, comprising patients' relatives and unrelated individuals, were invited to participate to form the control group. Consequently, a final cohort of 200 participants, comprising 100 patients clinically diagnosed with non-segmental vitiligo (NSV) and 100 healthy volunteers matched for age, sex, and ethnicity, was consecutively enrolled in the study. To account for familial genetic influences, the study population was categorized into two cohorts, each subdivided into two subgroups (n = 50 per group). The patient cohort consisted of Group 1 and Group 2. Group 1 comprised vitiligo patients who participated individually, without any relatives enrolled in the study. Group 2 included vitiligo patients with a relative participating in the study. The Healthy Control Cohort consisted of Groups 3 and 4. Group 3 comprised the healthy first- or second-degree relatives of the patients in Group 2. Group 4 included healthy individuals with no personal or familial history of vitiligo, serving as an independent control group. Patients with other concurrent autoimmune diseases were excluded from the study to evaluate the potential genetic association between SOCS polymorphisms and vitiligo. Demographic and clinical parameters—including age, sex, disease triggers, age at onset, disease duration, clinical subtype, disease stage, presence of leukotrichia, poliosis, halo nevus, Koebner phenomenon, and family history of autoimmune diseases—were recorded for all participants. Disease onset was categorized as early-onset (< 12 years) or late-onset (≥ 12 years).[7] Disease activity was defined by the presence of the Koebner phenomenon, the development of new lesions within the past 12 months, or the progression of existing lesions.[8]

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Uludağ University Institutional Ethics Committee (date: 05 March 2019; approval no: 2019-5/9), and written informed consent was obtained from all participants prior to sample collection.

Genetic Analysis

Polymorphisms in the *SOCS1* and *SOCS3* genes were selected from the National Center for Biotechnology Information database (Table 1). Genomic DNA was isolated from peripheral blood samples using the Blood-Animal-Plant DNA Preparation Kit (Jena Bioscience, Germany, PP213) according to the manufacturer's protocol. DNA concentration and purity were assessed spectrophotometrically to ensure high-quality templates for downstream analysis. Genotyping was performed

Table 1. *SOCS1* rs33989964, *SOCS3* rs4969168, and *SOCS3* rs4969170 polymorphisms

Chromosomes	Genes	Locus	Polymorphisms	Alleles	The effect of polymorphism on expression
16p13.13	*SOCS1*	-1478 rs33989964	Deletion	TG > del	**del allele/del/del genotype:** Reduced promoter activity and decreased *SOCS1* protein expression[9]
17q25.3	*SOCS3*	+1383 rs4969168	SNP	A > G	**Variant alleles:** Altered mRNA stability and post-transcriptional regulation via 3' UTR modification[10]
17q25.3	*SOCS3*	-4874 rs4969170	SNP	A > G	**A allele/AA genotype:** Enhanced promoter activity, leading to increased levels of *SOCS3* mRNA and protein[11]

SOCS: Suppressor of cytokine signaling, del: Deletion, SNP: Single nucleotide polymorphism, 3' UTR: 3′ untranslated region

by allelic discrimination assay using the TaqMan system with specific primer-probe mixes and quantitative polymerase chain reaction (qPCR) ProbesMaster (Jena Bioscience, Germany). The PCR reactions were carried out in a total volume of 20 µL, containing 10 µL of qPCR ProbesMaster, 1 µL of Primer-Probe Mix, 7 µL of PCR-grade water, and 2 µL of genomic DNA. Amplification was performed on a Bio-Rad CFX Real-Time PCR Detection System with the following thermal cycling conditions: initial denaturation at 95 °C for 2 minutes, followed by 40 cycles of 95 °C for 15 seconds and 60 °C for 1 minute. To ensure quality control, genotyping analyses were performed blinded to case/control status, and 10% of the samples were randomly selected and re-genotyped to confirm reproducibility, yielding a 100% concordance rate. To align with modern genomic databases and TaqMan assay outputs, the *SOCS1* rs33989964 deletion polymorphism is denoted TG > del, corresponding to the historical CA > del nomenclature.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was utilized to assess the normality of continuous variables. For comparisons involving more than two groups with normally distributed data, a one-way analysis of variance was applied. Categorical variables, including genotype and allele frequencies, were analyzed using Pearson's chi-square test, Fisher's exact test, or the Fisher–Freeman–Halton test, as appropriate. To assess genetic susceptibility and intrafamilial allele segregation, comparative analyses were conducted using three specific stratification models: (i) overall susceptibility (Group 1 + 2 vs. Group 3 + 4); (ii) intrafamilial genetic segregation (Group 2 vs. Group 3); and (iii) background risk allele carriage (Group 3 vs. Group 4).

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the relative disease risk conferred by variant alleles across different genetic models (e.g., allelic, dominant, and recessive). In instances where zero observations occurred within a contingency table cell, the Haldane–Anscombe correction (adding 0.5 to each cell) was applied to allow for OR and CI estimation, although such small cell counts can lead to wide CIs and statistical instability. However, in specific clinical subgroup analyses in which a reliable OR could not be computed because a genotype was completely absent, the association was evaluated solely on the exact *P*-value. Genotype frequencies in the control group were tested for Hardy–Weinberg equilibrium (HWE) using a goodness-of-fit chi-square test, with $P > 0.05$ indicating conformity. A two-tailed *P*-value < 0.05 was considered statistically significant for the primary susceptibility analyses; however, for the secondary clinical subgroup evaluations, *P*-values were interpreted as nominal, uncorrected, exploratory signals because no corrections for multiple testing were applied. A post-hoc power analysis was conducted using G*Power software (version 3.1.9). Based on the genotype distribution data, the input parameters were set as follows: a moderate effect size ($w = 0.3$), a statistical significance level (α) of 0.05, and a total sample size of 200 individuals. The calculation yielded an estimated statistical power of 98.9% for the allelic analysis (degrees of freedom = 1) and 96.2% for the genotypic analysis (degrees of freedom = 2). These results indicate adequate power for the overall analyses. However, we acknowledge that this approach neither substitutes for an a priori sample size calculation nor resolves the limited statistical power of the exploratory clinical subgroup analyses.

Results

Demographic and baseline clinical characteristics were similarly distributed between the patient and control groups, with generalized vitiligo being the most prevalent clinical subtype among the cases (Table 2). Disease onset was primarily observed before early adulthood, although a distinct subgroup presented with late-onset vitiligo. While most patients reported no specific precipitating event, emotional stress was the most frequent trigger among those with identifiable precipitating factors, followed by ultraviolet (UVB) exposure and physical trauma (Table 3).

Table 2. Age and gender distribution of patient and control subgroups

	Group 1 (patient)	Group 2 (patient)	Group 3 (control)	Group 4 (control)	*P*
n	50	50	50	50	
Age					0.917
Mean age ± SD	34.76 ± 16.04	34.7 ± 17.95	34.49 ± 11.49	36.40 ± 9.53	
Median age; min-max	35;7–73	35.5;6–74	35;9–64	38;7–54	
Gender					0.278
Female	26	28	28	35	
Male	24	22	22	15	

Statistically significant *P*-values ($P < 0.05$) are indicated in bold where applicable
SD: Standard deviation, min: Minimum, max: Maximum

Table 3. Clinical and demographic characteristics of vitiligo patients

	n
n	100
Age (years) Mean ± SD Median; min-max	 34.73 ± 16.94 35;6–74
Age of onset of disease (years) Mean ± SD Median; min-max Early onset (< 12 years) Late onset (> 12 years) Unknown	 26.71 ± 17.11 25.5 (1–71) 24 75 1
Disease duration (years) Mean ± SD Median; min-max	 6.43 ± 6.63 4;1–35
Triggering factors Stress Ultraviolet Trauma No Unknown	 29 6 3 47 15
Clinical type Generalized Focal Acral/acrofacial	 55 18 27
Disease stage Active-progressive Stable	 50 50
Koebner phenomenon Yes No	 20 80
Halo nevus Yes No Unknown	 8 87 5
Leukotrichia Yes No	 34 66
Poliosis Yes No	 17 83
Family history of autoimmune disease Yes No Unknown	 40 55 5

"Unknown" categories represent missing clinical data for specific parameters
SD: Standard deviation, min: Minimum, max: Maximum

The genotype distributions of all investigated polymorphisms in the control group were consistent with the HWE ($P = 0.618$ for *SOCS1* rs33989964; $P = 0.613$ for *SOCS3* rs4969168; and $P = 0.477$ for *SOCS3* rs4969170). According to our stratification models, the evaluation of overall susceptibility (Group 1 + 2 vs. Group 3 + 4) revealed no significant differences in genotype or allele frequencies for any of the investigated polymorphisms ($P > 0.05$). Similarly, intrafamilial genetic segregation analysis (Group 2 vs. Group 3) and background risk evaluation (Group 3 vs. Group 4) did not reach statistical significance (Table 4).

Further stratifications based on clinical and demographic variables indicated several potential genotype-phenotype correlations among the vitiligo patients (Tables 5 and 6). Regarding disease activity, at an uncorrected level, the *SOCS1* rs33989964 del/del genotype was observed to be more frequent among patients with progressive disease than among those with stable disease (TG/del + TG/TG genotypes) ($P = 0.025$; OR = 5.27, 95% CI: 1.08–25.78). Evaluation of the *SOCS3* rs4969168 variant showed a potential association with the Koebner phenomenon, with the AA genotype more frequent in affected patients; this was an uncorrected exploratory finding ($P = 0.049$; OR = 4.75, 95% CI: 1.07–21.01). This AA genotype was also suggestively associated with the absence of identifiable triggering factors at disease onset ($P = 0.031$). However, due to the small sample size within this specific subgroup, which necessitated exact statistical corrections, the corresponding OR exhibited a wide CI that crossed 1.0 (OR = 0.08, 95% CI: 0.003–2.07). In addition to these clinical features, the *SOCS3* rs4969168 A allele demonstrated an unadjusted, exploratory association with a positive family history of autoimmune diseases ($P = 0.036$; OR = 1.83, 95% CI: 1.03–3.23). Regarding follicular involvement, the *SOCS3* rs4969170 polymorphism was potentially associated with both poliosis and leukotrichia. Specifically, the AA genotype ($P = 0.024$; OR = 2.77, 95% CI: 1.12–6.85) and the A allele ($P = 0.006$; OR = 1.97, 95% CI: 1.21–3.22) demonstrated a potential uncorrected association with the presence of poliosis, while carriage of the A allele showed a borderline uncorrected exploratory association with leukotrichia ($P =$

0.048; OR = 1.65, 95% CI: 1.002–2.72). Certain ORs in these clinical subgroups exhibit wide CIs due to small sample sizes, necessitating the Haldane-Anscombe correction. Given this statistical instability and the fact that the reported *P*-values are exploratory and uncorrected for multiple testing, these clinical correlations should be interpreted cautiously as preliminary signals.

Table 4. Genotype and allele distribution of the polymorphisms *SOCS1* rs33989964, *SOCS3* rs4969168, *SOCS3* rs4969170 in patients with vitiligo and healthy controls

	Patient (P)		Control (C)			*P* (P-C)
Polymorphisms	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Total**	
SOCS1 rs33989964						
TG/TG	21	20	23	25	89	0.577
TG/del	24	24	21	20	89	
del/del	5	6	6	5	22	
TG	66	64	67	70	267	0.458
del	34	36	33	30	133	
SOCS3 rs4969168						
GG	27	30	26	34	117	0.491
AG	18	17	22	14	71	
AA	5	3	2	2	12	
G	72	77	74	82	305	0.411
A	28	23	26	18	95	
SOCS3 rs4969170						
GG	12	9	10	9	40	0.414
AG	21	27	27	30	105	
AA	17	14	13	11	55	
-G	45	45	47	48	185	0.616
A	55	55	53	52	215	

SOCS: Suppressor of cytokine signaling; del: deletion. $P < 0.05$ was considered statistically significant

Table 5. Significant associations between clinical/demographic features and *SOCS1* and *SOCS3* polymorphisms

***SOCS1* rs33989964**	**Genotype**										**Alleles**		
	TG/TG	**TG/del**	**del/del**	***P***	**del/del**	**TG/TG + TG/del**	***P***	**TG/TG**	**TG/del + del/del**	***P***	**TG**	**del**	***P***
Stage of disease													
Progressive	18	23	9	0.076	9	41	**0.025**	18	32	0.443	59	41	0.075
Stable	23	25	2		2	48		23	27		71	29	
***SOCS3* rs4969168**	**Genotype**										**Alleles**		
	AA	**AG**	**GG**	***P***	**GG**	**AG + AA**	***P***	**AA**	**AG + GG**	***P***	**G**	**A**	***P***
Triggering factors													
Yes	0	13	25	0.070	25	13	0.241	0	38	**0.031**	63	13	0.055
No	6	16	25		25	22		6	41		66	28	
Koebner phenomenon													
Yes	4	5	11	0.073	11	9	0.840	4	16	**0.049**	27	13	0.256
No	4	30	46		46	34		4	76		122	38	
Familial autoimmunity													
Yes	4	17	19	0.138	19	21	0.053	4	36	0.236	55	25	**0.036**
No	2	16	37		37	18		2	53		90	20	

Table 5. Continued

SOCS3 rs4969170	Genotype										Alleles		
	AA	AG	GG	*P*	GG	AG + AA	*P*	AA	AG + GG	*P*	G	A	*P*
Leukotrichia													
Yes	14	16	4	0.148	4	30	0.104	14	20	0.114	24	44	0.048
No	17	32	17		17	49		17	49		66	66	
Poliosis													
Yes	9	8	0	**0.024**	0	17	**0.020**	9	8	**0.032**	8	26	0.006
No	22	40	21		21	62		22	61		82	84	

SOCS: Suppressor of cytokine signaling; del: deletion. $P < 0.05$ was considered to be statistically significant

Table 6. Significant associations and risk estimates (odds ratios)

Clinical parameter	Polymorphism	Model/comparison	*P*-value	OR (95% CI)
Disease progression	*SOCS1* rs33989964	del/del vs. TG/TG + TG/del	0.025	5.27 (1.08–25.78)
Koebner's phenomenon	*SOCS3* rs4969168	AA vs. AG + GG	0.049	4.75 (1.07–21.01)
Absence of triggering Factors	*SOCS3* rs4969168	AA vs. AG + GG	0.031	0.08[†] (0.003–2.07
Familial autoimmunity	*SOCS3* rs4969168	A allele frequency	0.036	1.83 (1.03–3.23)
Poliosis	*SOCS3* rs4969170	AA vs. AG + GG (recessive)	0.024	2.77 (1.12–6.85)
Poliosis	*SOCS3* rs4969170	GG vs. AG + AA (dominant)	0.020	N/A[‡†] (-)
Poliosis	*SOCS3* rs4969170	A allele frequency	0.006	1.97 (1.21–3.22)
Leukotrichia	*SOCS3* rs4969170	A allele frequency	0.048	1.65(1.002–2.72)

[†]Haldane–Anscombe Correction: Applied to estimate the OR and 95% CI due to zero observations in contingency table cells
[‡]Zero Frequency: A reliable odds ratio could not be computed because of the complete absence of the specified genotype in the clinical subgroup
CI: Confidence interval, N/A: Not applicable, OR: Odds ratio, SOCS: Suppressor of cytokine signaling

Discussion

To the best of our knowledge, the current study represents the first investigation into the association between *SOCS1* and *SOCS3* gene polymorphisms and NSV. The primary finding of our study is the lack of significant association between the investigated SOCS polymorphisms and overall susceptibility to disease onset. Instead, uncorrected exploratory subgroup analyses suggest that *SOCS1* and *SOCS3* variants may act as modulators of specific clinical phenotypes and disease severity and may be more closely related to phenotypic variation than to overall disease susceptibility. This observation aligns with existing literature on other autoimmune conditions, where *SOCS* variants often influence clinical heterogeneity rather than absolute risk.[4]

Specifically, our study revealed a preliminary, uncorrected association between the *SOCS1* rs33989964 del/del genotype and progressive vitiligo (OR = 5.27). Mechanistically, this potential link parallels recent discoveries regarding human *SOCS1* haploinsufficiency, wherein loss-of-function variants lead to severe autoimmunity characterized by hyperactivation of the JAK/STAT pathway.[12] Although functional protein activity was not directly evaluated in our cohort, the reduced promoter activity associated with the del/del genotype may fail to provide the necessary negative feedback against IFN-γ-driven CD8+ T-cell cytotoxicity. Consequently, this dysregulated signaling might facilitate the heightened proinflammatory environment required for progressive melanocyte destruction.[13]

Regarding follicular involvement, the *SOCS3* rs4969170 polymorphism exhibited potential associations with both poliosis (AA genotype and A allele) and leukotrichia (A allele). These genotype-phenotype correlations can be elucidated by existing functional in vitro data, which demonstrate that the AA genotype at the *SOCS3* rs4969170 promoter locus enhances transcriptional activity, leading to increased *SOCS3* mRNA and protein expression.[14] In the context of vitiligo, this constitutive overexpression of *SOCS3* is hypothesized to act as a negative regulator that excessively suppresses downstream signaling. Because the balanced activation of STAT3 is crucial for the survival, proliferation, and migration of melanocyte stem cells located in the follicular bulge, its potential inhibition by genetically driven overexpression of *SOCS3* may impair the regenerative capacity of the hair follicle, which may clinically manifest as leukotrichia and poliosis. However, due to the limited sample sizes in these clinical subgroups, these secondary findings must be interpreted with caution, as they represent uncorrected exploratory signals rather than definitive prognostic markers.

Furthermore, evaluation of the *SOCS3* rs4969168 variant showed a potential association with Koebner phenomenon, with the AA genotype being more frequent in affected

patients, which was an uncorrected finding (OR = 4.75). This AA genotype was also potentially associated with the absence of identifiable triggering factors at disease onset. Although the corresponding OR exhibited a wide CI due to the small sample size in this subgroup, this association suggests that the variant may indicate an intrinsic genetic predisposition contributing to spontaneous immune dysregulation, potentially circumventing the need for external environmental stimuli. Additionally, the *SOCS3* rs4969168 A allele was observed to be more prevalent among patients with a positive family history of autoimmune diseases, as an uncorrected exploratory finding (OR = 1.83). Collectively, these exploratory clinical correlations support the hypothesis that *SOCS3* polymorphisms act as potential systemic modulators of immune tolerance, extending their impact beyond localized depigmentation to a broader autoimmune diathesis.

The lack of an overall association with susceptibility in our cohort is consistent with previous research on SOCS polymorphisms across various immune-mediated and malignant diseases in the Turkish population. Studies evaluating the *SOCS1* rs33989964 polymorphism found no association with overall susceptibility to ulcerative colitis or colorectal cancer, and similarly, the *SOCS3* variants showed no significant association with psoriasis in Turkish cohorts.[15-17] Conversely, the *SOCS1* rs33989964 del/del genotype has been significantly associated with disease characteristics in hematological malignancies, such as multiple myeloma, and in gastric cancer.[9,10]

Although these studies encompass diverse disease groups, the consistent finding is that *SOCS* polymorphisms rarely confer overall disease susceptibility but may influence clinical course or prognosis. Importantly, the lack of significant associations in Turkish populations for autoimmune diseases such as ulcerative colitis, psoriasis, and vitiligo (including our study) may also reflect ethnic and genetic background differences that shape *v* gene function.

Furthermore, our observation that *SOCS* polymorphisms may influence disease characteristics rather than overall susceptibility aligns with the concept of gene–environment interactions in multifactorial diseases. In the dermatological context, *SOCS3* functions as a key JAK/STAT modulator in immune-mediated diseases triggered by environmental factors. For instance, in atopic dermatitis, *SOCS3* regulates Th2-mediated allergic responses provoked by environmental allergens and pathogens.[11]

Similarly, in psoriasis, environmental triggers such as mechanical stress and trauma exacerbate inflammation, a process in which *SOCS3* expression is often dysregulated, leading to sustained STAT3 activation.[18] Furthermore, chronic UVB exposure has been shown to directly suppress *SOCS3* expression in the skin, thereby amplifying local inflammatory responses.[18] Together, these findings underscore that genetic polymorphisms rarely act in isolation but rather function within complex biological networks shaped by environmental exposures. In this context, our study's observation that SOCS variants were not directly associated with vitiligo susceptibility but showed exploratory correlations with clinical features such as Koebner phenomenon, leukotrichia, and disease progression suggests that *SOCS* variants may modulate the phenotypic expression of vitiligo in conjunction with environmental triggers, including psychological stress, UVB exposure, or local trauma.

Given the uncorrected exploratory associations observed between *SOCS* variants and adverse clinical features, our findings suggest that these genetic variants may impair the negative feedback regulation of the JAK/STAT signaling pathway, potentially contributing to melanocyte destruction mediated by IFN-γ and interleukin-6.[2,19]

Ultimately, this highlights the potential role of the SOCS/JAK/STAT signaling axis in vitiligo pathogenesis. Targeted modulation of this pathway, potentially through topical or systemic SOCS mimetics and through selective JAK inhibitors, may offer therapeutic avenues for patients with progressive and refractory variants of vitiligo.[2,20]

Study Limitations

Several limitations of this study should be acknowledged. First, while the overall sample size (n = 200) provided a basis for evaluating general susceptibility, the limited number of patients in specific clinical subgroups restricted the statistical power of the sub-phenotype analyses, necessitating the use of exact *P*-values and the Haldane-Anscombe correction for zero frequencies. Because of these small subgroup sizes, multivariable logistic regression, adjusted for confounding clinical variables, could not be performed reliably. Furthermore, no formal multiple testing correction (such as Bonferroni) was applied to the subgroup analyses to avoid substantially increasing the risk of Type II (false-negative) errors; therefore, these uncorrected clinical associations should be interpreted as exploratory findings rather than definitive risk factors.

Second, the study was conducted within a specific demographic cohort, the Turkish population, which may limit the generalizability of the findings to populations with different genetic backgrounds. Third, the cross-sectional, hospital-based design inherently restricts the ability to establish definitive causal relationships, and because some healthy controls were relatives of patients, a potential lack of statistical independence due to familial clustering could not be entirely excluded. The

absence of functional molecular assays, such as measuring *SOCS1* and *SOCS3* mRNA or protein expression in skin biopsies or serum, prevents direct confirmation of the biological mechanisms by which these genetic variants exert their phenotypic effects; consequently, our mechanistic explanations remain hypothetical and are based on existing literature.

Conclusion

The primary finding of this case-control study *is* that *SOCS1* (rs33989964) and *SOCS3* (rs4969168, rs4969170) gene polymorphisms may not confer overall susceptibility to NSV. However, uncorrected exploratory subgroup analyses suggest that these variants may influence the clinical phenotype and disease severity. Our preliminary data suggest that the *SOCS1* rs33989964 del/del genotype is potentially associated with progressive vitiligo, whereas the *SOCS3* rs4969168 AA genotype is potentially associated with an increased frequency of the Koebner phenomenon. Additionally, the *SOCS3* rs4969170 AA genotype exhibited an exploratory correlation with follicular depigmentation, particularly poliosis. These results suggest that *SOCS* variants may act as modulators of disease phenotype and may be more closely related to phenotypic variation than to overall disease susceptibility. Identifying these genetic modulators provides deeper insights into the complex pathogenesis of vitiligo; however, these exploratory signals require further validation in larger, independent, multivariable cohorts before they can be considered clinically actionable.

Ethics

Ethics Committee Approval: The study protocol was approved by the Uludağ University Institutional Ethics Committee (date: 05 March 2019; approval no: 2019-5/9).

Informed Consent: Written informed consent was obtained from all participants prior to sample collection.

Authorship Contributions

Surgical and Medical Practices: E.I.Y., H.S., Ş.G.T., E.B.B., K.A., S.Y., Concept: E.I.Y., H.S., Ş.G.T., E.B.B., K.A., S.Y., G.Ö., H.B.O., Design: E.I.Y., H.S., Ş.G.T., E.B.B., K.A., S.Y., G.Ö., H.B.O., Data Collection or Processing: E.I.Y., H.S., Ş.G.T., H.B.O., Analysis or Interpretation: E.I.Y., H.S., G.Ö., Literature Search: E.I.Y., H.S., Writing: E.I.Y., H.S., Ş.G.T., E.B.B., K.A., S.Y., G.Ö., H.B.O.

Footnotes

Conflict of Interest: One of the authors, Emel Bülbül Başkan, is a member of the Editorial Board of the Turkish Journal of Dermatology. However, she was not involved in any stage of the editorial decision-making process for this manuscript. The manuscript was evaluated independently by editors from other institutions. The other authors declare no conflicts of interest.

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