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***IFNG* rs2430561 polymorphism and its association with disease onset, cutaneous severity, and activity in Vietnamese patients with lupus erythematosus**

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Availability of data and materials: the datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Abstract

Interferon (IFN)- γ plays a central role in lupus pathogenesis, and the *IFNG* rs2430561 (+874 T/A) polymorphism has been linked to systemic lupus erythematosus (SLE) in several populations. This study investigated the association of rs2430561 with disease onset, cutaneous severity, and global activity in Vietnamese patients with lupus erythematosus (LE). A case-control study was conducted on 34 LE patients and 34 age- and sex-matched healthy controls. Clinical characteristics, Cutaneous Lupus Disease Area and Severity Index (CLASI), and Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) were collected. Genotyping was performed using allele-specific polymerase chain reaction (PCR). Genotype distribution differed significantly between patients and controls ($p=0.048$). Carriers of the A allele had a younger disease onset than TT patients (33.6 ± 7.7 vs. 47.1 ± 13.6 years) and showed a higher likelihood of onset ≤ 40 years (odds ratio [OR]=2.4; $p=0.026$). The rs2430561 genotype was associated with cutaneous severity: mean CLASI scores were AA 14.7, TA 11.8, and TT 5.8 ($p=0.003$). A-allele carriers had a 5.8-fold higher prevalence of severe CLASI (≥ 21 ; $p=0.010$). Systemic disease activity also differed: mean SLEDAI-2K scores were AA 12.0, TA 11.8, and TT 6.3 ($p=0.010$). The A allele was associated with a 4.7-fold higher prevalence of severe activity (>12 ; $p=0.001$). The *IFNG* rs2430561 A allele is associated with earlier onset and more severe cutaneous and systemic disease in Vietnamese LE patients, highlighting the potential contribution of IFN- γ pathway variation to disease expression.

Introduction

Interferon (IFN)- γ is a key pro-inflammatory cytokine produced mainly by T lymphocytes and natural killer cells, and plays a central role in both innate and adaptive immunity.¹ In systemic lupus erythematosus (SLE), activation of the IFN- γ signaling pathway has been repeatedly observed, and several studies have proposed IFN- γ activity as a marker of disease activity.² The *IFNG* gene, located on chromosome 12q24, consists of four exons and three introns, and has been implicated in multiple immune-mediated conditions including autoimmune encephalitis, disseminated tuberculosis, schizophrenia, rheumatoid arthritis, and lupus.^{3,4} Through the Janus kinase (JAK)1/JAK2-signal transducer and activator of transcription (STAT)1 pathway, IFN- γ enhances macrophage activation, cytotoxic T-cell function and T helper (Th)1 differentiation.^{5,6}

Genetic variation within *IFNG* and its receptors may modulate disease susceptibility. In Japanese SLE patients, polymorphisms in *IFNGR1* and *IFNGR2* were more frequent than in healthy controls, suggesting

impaired receptor function may contribute to lupus pathogenesis.⁷ Several *IFNG* single-nucleotide polymorphisms (SNPs) have been associated with SLE across populations. In Korean studies, risk alleles within nuclear factor (NF)- κ B binding regions increased *IFNG* expression and were linked to higher SLE susceptibility.⁸ Marut *et al.* also reported associations between *IFNG* (+874A) and joint manifestations.⁹ Additional variants in the IFN-STAT-interferon regulatory factor (IRF) axis (*IRF3*, *IRF5*, *IRF8*, *STAT4*) further highlight the importance of IFN signaling in SLE.¹⁰⁻¹³ Epigenetic dysregulation, including DNA methylation and histone acetylation at the *IFNG* locus, can increase Th1 activation and intracellular IFN- γ transcription, promoting inflammatory responses that contribute to lupus development.¹⁴

The SNP rs2430561 (+874 T/A), located in intron 1 of *IFNG* within a putative NF- κ B binding site, is the most widely studied polymorphism.¹⁵ Although functional data remain inconsistent – some studies report higher IFN- γ levels in TT carriers while others find no difference⁶ – rs2430561 has been linked to SLE susceptibility in multiple populations. Experimental lupus models strongly support a pathogenic role of IFN- γ , showing that increased IFN- γ accelerates nephritis and mortality, whereas IFN- γ blockade ameliorates disease.⁶

Human association studies of rs2430561 are population-specific. In Chinese SLE patients, TA and TA+AA genotypes increased disease risk and were associated with nephritis and anti-double-stranded (ds)DNA positivity.¹⁶ Thai studies linked AA/AT genotypes with lupus arthritis.⁹ In Egyptian lupus nephritis patients, the AT genotype increased renal involvement.¹⁷ Korean studies confirmed rs2430561 as a susceptibility variant, with the A allele associated with higher *IFNG* expression.⁸ Brazilian women with SLE showed a higher frequency of the TA genotype.¹⁸ Meta-analyses also support a modest association between +874 T>A and SLE.¹⁹

Despite extensive global research, no studies have examined rs2430561 in Vietnamese patients. Given ethnic differences in allele distribution and inconsistent functional findings, investigating the clinical and genetic impact of *IFNG* rs2430561 in Vietnamese lupus patients is needed to clarify its relevance in this population.

Materials and Methods

Study design and ethical approval

This investigation was conducted as a case-control study. The study protocol was approved by the Ethics Council of Pham Ngoc Thach University of Medicine (Vietnam; Decision No. 918/TĐHYKPNT-HĐĐĐ, dated November 14, 2023). All participants provided written informed consent prior to enrollment.

Study population

We recruited 34 patients with lupus erythematosus (LE) and 34 healthy controls at the Ho Chi Minh City Hospital of Dermato-Venereology (Vietnam) between February 2024 and December 2024. Patients were included if they were ≥ 18 years old, of Vietnamese nationality, and fulfilled the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology²⁰ classification criteria for SLE or the 2021 European Society of Dermatology and Psychiatry guideline criteria for cutaneous lupus erythematosus (CLE).²¹ The control group consisted of age- and sex-matched healthy volunteers ≥ 18 years old without clinical features of lupus or other autoimmune diseases based on clinical assessment at recruitment. Eligibility was determined through clinical history-taking and examination; formal serological screening was not conducted in the control group. Exclusion criteria for both groups included pregnancy, breastfeeding, severe or life-threatening concurrent illness, and other autoimmune diseases.

Clinical and laboratory assessment

For all patients, demographic data, clinical history, and laboratory parameters including complete blood count, urinalysis, serum creatinine, C3, C4, and anti-dsDNA were collected from patient records. Cutaneous disease severity was quantified using the Cutaneous Lupus Disease Area and Severity Index (CLASI).²² Systemic disease activity was measured using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K).²³

Genotyping

Venous blood (2 mL) was collected from all participants into ethylene diamine tetraacetic acid tubes. Genomic DNA was isolated from peripheral blood leukocytes using a TopPureBlood DNA Extraction Kit (ABT, Vietnam) according to the manufacturer's protocol. The *IFNG* rs2430561 polymorphism was genotyped using an allele-specific polymerase chain reaction (PCR) protocol. PCR products were amplified using MyTaq™ HS Mix (Bioline, UK) and visualized on a 1.0% agarose gel stained with ethidium bromide. Genotypes (AA, TT, or AT) were determined based on the band patterns in the allele-specific lanes.

Statistical analysis

Data were managed using EpiData 3.1 and analyzed with SPSS Statistics version 20. Categorical variables were expressed as frequencies and percentages, and differences between groups were assessed using the Chi-square test or Fisher's exact test, as appropriate. Quantitative variables were tested for normality; normally distributed data were presented as mean $\pm$ standard deviation and compared using Student's *t*-test or one-way analysis of variance, while non-normally distributed data were presented as median and interquartile range and compared using the Mann-Whitney U test or Kruskal-Wallis H test. Odds ratios (OR) were calculated to assess risk. A two-sided *p*-value <0.05 was considered statistically significant. Deviation from Hardy-Weinberg equilibrium in the control group was assessed using the Chi-square test.

Results

The study cohort included 34 LE patients and 34 healthy controls, who were successfully matched for age (mean 49.6 ± 11.2 vs. 46.5 ± 14.7 years, $p=0.576$) and sex (73.5% female in both groups, $p=1.000$). Among the patients, the mean age of disease onset was 43.0 ± 13.7 years, with 50% classified as SLE.

Key clinical findings included skin pigmentation disorders (64.7%) and photosensitivity (50.0%), while serological analysis showed anti-dsDNA positivity in 44.1% of patients, low C3 in 20.6%, and low C4 in 14.7%. Disease severity and activity were generally mild to moderate, with a mean CLASI score of 8.2 ± 5.9 and a mean SLEDAI-2K score of 8.26 ± 5.20 .

In the control group, the observed genotype distribution was consistent with Hardy-Weinberg equilibrium, which supports the quality of genotyping and suggests that the control sample was representative of the underlying population for this *locus*. A significant difference in the *IFNG* rs2430561 genotype distribution was observed between groups ($p=0.048$). The patient group consisted of 64.7% TT, 26.5% TA, and 8.8% AA, whereas the control group comprised 50% TT, 50% TA, and 0% AA. No significant difference was found in overall allele frequencies ($p=0.084$) (Table 1).

The rs2430561 genotype was significantly associated with age of disease onset ($p=0.037$). Patients with the TA genotype had the earliest mean onset (33.6 ± 7.7 years), and patients carrying an A allele (AA/TA) were 2.4 times more likely to have disease onset at or before 40 years of age ($p=0.026$).

Furthermore, the genotype was significantly associated with mean CLASI score ($p=0.003$) and mean SLEDAI-2K score ($p=0.010$). Mean scores for both CLASI (AA: 14.7, TA: 11.8) and SLEDAI-2K (AA: 12, TA: 11.8) were highest in A-allele carriers compared to the TT genotype (CLASI: 5.8; SLEDAI-2K: 6.3) (Tables 2 and 3).

Patients with the A allele had a 5.8-fold increased risk of severe skin disease (CLASI ≥ 21 , $p=0.010$) (Table 4) and a 4.7-fold increased risk of severe systemic activity (SLEDAI-2K >12 , $p=0.001$) (Table 5). When AA+TA were compared to TT, the odds of severe activity were 21-fold higher (OR=21.0; 95% confidence interval [CI]: 2.09-210.14; $p=0.004$) (data not shown).

No significant associations were found between the genotype and specific cutaneous lesions, hematological parameters, renal function, or serological markers like anti-dsDNA, C3, or C4 (data not shown).

Discussion

This study is the first, to our knowledge, to investigate the *IFNG* rs2430561 SNP in a Vietnamese population with LE. Our discussion focuses on the primary findings from our results.

Genotype distribution of rs2430561

In the patient group, the genotype frequencies of *IFNG* rs2430561 were TT 64.7%, TA 26.5%, and AA 8.8%. In the control group, TT and TA each accounted for 50.0%, and no AA genotype was observed. The difference in genotype distribution between cases and controls was statistically significant ($p=0.048$), consistent with previous reports by Hildson *et al.* ($p=0.00$), Liu *et al.* ($p=0.035$), Seleem *et al.* ($p=0.038$), and Kim *et al.* ($p=0.029$).^{8,16-18}

The genotype frequencies in this Vietnamese lupus cohort closely resemble those reported in East Asian SLE cohorts: Kim *et al.* (TT 67.8%, TA 22.5%, AA 2.4%) and Liu *et al.* (TT 74.3%, TA 23.7%, AA 2%).^{8,16} They also align with the 1000 Genomes data for East Asians (TT 71.2%, TA 25.8%, AA 3%), suggesting an ethnicity-specific distribution of rs2430561. In contrast, studies in other populations or in specific clinical subsets (joint-dominant SLE, lupus nephritis, female-only cohorts) have reported markedly different genotype patterns, for example: Marut *et al.* (TT 5.8%, TA 42.8%, AA 51.3%), Hildson *et al.* (TT 3.03%, TA 88.87%, AA 8.08%), and Seleem *et al.* (TT 5.6%, TA 41.6%, AA 52.8%).^{9,17,18} These discrepancies likely reflect differences in ethnicity, clinical phenotype, and recruitment criteria. Interestingly, AA was observed only in lupus patients (8.8%) and not in controls. Together with the higher frequency of TT in patients, this suggests that both homozygous genotypes (TT and AA) may confer increased susceptibility in this population. Experimental data indicate that the TT genotype is associated with increased IFN- γ production, whereas AA may reduce IFN- γ , potentially disturbing Th2 regulation and enhancing type I IFN responses – both pathways implicated in lupus pathogenesis.^{15,24-26} Furthermore,

while IFN- γ is traditionally implicated in lupus progression through Th1 activation, our study revealed an inverse association where the “low-producing” A allele correlated with greater disease severity. This finding aligns with the concept of a protective role for IFN- γ during specific disease stages. Evidence from Murphy Roths Large-lymphoproliferation murine models suggests that early IFN- γ signaling is crucial for the efficient clearance of apoptotic debris and the prevention of hyperinflammation. We propose that the A allele may result in insufficient baseline IFN- γ , leading to defective removal of endogenous antigens or an inability to constrain the inflammatory Th17 lineage, thereby accelerating disease onset and exacerbating both cutaneous and systemic activity.²⁷ Evidence from other autoimmune diseases, such as multiple sclerosis, also supports a role for the A allele in increasing disease susceptibility and organ damage.²⁸ While Liu *et al.* reported TA+AA (rather than TT+AA) as the risk genotypes,¹⁶ the present study suggests a different pattern. Given the limited sample size, larger multi-center studies are needed to clarify the precise genetic model (dominant, recessive or over-dominant) by which rs2430561 influences lupus risk.

Associations with epidemiologic and clinical features

The mean age of patients was 49.6 $\pm$ 11.2 years, higher than in previous rs2430561 lupus studies,¹⁶⁻¹⁸ but no significant association was found between genotype and patient age ($p=0.173$). Likewise, although women predominated (73.5%; female:male ratio 2.7:1), there was no significant association between rs2430561 and sex ($p=0.483$), in contrast to Liu *et al.*, who reported TA and AA as risk genotypes in women.¹⁶

A key novel finding of this study is the association between rs2430561 and age at disease onset. The mean onset age was 43.0 $\pm$ 13.8 years overall, but patients with the TA genotype had the earliest onset (33.6 $\pm$ 7.7 years). Genotype distribution differed significantly by onset age ($p=0.037$), and when patients were stratified into <40 vs. $\geq$ 40 years, carriers of AA or TA were 2.4 times more likely to develop lupus before age 40 than TT carriers (OR=2.4; 95% CI: 1.1-5.4; $p=0.036$). This is, to our knowledge, the first report linking rs2430561 to age at onset. We propose a mechanistic link *via* *STAT4*, which regulates *IFNG* transcription and Th1 responses. Increased *STAT4* expression has been associated with lupus nephritis, renal failure, and earlier lupus onset.²⁹⁻³¹ Thus, rs2430561 may affect age at onset through *IFNG-STAT4*-Th1 pathways, although further molecular studies are required to confirm this hypothesis.

Regarding skin and mucosal manifestations, photosensitivity, malar rash, discoid lesions, dyspigmentation, mucosal lesions, and patchy alopecia were distributed across genotypes, and no

significant association was found between rs2430561 and any specific cutaneous pattern. This agrees with Liu *et al.*, who found no genotype-phenotype association for skin rash, photosensitivity or mucosal lesions,¹⁶ but differs from Hildson *et al.*, who reported an association with photosensitivity ($p=0.01$).¹⁸ Environmental UV exposure, geographical latitude, outdoor habits, diet, smoking, alcohol and medication use, together with the dynamic nature of cutaneous lesions and the immunomodulatory role of IFN- γ on Th2-mediated inflammation, are likely contributors to these discrepancies.³²⁻³⁴

Associations with laboratory parameters

No statistically significant associations were observed between rs2430561 and hematologic abnormalities (anemia, leukopenia, thrombocytopenia), consistent with the negative findings of Liu and Hildson.^{16,18} Experimental data in other diseases (*e.g.*, acute myeloid leukemia) suggest that combined dysregulation of pro- and anti-inflammatory cytokines, including IFN- γ , interleukin (IL)-4, and IL-10, can influence bone marrow hematopoiesis,^{35,36} but such mechanisms have not yet been demonstrated in lupus cohorts. Similarly, rs2430561 showed no significant association with urinalysis abnormalities (hematuria, leukocyturia, proteinuria), estimated glomerular filtration rate (eGFR) categories, or C3, C4, and anti-dsDNA status (all $p>0.05$), in contrast to previous studies where TA+AA genotypes were linked to lupus nephritis and anti-dsDNA positivity.^{16,17} Possible explanations include the predominance of mild renal dysfunction (G2-G3a rather than G3b+), absence of renal biopsy data, qualitative rather than quantitative urine testing, and the impact of ongoing treatment.³⁶⁻³⁸

Although anti-dsDNA has high specificity for SLE and is closely related to type I IFN activity,³⁷ the exact interplay between rs2430561-mediated IFN- γ modulation and anti-dsDNA production in humans is still unclear. Animal studies suggest a positive correlation between IFN- γ and anti-dsDNA levels,³⁸ supporting the hypothesis that *IFNG* variants could influence autoantibody profiles, but this was not demonstrated in the current sample.

Associations with CLASI and SLEDAI-2K

The most important and novel result of this study is the strong association between rs2430561 and both CLASI and SLEDAI-2K.

For CLASI, mean scores differed significantly by genotype: AA: 14.7 ± 7.2 , TA: 11.8 ± 7.9 , TT: 5.8 ± 3.1 ($p=0.003$). When CLASI was categorized (mild, moderate, severe), the distribution of genotypes differed significantly ($p=0.001$). Carriers of the A allele had a 5.8-fold higher prevalence of severe cutaneous lupus

(CLASI ≥ 21) than T-only carriers (OR=5.8; 95% CI: 1.6-21.9; $p=0.010$). These findings complement previous work by Braunstein *et al.*, who showed a positive correlation between an *IFNG*-expression signature and CLASI in CLE and SLE (Spearman $r=0.55$; $p=0.0017$), suggesting that IFN pathway activation is directly reflected in cutaneous disease burden.³⁹

For SLEDAI-2K, mean scores also differed by genotype: AA: 12 ± 1.7 , TA: 11.8 ± 6.6 , TT: 6.3 ± 3.9 ($p=0.010$). Disease activity categories (inactive, mild-moderate, severe) were significantly associated with genotype ($p=0.019$). The A allele conferred a 4.7-fold higher prevalence of severe disease (SLEDAI-2K >12) compared with the T allele (OR=4.7; 95% CI: 1.9-11.4; $p=0.001$). Combined AA/TA genotypes were associated with markedly higher odds of severe activity compared with TT (OR=21.0; 95% CI: 2.09-210.14; $p=0.004$). These results differ from Liu *et al.*, who did not observe a significant association between AA+TA and severe SLEDAI scores (OR=2.01; 95% CI: 0.62-6.48; $p=0.237$) but did find an association between AA and organ damage assessed by the Slicc Damage Index (SDI; OR=4.15; 95% CI: 1.12-15.45; $p=0.022$).¹⁶ Differences in time windows and indices (10-day SLEDAI vs. 30-day SLEDAI-2K vs. 6-month SDI) and the requirement for more advanced investigations for SDI assessment may explain part of the discrepancy.^{40,41}

Limitations

This study has several limitations. First, the relatively small sample size and single-center design may have limited statistical power and precision, as reflected by the wide confidence intervals, and may reduce the generalizability of our findings. Second, the inclusion of heterogeneous lupus phenotypes (*e.g.*, SLE and cutaneous lupus) could have introduced clinical variability that may influence genotype-phenotype associations; therefore, our results should be interpreted cautiously until confirmed in larger, well-characterized cohorts with stratified analyses. Third, potential confounders such as disease duration, treatment regimens, and other clinical or environmental factors were not fully adjusted for, which may have affected the observed associations with disease activity and severity. Fourth, we did not measure circulating IFN- γ levels or IFN-related signatures, preventing direct linkage between rs2430561 genotypes and functional immune outcomes. Finally, although allele-specific PCR was used for genotyping, additional quality-control steps such as replication in an independent cohort and validation by alternative methods would strengthen the robustness of these results.

Conclusions

Taken together, the present data support the A allele of rs2430561 as a functional risk allele associated with more severe cutaneous involvement and higher overall lupus activity. Nonetheless, further studies combining genotyping with direct measurement of IFN- γ levels and IFN signatures in larger lupus cohorts will be required to fully elucidate these mechanisms.

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Table 1. Distribution of rs2430561 genotypes and alleles in the patient and control groups.

		Study group		p
		Patients (n=34) n (%)	Control (n=34) n (%)	
Genotype	AA	3 (8.8)	0	0.048 ^a
	TA	9 (26.5)	17 (50)	
	TT	22 (64.7)	17 (50)	
Allele type	A	15 (22.1)	17 (25)	0.084 ^a
	T	53 (77.9)	51 (75)	

^aFisher's exact test.**Table 2.** Association between rs2430561 polymorphism and disease severity based on the CLASI score.

	Total	AA	TA	TT	p
CLASI score	8.2±5.9	14.7±7.2	11.8±7.9	5.8±3.1	0.003 ^a
CLASI severity categories, n (%)					
Mild	25	0	5 (20)	20 (80)	0.001 ^b
Moderate	5	2 (40)	1 (20)	2 (40)	
Severe	4	1 (25)	3 (75)	0	

CLASI, Cutaneous Lupus Disease Area and Severity Index; ^aone-way ANOVA test; ^bFisher's exact test.**Table 3.** Association between rs2430561 polymorphism and disease activity based on the SLEDAI-2K score.

	Total	AA	TA	TT	p
SLEDAI-2K score	8.3±5.3	12±1.73	11.8±6.6	6.3±3.9	0.010 ^a
SLEDAI-2K activity categories, n (%)					
Inactive	6	0	1 (16.7)	5 (83.3)	0.019 ^b
Mild-moderate activity	21	1 (4.8)	4 (19.0)	16 (76.2)	
Severe activity	7	2 (28.6)	4 (57.1)	1 (14.3)	

SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2K; ^aone-way ANOVA test; ^bFisher's exact test.

Table 4. Characteristics of A and T alleles in relation to CLASI severity.

		Severe CLASI ≥21 points n (%)	Mild-moderate CLASI (0-21 points) n (%)	OR	CI 95%	p
Allele type	A	5 (33.3)	10 (66.7)	5.8	1.6-21.9	0.010 ^a
	T	3 (5.7)	50 (94.3)			

CLASI, Cutaneous Lupus Disease Area and Severity Index; OR, odds ratio; CI, confidence interval; ^aFisher's exact test.

Table 5. Characteristics of A and T alleles in relation to SLEDAI-2K activity categories.

		Severe SLEDAI activity (>12 points) n (%)	Non-active and mild- moderate SLEDAI activity (0-12 points) n (%)	OR	CI 95%	p
Allele type	A	8 (53.3)	7 (46.7)	4.7	1.9-11.5	0.001 ^a
	T	6 (11.3)	47 (88.7)			

SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; OR, odds ratio; CI, confidence interval; ^aFisher's exact test.