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Association Between HLA-B5801 Positivity and Patient Characteristics and Clinical Outcomes in Gout

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Abstract

Background/Aim: Allopurinol is a standard agent used for lowering uric acid levels. Human leukocyte antigen (HLA)-B5801 positivity increases the incidence of severe cutaneous adverse reactions (SCARs) in allopurinol users. HLA alleles HLA-B27 and HLA-B51 are frequently found in patients with ankylosing spondylitis and Behçet's disease, showing an association with distinct clinical features. In this study, we investigated the association between the HLA-B5801 genotype and patient characteristics and outcomes in gout.

Patients and Methods: We retrospectively reviewed the medical records of 263 patients with gout who were not receiving uric acid-lowering therapy and were tested for HLA-B5801 positivity between March 2020 and February 2024. Patients were classified according to their HLA-B5801 status, and patient demographics and laboratory variables were compared. The incidence of gout flares or severe flares requiring hospital care within one year was investigated.

Results: A total of 37 participants were HLA-B5801 positive (37/263, 14.1%). However, no significant differences were observed in demographic or laboratory variables between the HLA-B5801 positive and negative groups. Subgroup analyses of patients with new-onset gout, males, and those with an estimated glomerular filtration rate ≥60 ml/min/1.73 m^2 also demonstrated no significant differences related to HLA-B5801 genotype positivity. The incidence of disease flares or severe flares between patients in the HLA-B5801 positive and negative groups was comparable during the one-year follow-up.

Conclusion: Although HLA-B5801 was a significant predictor of allopurinol-associated SCARs, the impact of HLA-B5801 positivity on the clinical characteristics or flares was not evident in this population of patients with gout.

Keywords: Gout, HLA-B5801, allopurinol, characteristics, flare.

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Introduction

Gout is a form of inflammatory arthritis that usually affects men and manifests as intense pain in the lower extremity joints (1). Gout, which is closely associated with an affluent lifestyle and excessive intake of purine-rich diets, is commonly referred to as "the disease of kings" (2). The increase in uric acid in circulation and its deposition within the joints are thought to be the primary events causing acute and excruciating inflammation in gout, also known as gout attacks, which generally exhibit a self-limiting course. Although hyperuricemia is a typical laboratory finding in patients with gout, it may not be apparent in a subset of patients. For long-term management, the use of uric acid-lowering agents is required to prevent recurrent episodes of gout attacks and the onset of disease-associated complications (3). Among the indicated medications to treat hyperuricemia, xanthine oxidase inhibitors or uricosuric agents are widely used to reduce uric acid levels, with allopurinol being the most commonly prescribed (4). However, there is a potential risk of developing severe cutaneous adverse reactions (SCARs) in patients treated with allopurinol, especially in the presence of the human leukocyte antigen (HLA)-B5801 allele. Therefore, testing patients with gout for the HLA-B5801 genotype in a highly HLA-B5801 prevalent region is recommended prior to starting treatment with allopurinol (5).

Notably, the genetic predisposition conferred by specific HLA alleles has been well described in various inflammatory and autoimmune diseases (6). Previous studies revealed an association between HLA-DRB1 alleles and susceptibility to rheumatoid arthritis and systemic lupus erythematosus. Additionally, the HLA-DR and HLA-DQ alleles DQA1*05:01, DQB1*02:01, and DRB1*03:01 have been reported as risk factors for Sjögren's syndrome. Specifically, HLA alleles HLA-B27 and HLA-B51 are representative laboratory findings in patients with ankylosing spondylitis (AS) and Behçet disease (BD) (7). Although HLA-B5801 is a typical HLA allele tested to evaluate allopurinol hypersensitivity in patients with gout, it remains unclear whether there are differences in patient characteristics based on HLA-B5801 positivity. Therefore, this study aimed to compare the characteristics and clinical outcomes of patients with gout based on their HLA-B5801 status.

Patients and Methods

Patients. This retrospective, single-center study was conducted by reviewing the records of patients with gout who visited the rheumatology department of our hospital between March 2020 and February 2024. Diagnosis was made in accordance with the 1977 American Rheumatism Association criteria (8). The inclusion criteria were as follows: i) patients were tested for HLA-B5801; ii) patients who were not on uric acid-lowering agents; iii) patients who had body mass index (BMI), alcohol consumption, and current smoking information as clinical information; and iv) patients who had laboratory variables of uric acid, fasting glucose, C-reactive protein (CRP), and cholesterol profiles. The patients were divided into two groups based on the results of the HLA-B5801 test (positive and negative). Furthermore, for patients who were followed up for more than one year, the clinical outcomes of disease flares and flares requiring hospital care were investigated. This study was conducted in accordance with the 1964 Declaration of Helsinki, and ethical approval was obtained from the Yongin Severance Hospital Institutional Review Board (2023-0629-001).

Patient data. The demographic data and laboratory variables of the patients were reviewed when HLA-B5801 was tested. The patient demographic data included age, sex, BMI, current smoking and alcohol consumption status, presence of new-onset gout (defined as a disease duration of less than one month), and history of hypertension, diabetes mellitus, and dyslipidemia. For the laboratory variables, uric acid, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR) (according to the Chronic Kidney Disease Epidemiology Collaboration equation) (9), aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose,

Table I. *Comparison of patient clinical and laboratory variables according to HLA-B5801 status.*

	Total (n=263)	HLA-B5801 (+) (n=37)	HLA-B5801 (–) (n=226)	*p*-Value
Demographics				
Age (years)	47.9±17.2	47.6±19.3	48.0±16.9	0.904
Male	244 (92.8)	34 (91.9)	210 (92.9)	0.737
BMI (kg/m^2)	27.3±4.7	27.5±4.1	27.3±4.8	0.229
Alcohol drinking	164 (62.4)	21 (56.8)	143 (63.3)	0.468
Current smoking	92 (35.0)	13 (35.1)	79 (35.0)	1.000
New-onset disease	79 (30.0)	11 (29.7)	68 (30.1)	1.000
Comorbidities				
Hypertension	168 (63.9)	24 (64.9)	144 (63.7)	1.000
Diabetes	33 (12.5)	3 (8.1)	30 (13.3)	0.591
Dyslipidemia	182 (69.2)	25 (67.6)	157 (69.5)	0.849
Laboratory variables				
Uric acid (mg/dl)	7.9±1.7	7.8±1.7	7.9±1.7	0.646
BUN (mg/dl)	15.4±8.3	14.9±7.3	15.4±8.5	0.734
Creatinine (mg/dl)	1.0±0.3	1.0±0.3	1.0±0.3	0.617
eGFR (ml/min/1.73 m^2)	89.3±24.1	90.9±25.7	89.2±23.8	0.680
AST (IU/l)	28.8±27.4	23.2±10.1	29.7±29.2	0.184
ALT (IU/l)	36.9±31.5	32.1±33.7	37.7±31.1	0.310
Fasting glucose (mg/dl)	103.0±23.7	99.0±15.2	103.7±24.8	0.268
Total cholesterol (mg/dl)	185.5±47.6	194.2±42.7	184.0±48.3	0.229
Triglyceride (mg/dl)	183.2±139.8	181.0±126.9	183.8±142.0	0.916
LDL-C (mg/dl)	121.4±40.5	131.2±37.1	119.8±40.9	0.113
HDL-C (mg/dl)	46.0±12.8	44.7±9.0	48.0±16.9	0.348
CRP (mg/l)	13.4±28.8	11.2±19.3	13.7±30.1	0.618

Data are presented as means with standard deviations for continuous variables and as frequencies and percentages for categorical variables. HLA: Human leukocyte antigen; BMI: body mass index; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein.

total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and CRP were investigated.

Hypertension was defined as the requirement for antihypertensive medications, systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg. Diabetes mellitus was defined as the use of medication for diabetes mellitus or an HbA1c level of ≥6.5%. Dyslipidemia was defined as the administration of medications for dyslipidemia or when laboratory results were compatible according to the diagnostic criteria proposed by the Korea National Health Screening Program (10).

Statistical analysis. Continuous variables are presented as means with standard deviations, while categorical variables are presented as frequencies and percentages. Statistical differences between groups were assessed using Student's *t*-test, chi-square test, or Fisher's exact test, as indicated. All statistical analyses were conducted using IBM SPSS statistics software (version 21.0; IBM Corp., Armonk, NY, USA), and a *p*-value of <0.05 was considered statistically significant.

Results

Baseline patient characteristics. The study included 263 patients with a mean age of 47.9 years, predominantly males (92.8%), and a mean BMI of 27.3 kg/m^2. The proportions of patients who consumed alcohol, smoked, and had a new-onset disease were 62.4%, 35.0%, and

Table II. *Differences in patient variables among patients with new-onset gout.*

	Total (n=79)	HLA-B5801 (+) (n=11)	HLA-B5801 (–) (n=68)	*p*-Value
Demographics				
Age (years)	49.0±19.8	54.6±27.7	48.1±18.3	0.464
Male	67 (84.8)	9 (81.8)	58 (85.3)	0.671
BMI (kg/m^2)	27.1±4.1	27.5±3.1	27.1±4.3	0.742
Alcohol drinking	47 (59.5)	4 (36.4)	43 (63.2)	0.109
Current smoking	24 (30.4)	2 (18.2)	22 (32.4)	0.489
Comorbidities				
Hypertension	48 (60.8)	6 (54.5)	42 (61.8)	0.744
Diabetes	9 (11.4)	2 (18.2)	7 (10.3)	0.605
Dyslipidemia	56 (70.9)	8 (72.7)	48 (70.6)	1.000
Laboratory variables				
Uric acid (mg/dl)	7.5±1.5	7.8±1.7	7.5±1.5	0.501
BUN (mg/dl)	16.7±12.0	17.8±9.7	16.5±12.3	0.757
Creatinine (mg/dl)	1.1±0.5	1.2±0.5	1.0±0.5	0.445
eGFR (ml/min/1.73 m^2)	88.7±26.7	79.4±37.1	90.2±24.7	0.370
AST (IU/l)	24.9±10.8	24.3±11.2	25.0±10.8	0.830
ALT (IU/l)	34.8±23.7	35.5±31.4	34.7±22.5	0.918
Fasting glucose (mg/dl)	103.8±31.1	99.9±22.6	104.5±32.3	0.654
Total cholesterol (mg/dl)	189.8±46.4	203.9±46.5	187.6±46.3	0.281
Triglyceride (mg/dl)	177.4±168.1	158.5±60.0	180.5±179.7	0.689
LDL-C (mg/dl)	126.8±40.8	144.5±43.5	123.9±39.9	0.120
HDL-C (mg/dl)	46.8±13.0	44.8±5.9	47.1±13.8	0.356
CRP (mg/l)	13.6±27.2	12.6±13.6	13.8±28.8	0.895

Data are presented as means with standard deviations for continuous variables and as frequencies and percentages for categorical variables. HLA: Human leukocyte antigen; BMI: body mass index; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein.

30.0%, respectively. Regarding laboratory variables, the mean level of serum uric acid and eGFR was 7.9 mg/dl and 89.3 ml/min/1.73 m^2, respectively (Table I).

Patient characteristics based on HLA-B5801 positivity and subgroup analyses. Comparison of patient characteristics between the HLA-B5801 (+) and (–) groups showed no significant differences in demographics, comorbidities, and laboratory variables (Table I). Furthermore, when subgroup analyses were performed for patients with new-onset gout, males, and those with eGFR ≥60 ml/min/1.73 m^2, it was found that the characteristics of patients were comparable (Table II, Table III, and Table IV).

Patient outcomes according to HLA-B5801 status. Evaluation of the patient outcomes of disease flares, as well as flares that required hospitalization during the one-year follow-up revealed that significant differences in disease outcomes were not apparent, although there was a tendency for increased disease flares in patients who were HLA-B5801 (–) compared to those who were HLA-B5801 (+) (42.7% *vs*. 14.3%, p=0.070) (Table V).

Discussion

Human leukocyte antigen genes, which are members of the major histocompatibility complex (MHC) gene family, are located on chromosome six. The MHC class I region encodes the HLA molecules HLA-A, HLA-B, and HLA-C, which play a crucial role in immune regulation by presenting antigens to T cells (11). Similarly, evidence indicates that the presence of a specific HLA genotype can

Table III. *Patient clinical and laboratory variables in a subgroup of men.*

	Total (n=244)	HLA-B5801 (+) (n=34)	HLA-B5801 (–) (n=210)	*p*-Value
Demographics				
Age (years)	46.3±15.9	45.3±16.9	46.5±15.7	0.684
BMI (kg/m^2)	27.6±4.6	27.6±4.2	27.6±4.6	0.954
Alcohol drinking	160 (65.6)	19 (55.9)	141 (67.1)	0.243
Current smoking	89 (36.5)	12 (35.3)	77 (36.7)	1.000
New onset disease	67 (27.5)	9 (26.5)	58 (27.6)	1.000
Comorbidities				
Hypertension	155 (63.5)	21 (61.8)	134 (63.8)	0.849
Diabetes	29 (11.9)	2 (5.9)	27 (12.9)	0.390
Dyslipidemia	167 (68.4)	23 (67.6)	144 (68.6)	1.000
Laboratory variables				
Uric acid (mg/dl)	7.9±1.6	7.7±1.7	8.0±1.6	0.386
BUN (mg/dl)	14.7±7.7	14.3±6.7	14.8±7.8	0.716
Creatinine (mg/dl)	1.0±0.3	1.0±0.3	1.0±0.3	0.659
eGFR (ml/min/1.73 m^2)	91.6±22.0	93.5±22.8	91.4±21.9	0.597
AST (IU/l)	29.2±28.3	23.4±10.5	30.2±30.2	0.194
ALT (IU/l)	38.0±31.7	33.7±34.6	38.7±31.2	0.393
Fasting glucose (mg/dl)	102.7±24.0	97.3±12.9	103.6±25.3	0.157
Total cholesterol (mg/dl)	187.2±46.1	192.6±39.7	186.3±47.1	0.460
Triglyceride (mg/dl)	187.7±138.5	170.6±93.2	190.5±144.5	0.439
LDL-C (mg/dl)	123.1±39.6	131.4±37.2	121.7±39.8	0.184
HDL-C (mg/dl)	45.7±12.3	44.3±9.2	45.9±12.7	0.499
CRP (mg/l)	11.7±24.5	11.0±19.9	11.8±25.2	0.865

Data are presented as means with standard deviations for continuous variables and as frequencies and percentages for categorical variables. HLA: Human leukocyte antigen; BMI: body mass index; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein.

provoke a dysregulated immune response and development of immune-mediated inflammatory diseases (12). Accordingly, it could be hypothesized that there is an association between certain HLA alleles and patient characteristics in patients with inflammatory disorders. Intriguingly, for AS and BD, the characteristics and prognosis of patients possessing HLA-B27 and HLA-B51 have been shown to be disparate. For instance, patients with AS and HLA-B27 have more apparent radiographic damage and uveitis than those without AS (13, 14). In contrast, HLA-B51 positivity is associated with an increased probability of skin lesions and eye diseases in BD (15). Considering these associations, we hypothesized that HLA-B5801 may also influence the clinical features and outcomes of patients with gout. In the present study, the characteristics and clinical outcomes of 263 patients with gout who were not receiving treatment with uric acid-lowering agents and had undergone HLA-B5801 testing showed no significant differences in the demographics or laboratory variables based on the presence or absence of HLA-B5801. Furthermore, no statistically significant difference was observed between the groups regarding the proportion of disease flares and the necessity for hospitalization during the one-year follow-up.

Allopurinol is the most commonly prescribed agent for lowering serum uric acid levels owing to its efficacy in reducing uric acid production and its lower rate of side effects. Importantly, the development of SCARs, including Stevens–Johnson syndrome or toxic epidermal necrolysis, a rare but potentially life-threatening complication, is markedly increased in those with HLA-B5801 positivity

Table IV. *Comparison of patient characteristics in individuals with eGFR ≥60 ml/min/1.73 m^2.*

	Total (n=229)	HLA-B5801 (+) (n=33)	HLA-B5801 (–) (n=196)	*p*-Value
Demographics				
Age (year)	44.0±14.1	43.0±14.4	44.1±14.1	0.677
Male	221 (96.5)	32 (97.0)	189 (96.4)	1.000
BMI (kg/m^2)	27.7±4.7	27.6±4.3	27.7±4.8	0.934
Alcohol drinking	159 (69.4)	20 (60.6)	139 (70.9)	0.307
Current smoking	91 (39.7)	13 (39.4)	78 (39.8)	1.000
New onset disease	68 (29.7)	7 (21.2)	61 (31.1)	0.306
Comorbidities				
Hypertension	142 (62.0)	21 (63.6)	121 (61.7)	0.850
Diabetes	20 (8.7)	2 (6.1)	18 (9.2)	0.746
Dyslipidemia	153 (66.8)	23 (69.7)	130 (66.3)	0.842
Laboratory variables				
Uric acid (mg/dl)	7.9±1.6	7.7±1.7	7.9±1.6	0.429
BUN (mg/dl)	13.4±4.3	13.3±5.5	13.4±4.1	0.881
Creatinine (mg/dl)	0.9±0.1	0.9±0.2	0.9±0.1	0.814
AST (IU/l)	29.8±29.1	23.9±10.5	30.8±31.0	0.207
ALT (IU/l)	39.4±32.5	34.6±34.8	40.2±32.1	0.356
Fasting glucose (mg/dl)	100.7±17.3	98.1±12.8	101.1±17.9	0.349
Total cholesterol (mg/dl)	190.5±45.3	196.9±42.2	189.4±45.8	0.379
Triglyceride (mg/dl)	193.6±145.1	190.5±130.7	194.1±147.0	0.893
LDL-C (mg/dl)	125.4±38.4	132.9±36.8	124.2±38.6	0.229
HDL-C (mg/dl)	46.1±12.4	44.3±9.5	46.4±12.9	0.374
CRP (mg/l)	10.5±24.1	9.8±19.3	10.7±24.8	0.850

Data are presented as means with standard deviations for continuous variables and as frequencies and percentages for categorical variables. eGFR: Estimated glomerular filtration rate; HLA: human leukocyte antigen; BMI: body mass index; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein.

Table V. *Comparison of patient characteristics in individuals with eGFR ≥60 ml/min/1.73 m^2.*

	Total (n=89)	HLA-B5801 (+) (n=14)	HLA-B5801 (–) (n=75)	*p*-Value
Disease outcomes				
Disease flare	34	2 (14.3)	32 (42.7)	0.070
Flare requiring hospital care	19	2 (14.3)	17 (22.7)	0.725

Data are presented as frequencies and percentages. HLA: Human leukocyte antigen.

(16). In particular, considering that HLA-B5801 positivity is more prevalent in the Asian subpopulation than in other geographic regions, the American College of Rheumatology guidelines for the management of gout conditionally recommend testing for the HLA-B5801 genotype in individuals of Southeast Asian descent prior to allopurinol initiation (17).

In the existing literature, the prevalence of HLA-B5801 among South Koreans has been reported to range from 5.7 to 12.2%. These findings are comparable to our data (14.1%) (18). Furthermore, the proportion of males in our cohort was 92.8%, which is consistent with data showing that the majority of patients with gout are male in the South Korean population. Importantly, we failed to identify

any differences in patient demographics, comorbidities, or laboratory data between the HLA-B5801 positive and negative groups. The lack of significant differences was found to be identical even when subgroup analyses based on new-onset disease, sex, and eGFR were conducted and were irrelevant to gout flares. This non-significant clinical association appears to be attributable to the fact that a T-cell-mediated immune reaction, intensified by the presence of specific HLA alleles, does not occur *per se* but only develops as a consequence of the interaction between a certain drug and an immune receptor (19, 20). Altogether, these findings indicate that HLA-B5801 is primarily correlated with hypersensitivity to allopurinol, rather than with specific patient characteristics or disease prognosis.

Study limitations. First, although we investigated a range of clinical and laboratory variables, data were collected retrospectively. Second, the patients were selected from those who visited a single center, the rheumatology department, with available clinical and laboratory data, which may have resulted in selection bias. Third, although the selection of uric acid-lowering agents, drug adherence, and unmeasured factors could have affected the onset of disease flares in our study population, a precise estimation of these aspects could not be performed. Fourth, as the follow-up period (one year) was relatively short to determine long-term outcomes, well-designed larger studies are necessary to better elucidate the clinical impact of HLA-B5801 positivity in patients with gout.

Conclusion

This study found no significant differences in demographics, comorbidities, or laboratory variables between patients with gout who were HLA-B5801 positive and those who were HLA-B5801 negative. Furthermore, HLA-B5801 positivity was not associated with an increase in flare rates or requirement for hospitalization within a one-year follow-up period. These findings suggest that although the presence of the HLA-B5801 genotype is associated with the risk of adverse reactions to allopurinol, it does not appear to influence the clinical characteristics or disease outcomes of patients with gout.

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None.

Conflicts of Interest

The Authors have no potential conflicts of interest to disclose in relation to this study.

Authors' Contributions

Sung Soo Ahn: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. Jiyoung Agatha Kim: Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Roles/Writing - original draft. Kunhyung Bae: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Software; Supervision; Roles/Writing - original draft; Writing - review & editing.

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