Original Article

Clinical Findings of Ankylosing Spondylitis With and Without Human Leukocyte Antigen (HLA)-B27 and HLA-B51

Jae Hyun Jung, [1,2]*MD, PhD*, Cho Hee Bang, [3]*RN, MS,* Hongdeok Seok, [4]*MD, PhD,* Sung Jae Choi, [1,2]*MD, PhD*, Gwan Gyu Song, [1,5]*MD, PhD*

Abstract

Introduction: Ankylosing spondylitis (AS) and Behçet's disease are known to be associated with the human leukocyte antigen (HLA)-B27 and HLA-B51 genes, respectively. However, many of their clinical findings—including articular and extra-articular symptoms—are similar, making diagnosis a challenge in the early stage of the disease. The aim of this study was to investigate the differences in clinical findings of AS patients with and without the HLA-B27 gene. Materials and Methods: We performed a retrospective chart review of 151 AS patients. The following clinical findings were evaluated: oral ulcer, genital ulcer, skin manifestation, uveitis, peripheral arthritis; and gastrointestinal, cardiac and pulmonary involvement. Patients were divided into 4 groups based on absence or presence of the HLA-B27 and HLA-B51 genes. The number of patients with each clinical finding was subsequently examined in each group. Results: The incidence of uveitis was significantly higher in the HLA-B27-positive group (P = 0.004); however, other clinical findings did not differ significantly according to the absence or presence of the HLA-B27 gene. There were no significant differences in the clinical findings of patients with positive and negative HLA-B51. Conclusion: HLA-B27 was associated with the development of uveitis but not with other clinical findings or disease activity in AS patients. HLA-B51 was not associated with the clinical findings or disease activity of AS.

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Key words: Axial spondyloarthritis, Behçet's disease, Uveitis

Introduction

Ankylosing spondylitis (AS) is a type of spondyloarthropathy, a chronic rheumatic disease that is characterised by sacroiliitis.[1] Other than sacroiliitis, AS has various spondyloarthropathy features and is closely related to human leukocyte antigen (HLA)-B27.[2,3] Behçet's disease (BD) is a systemic inflammatory disease of unknown aetiology. It is classified as a type of vasculitis and is known to be associated with HLA-B51.[4] The main symptom in AS is inflammatory low back pain and the disease mainly occurs in young adults.[1,5] On the other hand, the major symptom in BD is oral ulcer (>80% of cases). Cases occur regardless of age and arthritic symptoms vary from 5–90%.[6] After the 1984 New York criteria, a new set of criteria for classifying and diagnosing spondyloarthritis called the Assessment of SpondyloArthritis International Society was developed.[7] However, sacroiliitis is often not clear in radiologic studies of axial spondyloarthritis, while inflammatory low back pain occurs in approximately 12% of BD patients.[6,8] In some cases of low back pain in BD—which is an inflammatory vasculitis—abdominal aortic aneurysm may be the cause and will need to be evaluated.[9] Although AS is classified as

[1]Korea University College of Medicine, Republic of Korea
[2]Division of Rheumatology, Department of Internal Medicine, Korea University Ansan Hospital, Republic of Korea
[3]Ewha Womans University, College of Nursing, Republic of Korea
[4]Department of Occupational and Environmental Medicine, Busan Adventist Hospital, Republic of Korea
[5]Division of Rheumatology, Department of Internal Medicine, Korea University Guro Hospital, Republic of Korea
Address for Correspondence: Dr Song Gwan Gyu, Division of Rheumatology, Department of Internal Medicine, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 08308, Republic of Korea.
Email: gsong@kumc.or.kr

a spondyloarthritis and BD as a vasculitis, they share many similar symptoms. AS and BD may both cause peripheral arthritis and show extra-skeletal involvement such as uveitis, inflammatory bowel disease (IBD) and cardiovascular diseases.[1] In most cases, it is easy to differentiate between AS and BD; however, there are some cases in which the typical clinical findings are not apparent, making it difficult to do so.[10]

HLA genes have a strong association with autoimmune diseases. AS patients with positive HLA-B27 are more likely to develop AS at a younger age, respond better to treatment with tumour necrosis factor-alpha (TNF-α) inhibitors, have a higher frequency of uveitis and a lower prevalence of psoriasis or IBD.[11] Although the association of AS with HLA-B27 and BD with HLA-B51 are well known, AS and BD can cause arthritis through a similar inflammatory pathway and are also responsive to TNF-α inhibitor treatment.[12] Case reports have shown that reactive arthritis of the spondyloarthropathy category is associated with HLA-B51.[13,14] In addition, AS is strongly associated with the carriage of certain amino acids at position 97 in HLA-B, and position 97 is also associated with the cell surface expression of HLA-B51.[15] Both HLA-B27 and HLA-B51 may play roles in a common inflammatory process and affect each other. In BD—when both HLA-B27 and HLA-B51 are positive—the prognosis of uveitis is better than other subgroups.[16] Therefore, both HLA-B27 and HLA-B51 may affect the manifestation or development of AS and BD. Investigating the clinical findings of AS patients based on the absence or presence of HLA-B27 and HLA-B51 may be useful for predicting and managing the disease. However, to date, there has been no study on the relationship between clinical findings of AS and HLA-B27 or HLA-B51. This study sought to do so.

Materials and Methods

Patients

A retrospective chart review was conducted of patients diagnosed with AS who visited Korea University Guro Hospital between 2007 and 2017 and who were tested for HLA-B27 and HLA-B51. The classification criteria for AS were based on the modified New York criteria proposed in 1984.[17] A total of 153 AS patients (120 males and 33 females) were included.

Main Outcome Variables

The following clinical findings were examined: oral ulcer, genital ulcer, skin manifestation, uveitis, peripheral arthritis; and gastrointestinal, cardiac and pulmonary involvement. Skin manifestations included erythema nodosum/multiform, acneiform lesion, furuncle, folliculitis and psoriasis. Gastrointestinal involvement included ulcerative colitis and Crohn's disease. Cardiac involvement included angina and myocardial infarction while pulmonary involvement included interstitial lung disease and pneumothorax. To determine patients' therapeutic responses, use and replacement frequency of non-steroidal anti-inflammatory drugs (NSAIDs) and use of sulfasalazine (SSZ), methotrexate (MTX) and TNF-α inhibitors were examined.

Study Factors

Patients were divided into 4 groups according to HLA-B gene types: 1) Group 1: HLA-B27-positive and HLA-B51-negative; 2) Group 2: HLA-B27-positive and HLA-B51-positive; 3) Group 3: HLA-B27-negative and HLA-B51-positive; and 4) Group 4: HLA-B27-negative and HLA-B51-negative.

Other Variables

Demographic features of age, diagnosis age, disease duration, sex, diabetes mellitus (DM), hypertension (HTN), dyslipidaemia, alcohol consumption and smoking status were also examined. Age, diagnosis age and disease duration were presented as mean ± standard deviation (SD) in years, while sex was classified into male and female. DM was defined as fasting plasma glucose level ≥126 mg/dL, with the diagnosis of DM by a clinician or prescription of an oral hypoglycaemic agent or insulin. HTN was defined as average systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg with the diagnosis of HTN by clinicians or prescription of antihypertensive drugs. Dyslipidaemia was defined based on the following: total cholesterol ≥200 mg/dL, triglyceride ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women or current use of any antidyslipidaemic drug for the purpose of controlling blood lipid concentrations. Alcohol drinker was defined by the consumption of an average of ≥5 units per week. Smoking status was defined as either current smoker or one who has never smoked or was a past smoker. Past smoker was defined as one who did not smoke for >1 year from the time of the medical examination.

Statistical Analysis

Descriptive statistics were used to analyse the frequency, mean and SD of the variables according to the patients' characteristics in each group. The differences in clinical findings were compared based on the absence or presence of HLA-B27 (groups 1 and 2 vs 3 and 4) and HLA-B51 (groups 2 and 3 vs 1 and 4). In the HLA-B27-positive and HLA-B27-negative groups, subgroup analyses were made according to HLA-B51 positive or negative status. For continuous variables, Mann-Whitney U test was used to compare both groups and Kruskal-Wallis H test was used to compare ≥3 groups. Categorical variables were subjected

to Fisher's exact test. All *P* values were two-tailed and *P* <0.05 was considered statistically significant. Data was analysed using IBM SPSS Statistics Version 23 software.

Results

Of the 153 patients, 106 were in Group 1, 16 were in Group 2, 8 were in Group 3 and 23 were in Group 4. The mean age of patients was 37.75 years (SD, 12.93) and the mean disease duration was 4.76 years (SD, 5.30). There were no significant differences in the demographic features and clinical findings among the groups except for uveitis (Table 1). There was a significant difference in the prevalence of uveitis between the HLA-B27-positive and HLA-B27-negative groups (Table 2). Uveitis occurred only in HLA-B27-positive patients. However, there was no significant difference in clinical findings according to the presence of HLA-B51 (Table 3). In addition, there were no significant differences in the clinical findings of patients with positive and negative HLA-B51 in both HLA-B27-positive and HLA-B27-negative groups (data not shown).

Discussion

HLA-B27 is a major histocompatibility complex molecule and is thought to cause inflammation by presenting intracellular peptides to CD8+ T lymphocytes.[18] AS is a representative disease that is closely related to HLA-B27.[19] The Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis lists HLA-B27 as a crucial criterion.[20] However, not all AS patients have HLA-B27, and not all the mechanisms by which HLA-B27 is involved in the pathogenesis of AS are fully understood. Thus, other factors may be associated with AS. HLA-B51 associated with BD with similar clinical manifestations may be associated with the clinical findings of AS. This study showed that in AS, the absence or presence of HLA-B27—but not HLA-B51—was associated with certain clinical findings.

Uveitis was more common with HLA-B27 positivity, irrespective of whether or not HLA-B51 was positive. HLA-B27 is mainly associated with acute anterior uveitis, and uveitis occurs in about half of AS patients with positive HLA-B27.[21] The role of HLA-B27 in the development of uveitis is not yet clear, but its molecule is thought to be activated by presentation of self-peptides to HLA-B27-restricted CD8+ T cells to induce inflammation in the eyes and joints.[22] Besides HLA-B27, other genes, including the interleukin(IL)-23 receptor gene, have been associated with uveitis.[21] HLA-B51 is significantly associated with uveitis in BD patients, but not with idiopathic uveitis.[23] This study also showed that HLA-B51 was not associated with uveitis in patients with AS. In this study, uveitis was diagnosed by ophthalmologists; when patients tested negative for HLA-B27, there was no uveitis. Thus, this study showed that HLA-B27 is strongly associated with uveitis in AS patients.

Although not statistically significant, as in a previous study, the diagnosis age was younger in AS patients with positive HLA-B27;[24] however, peripheral arthritis was more common with HLA-B27 negativity, which contradicted previous reports.[25] Cardiac involvement was found only in the HLA-B27-positive group, suggesting a higher prevalence of DM, HTN, dyslipidaemia and smokers among HLA-B27-positive patients compared to HLA-B27-negative patients. The mechanism by which smoking affects AS is unclear, but previous studies have shown that smoking increased disease activity and radiological progression of AS, especially on HLA-B27 positivity.[26,27] In this study, current smoking rates were significantly higher in the HLA-B27-positive group than the HLA-B27-negative group, suggesting that smoking is more closely related to the development of AS when the patient is HLA-B27-positive. Smoking raises C-reactive protein levels, which is associated with the development of inflammation, and aberrantly activates the Wnt pathway associated with new bone formation. However, the causal relationship between smoking and AS disease activity is ambiguous and a previous study did not show a causal effect of smoking on disease activity.[26] In addition, there is controversy on whether smoking reduces treatment response. In this study, drug usage was identified as an indicator of treatment response, and there was no difference whether HLA-B27 was absent or present.

Although the clinical findings of AS and BD were similar, HLA-B51 was not related to the clinical findings of AS. In addition, there were no differences in the use and frequency of replacement of NSAIDs or the use of SSZ, MTX or TNF-α inhibitors as indicators of the disease activity according to HLA-B type. Despite differences in smoking status among the groups, no significant difference on drug usage was found. In fact, there were some differences in the clinical manifestations of the same organs between AS and BD, which is a differentiating point. Uveitis occurs in 20–30% of cases of AS, mainly in the form of acute anterior uveitis—and oral ulcers are uncommon. In AS, skin manifestations primarily include psoriasis and pulmonary manifestations include interstitial lung diseases, emphysema, bronchiectasis and apical fibrosis.[28] On the other hand, in BD, uveitis often occurs in the form of panuveitis and oral ulcers occurs in >90% of cases. Typical skin manifestations are pseudofolliculitis, erythema nodosum, aphthosis and pathergy phenomenon while pulmonary manifestations include pulmonary infection, vasculitis, fibrosis and embolism.[6] The difference in these clinical findings is thought to occur because AS belongs to the

Table 1. Demographic Features and Clinical Findings of Ankylosing Spondylitis Patients With or Without HLA-B27 and HLA-B51 (n = 153)

Variable	Group 1 (n = 106) HLA-B27-Positive HLA-B51-Negative	Group 2 (n = 16) HLA-B27-Positive HLA-B51-Positive	Group 3 (n = 8) HLA-B27-Negative HLA-B51-Positive	Group 4 (n = 23) HLA-B27-Negative HLA-B51-Negative	*P* Value
Age, years (mean ± SD)	38.72 ± 12.87	39.50 ± 11.57	42.75 ± 8.43	37.00 ± 15.57	0.575
Diagnosis age, years (mean ± SD)	33.63 ± 12.48	34.44 ± 11.18	39.25 ± 8.86	33.57 ± 15.76	0.502
Disease duration, years (mean ± SD)	5.09 ± 5.99	5.06 ± 3.80	3.50 ± 2.72	3.43 ± 2.73	0.685
Sex (%)					0.548
Female	20 (18.9)	5 (31.2)	2 (25.0)	6 (26.1)	
Male	86 (81.1)	11 (68.8)	6 (75.0)	17 (73.9)	
Diabetes mellitus (%)					1.000
No	102 (96.2)	16 (100.0)	8 (100.0)	23 (100.0)	
Yes	4 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypertension (%)					0.900
No	88 (83.0)	14 (87.5)	7 (87.5)	21 (91.3)	
Yes	18 (17.0)	2 (12.5)	1 (12.5)	2 (8.7)	
Dyslipidaemia (%)					0.393
No	90 (84.9)	14 (87.5)	6 (75.0)	22 (95.7)	
Yes	16 (15.1)	2 (12.5)	2 (25.0)	1 (4.3)	
Alcohol consumption (%)					0.191
No	66 (62.3)	9 (56.3)	3 (37.5)	18 (78.3)	
Yes	40 (37.7)	7 (43.7)	5 (62.5)	5 (21.7)	
Smoking status (%)					0.001
None or past	68 (64.1)	9 (56.3)	6 (75.0)	23 (100.0)	
Current	38 (55.9)	7 (43.7)	2 (25.0)	0 (0.0)	
Oral ulcer (%)					0.905
No	71 (67.0)	10 (62.5)	5 (62.5)	14 (60.9)	
Yes	35 (33.0)	6 (37.5)	3 (37.5)	9 (39.1)	
Genital ulcer (%)					0.670
No	104 (98.1)	16 (100.0)	8 (100.0)	22 (95.7)	
Yes	2 (1.9)	0 (0.0)	0 (0.0)	1 (4.3)	
Skin manifestation (%)					0.499
No	76 (71.7)	12 (75.0)	6 (75.0)	13 (56.5)	
Yes	30 (28.3)	4 (25.0)	2 (25.0)	10 (43.5)	
Uveitis (%)					0.036
No	84 (79.2)	14 (87.5)	8 (100.0)	23 (100.0)	
Yes	22 (20.8)	2 (12.5)	0 (0.0)	0 (0.0)	
Peripheral arthritis (%)					0.695
No	47 (44.3)	6 (37.5)	2 (25.0)	11 (47.8)	
Yes	59 (55.7)	10 (62.5)	6 (75.0)	12 (52.2)	
Gastrointestinal involvement (%)					0.203
No	104 (98.1)	16 (100.0)	7 (87.5)	22 (95.7)	
Yes	2 (1.9)	0 (0.0)	1 (12.5)	1 (4.3)	
Cardiac involvement (%)					0.618
No	99 (93.4)	16 (100.0)	8 (100.0)	23 (100.0)	
Yes	7 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 1. Demographic Features and Clinical Findings of Ankylosing Spondylitis Patients With or Without HLA-B27 and HLA-B51 (n = 153) (Cont'd)

Variable	Group 1 (n = 106) HLA-B27-Positive HLA-B51-Negative	Group 2 (n = 16) HLA-B27-Positive HLA-B51-Positive	Group 3 (n = 8) HLA-B27-Negative HLA-B51-Positive	Group 4 (n = 23) HLA-B27-Negative HLA-B51-Negative	*P* Value
Pulmonary involvement (%)					0.111
No	105 (99.1)	16 (100.0)	7 (87.5)	22 (95.7)	
Yes	1 (0.9)	0 (0.0)	1 (12.5)	1 (4.3)	
NSAID use (%)					0.741
None	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	
1 type	80 (75.5)	10 (62.5)	6 (75.0)	19 (82.6)	
≥2 types	24 (22.6)	6 (37.5)	2 (25.0)	4 (17.4)	
Sulfasalazine use (%)					0.595
No	17 (16.0)	3 (18.8)	0 (0.0)	5 (21.7)	
Yes	89 (84.0)	13 (81.2)	8 (100.0)	18 (78.3)	
Methotrexate use (%)					0.786
No	82 (77.4)	13 (81.2)	7 (87.5)	20 (87.0)	
Yes	24 (22.6)	3 (18.8)	1 (12.5)	3 (13.0)	
TNF-α inhibitor use (%)					0.497
No	93 (87.7)	13 (81.2)	7 (87.5)	22 (95.7)	
Yes	13 (12.3)	3 (18.8)	1 (12.5)	1 (4.3)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 2. Comparison of Clinical Findings Between HLA-B27-Positive and HLA-B27-Negative Groups

Variable	Groups 1 and 2 (n = 122) HLA-B27-Positive	Groups 3 and 4 (n = 31) HLA-B27-Negative	*P* Value
Age, years (mean ± SD)	38.83 ± 12.66	38.48 ± 14.17	0.761
Diagnosis age, years (mean ± SD)	33.74 ± 12.28	35.03 ± 14.38	0.831
Disease duration, years (mean ± SD)	5.09 ± 5.74	3.45 ± 2.68	0.343
Sex (%)			0.625
Female	25 (20.5)	8 (25.8)	
Male	97 (79.5)	23 (74.2)	
Diabetes mellitus (%)			0.583
No	118 (96.2)	31 (100.0)	
Yes	4 (3.8)	0 (0.0)	
Hypertension (%)			0.573
No	102 (83.0)	28 (90.3)	
Yes	20 (17.0)	3 (9.7)	
Dyslipidaemia (%)			0.571
No	104 (84.9)	28 (90.3)	
Yes	18 (15.1)	3 (9.7)	
Alcohol consumption (%)			0.678
No	75 (62.3)	21 (67.7)	
Yes	47 (37.7)	10 (32.3)	
Smoking status (%)			0.001
None or past	77 (64.1)	29 (93.5)	
Current	45 (55.9)	2 (6.5)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 2. Comparison of Clinical Findings Between the HLA-B27-Positive and HLA-B27-Negative Groups (Cont'd)

Variable	Groups 1 and 2 (n = 122) HLA-B27-Positive	Groups 3 and 4 (n = 31) HLA-B27-Negative	*P* Value
Oral ulcer (%)			0.674
No	81 (67.0)	19 (61.3)	
Yes	41 (33.0)	12 (38.7)	
Genital ulcer (%)			0.496
No	120 (98.1)	30 (96.8)	
Yes	2 (1.9)	1 (3.2)	
Skin manifestation (%)			0.275
No	88 (71.7)	19 (61.3)	
Yes	34 (28.3)	12 (38.7)	
Uveitis (%)			0.004
No	98 (79.2)	31 (100.0)	
Yes	24 (20.8)	0 (0.0)	
Peripheral arthritis (%)			1.000
No	53 (44.3)	13 (41.9)	
Yes	69 (55.7)	18 (58.1)	
Gastrointestinal involvement (%)			0.183
No	120 (98.1)	29 (93.5)	
Yes	2 (1.9)	2 (6.5)	
Cardiac involvement (%)			0.346
No	115 (93.4)	31 (100.0)	
Yes	7 (6.6)	0 (0.0)	
Pulmonary involvement (%)			0.105
No	121 (99.1)	29 (93.5)	
Yes	1 (0.9)	2 (6.5)	
NSAID use (%)			0.771
None	2 (1.9)	0 (0.0)	
1 type	90 (75.5)	25 (80.6)	
≥2 types	30 (22.6)	6 (19.4)	
Sulfasalazine use (%)			1.000
No	20 (16.0)	5 (18.8)	
Yes	102 (84.0)	26 (81.2)	
Methotrexate use (%)			0.323
No	95 (77.4)	27 (87.1)	
Yes	27 (22.6)	4 (12.9)	
TNF-α inhibitor use (%)			0.531
No	106 (87.7)	29 (93.5)	
Yes	16 (12.3)	2 (6.5)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 3. Comparison of Clinical Findings Between the HLA-B51-Positive and HLA-B51-Negative Groups

Variable	Groups 2 and 3 (n = 24) HLA-B51-Positive	Groups 1 and 4 (n = 129) HLA-B51-Negative	*P* Value
Age, years (mean ± SD)	40.58 ± 10.55	38.41 ± 13.34	0.294
Diagnosis age, years (mean ± SD)	36.04 ± 10.53	33.62 ± 13.06	0.192
Disease duration, years (mean ± SD)	4.54 ± 3.50	4.80 ± 5.58	0.650
Sex (%)			0.416
Female	7 (29.2)	26 (20.2)	
Male	17 (70.8)	103 (79.8)	
Diabetes mellitus (%)			1.000
No	24 (100.0)	125 (96.9)	
Yes	0 (0.0)	4 (3.1)	
Hypertension (%)			1.000
No	21 (87.5)	109 (84.5)	
Yes	3 (12.5)	20 (15.5)	
Dyslipidaemia (%)			0.746
No	20 (83.3)	112 (86.8)	
Yes	4 (16.7)	17 (12.5)	
Alcohol consumption (%)			0.174
No	12 (50.0)	84 (65.1)	
Yes	12 (50.0)	45 (34.9)	
Smoking status (%)			0.473
None or past	15 (62.5)	91 (70.5)	
Current	9 (37.5)	38 (29.5)	
Oral ulcer (%)			0.816
No	15 (62.5)	85 (65.9)	
Yes	9 (37.5)	44 (34.1)	
Genital ulcer (%)			1.000
No	24 (100.0)	126 (97.7)	
Yes	0 (0.0)	3 (2.3)	
Skin manifestation (%)			0.635
No	18 (75.0)	89 (69.0)	
Yes	6 (25.0)	40 (31.0)	
Uveitis (%)			0.371
No	22 (91.7)	107 (82.9)	
Yes	2 (8.3)	22 (17.1)	
Peripheral arthritis (%)			0.371
No	8 (33.3)	58 (45.0)	
Yes	16 (66.7)	71 (55.0)	
Gastrointestinal involvement (%)			0.498
No	23 (98.4)	126 (97.7)	
Yes	1 (1.6)	3 (2.3)	
Cardiac involvement (%)			0.597
No	24 (100.0)	122 (94.6)	
Yes	0 (0.0)	7 (5.4)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

Table 3. Comparison of Clinical Findings Between the HLA-B51-Positive and HLA-B51-Negative Groups (Cont'd)

Variable	Groups 2 and 3 (n = 24) HLA-B51-Positive	Groups 1 and 4 (n = 129) HLA-B51-Negative	*P* Value
Pulmonary involvement (%)			0.403
No	23 (98.4)	127 (98.4)	
Yes	1 (1.6)	2 (1.6)	
NSAID use (%)			0.500
None	0 (0.0)	2 (1.6)	
1 type	16 (66.7)	99 (76.7)	
≥2 types	8 (33.3)	28 (21.7)	
Sulfasalazine use (%)			0.767
No	3 (12.5)	22 (17.1)	
Yes	21 (87.5)	107 (82.9)	
Methotrexate use (%)			0.786
No	20 (83.3)	102 (79.1)	
Yes	4 (16.7)	27 (20.9)	
TNF-α inhibitor use (%)			0.488
No	20 (83.3)	115 (89.1)	
Yes	4 (16.7)	14 (10.9)	

HLA: Human leukocyte antigen; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha
P values were determined using Kruskal-Wallis H test for continuous variables or Fisher's exact test for categorical variables.

spondyloarthritis category and BD belongs to the vasculitis category—but it remains unclear whether HLA-B27 and HLA-B51 influence each other in this process. Although the pathogenesis of AS is not clearly established, IL-17 and IL-23 are thought to cause AS.[29] HLA-B27 is associated with the IL-23/IL-17 pathway and is thought to affect the production and activation of IL-23 and IL-17,[30] whereas the role of HLA-B51 in AS is not likely to be significant. In this study, panuveitis did not occur regardless of the type of HLA-B, and the only pulmonary abnormality was pneumothorax. Therefore, the presence of the HLA-B51 gene in patients with AS does not appear to be effective in predicting the disease course. In patients with arthralgia and atypical extra-articular symptoms, determining HLA-B27 status may be useful to differentiate between AS and BD.

This is the first study to investigate clinical findings based on the absence or presence of HLA-B27 and HLA-B51 genes in AS patients. Clinical findings that were investigated included articular involvement and extra-articular manifestations of AS and BD that may be related to HLA-B27 and HLA-B51. In addition, demographic features and drug usage were also examined to reflect on patients' status and condition.

However, this study has some limitations. First, the number of patients included in the study, the number of patients between the groups and prevalence of clinical findings were small, making it difficult to clarify statistical significance. The small number of cases can cause type 2 errors. Type 2 errors are usually set at the acceptable level of 0.20.[31] No type 2 error was detected in the clinical findings of groups with or without HLA-B27. In groups classified by the absence or presence of HLA-B51, there was a possibility of type 2 error in the clinical findings of diagnosis age and alcohol consumption (Table 3). Second, the frequency or severity of clinical findings such as oral ulcers and uveitis were not considered, nor were the dose of drugs administered or the type of TNF-α inhibitor. Finally, as different subtypes of HLA-B27 affect the development or clinical manifestations of AS, analysis of the HLA-B27 subtype should have been performed.[19,32]

Conclusion

HLA-B27—rather than HLA-B51—was associated with the clinical manifestations of AS. Among the clinical findings, uveitis occurred when HLA-B27 was present; however, other clinical findings were not associated with HLA-B27. In addition, neither HLA-B27 nor HLA-B51 was associated with AS disease activity. The HLA-B51 gene test is not recommended because it does not diagnose or predict the progress or prognosis of AS. Instead, smoking status and extra-articular symptoms (including uveitis) may be helpful in the diagnosis and treatment of AS. Finally, the scale of this study was small and a larger scale investigation is warranted.

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