DOCTORAL THESIS

The influence of HLA-B51 on clinical manifestations among Japanese patients with Behçet's disease: A nationwide survey

（日本人ベーチェット病患者の臨床症状に対する *HLA-B*51* の影響を対象とした全国調査）

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ORIGINAL ARTICLE

The influence of HLA-B51 on clinical manifestations among Japanese patients with Behçet's disease: A nationwide survey

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ABSTRACT

Objectives: To scrutinize the influence of HLA-B51 to each clinical manifestation of patients with Behçet's disease (BD) using a database of the Ministry of Health, Labour and Welfare of Japan.

Methods: The database of newly registered patients with BD was obtained from the Japanese Ministry of Health, Labour and Welfare. Patients who met International Criteria for Behçet's Disease (ICBD) and had data for HLA-B51 were selected and analyzed.

Results: Among the 3044 analyzable cases, 1334 (43.8%) were men and 1710 (56.2%) were women; the median age was 38 years (IQR 29–48). HLA-B51 was positive for 1334 (44.5%). Prevalence of selected manifestations was 98.5% for oral ulceration, 85.5% for skin lesion, 42.1% for ocular lesion, 69.1% for genital ulceration, and 29.0% for gastrointestinal symptom. HLA-B51-positive patients had higher risk for ocular lesion (OR 1.59, 95%CI: 1.37–1.84; $p < .001$) and lower risk for genital ulceration (OR 0.72, 95%CI: 0.62–0.84; $p < .001$) and gastrointestinal symptom (OR 0.65, 95%CI: 0.55–0.77; $p < .001$). No significant difference was observed for other organ involvement; oral ulceration, skin lesion, positive pathergy test, arthritis, epididymitis, vascular lesion, or neurological manifestation. Subgroup analyses revealed that HLA-B51 was not related to genital ulceration in the cases with an ICBD score of 6 or higher and that HLA-B51 tended to more largely affect the risk of three manifestations for men compared to that for women.

Conclusion: HLA-B51 positive is a risk factor for ocular lesion and vice versa for genital ulceration and gastrointestinal symptoms in patients with Japanese BD.

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Introduction

Behçet's disease (BD) is a chronic immune-mediated disease characterized by mucous membrane ulceration and ocular involvement [1–3]. The etiology of BD is still unclear and human leukocyte antigen (HLA)-B51 is believed to be the strongest risk factor for BD [4]. The development of BD is considered to be influenced by many endogenous and exogenous elements, because most HLA-B51-positive individuals do not suffer from BD throughout their lives, and about a half of the patients with BD are negative for HLA-B51 [5,6]. To date, many genome-wide association studies have suggested that *IL-10*, *IL-23R-IL-12RB2*, *IL-1A-IL-1B*, *CCR1*, and *ERAP1* are the disease susceptible gene of BD [4,5]. On the other hand, the influence of the exogenous element, such as hygienic environment, socio-economic environment, or history of smoking remain unclear [7–9].

The Ministry of Health, Labour and Welfare (MHLW) of Japan has continuously recorded the clinical manifestations of the patients with BD for more than 50 years. Due not only to the Japanese universal medical care system but also to the further reduction of costs associated with registering in this national survey, almost all patients with BD in Japan will be registered into the MHLW database. Recently, we analyzed the database and reported epidemiological finding such as recent trend of patients with BD and sex differences [6,10–12]. In this study, we investigated the association between HLA-B51 and each clinical manifestation of BD using Japan's MHLW database.

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Methods

Overview

This ongoing nationwide survey project has been carried out by the Behçet's Disease Research Committee, MHLW of Japan since 1965 [13]. In this study, we analyzed the dataset of patients from 2003 to 2014. First, a physician who diagnoses a patient with BD registers the patient's data by filling in a questionnaire according to diagnostic criteria of the Behçet's Disease Research Committee of Japan [14]. As mentioned above, we believe almost all of the patients with BD in Japan will be registered in the MHLW database. The questionnaire requires the following, if applicable; recurrent aphthous oral ulcer, skin lesions, ocular inflammation, genital ulcer (these are called major symptoms), arthritis, epididymitis, intestinal ulcers, large vascular lesions, and neuropsychiatric manifestations (minor symptoms). The questionnaire also requires demography and background patient characteristics such as data on date of birth, sex, date of BD onset, and place of residence. A physician select 'Yes,' 'No,' or 'Unclear' for each BD manifestation [13]. This registration has two independent databases. The newly diagnosed cases are registered using a detailed form followed by annual renewal using a simple form. We discarded the renewal data to avoid using duplicate data from the same patient [13]. The Ministry provides a dataset for eligible researchers after un-linkable anonymization. Our analysis followed the Ethical Guidelines for Medical and Health Research Involving Human Subjects published in 2015 by the MHLW of Japan [15].

Diagnostic and inclusion criteria

Among the cases in the database, we selected patients who satisfied International Criteria for BD (ICBD) for the main analyses [2]. This criterion demands four or more points after adding two points each for ocular lesions, genital aphthosis, and oral aphtosis, and one point each for skin lesions, neurological manifestations, vascular manifestations, and positive pathergy test [2]. Our inclusion criteria did not require or exclude any specific treatment for BD, and we eliminated the following cases: duplicate registration, birth place outside of Japan, lack of age at diagnosis, lack of age at onset, diagnosis year before birth year, lack of HLA-B51 status, and not satisfying ICBD.

Specific description of each manifestation

Each manifestation was judged and registered by an attending physician who had diagnosed a patient with BD [13]. The physician was usually a rheumatologist supported by medical doctors with other specialties. However, a general physician, an ophthalmologist, a gastroenterologist, a dermatologist, or a neurologist could also have registered the patient data. The physician who registered a patient as BD could not always fill out all of the questionnaire, that would be eventually classified to be 'Unclear' for specific symptoms. In this study, our analysis focused on the prevalence of each manifestation. Prevalence was estimated from the number of patients with symptoms divided by the number of evaluated patients. Briefly, prevalence was judged from 'Yes/(Yes + No)' ignoring 'Unclear.'

Statistics

Statistical analysis was performed with using BellCurve for Excel 2013 (SSRI, Tokyo). The prevalence of manifestation between two groups were compared by odds ratio (OR). For continuous variables comparison, the Mann–Whitney test was used. Categorical variables were analyzed using the Fisher's exact test or Cochran–Armitage test. A value of $p < .05$ was considered statistically significant.

Results

Flow chart for patient screening

Figure 1 shows the flow chart of patient selection. A total of 9045 individual cases were newly diagnosed as BD from 2003 to 2014 according to the data of the MHLW of Japan. There were 379 duplicate registrations, 716 invalid cases, 4371 HLA-B51 status-unknown cases, and 535 cases that did not satisfy ICBD. These cases were eliminated from the study; the remaining 3044 cases were analyzable (Figure 1).

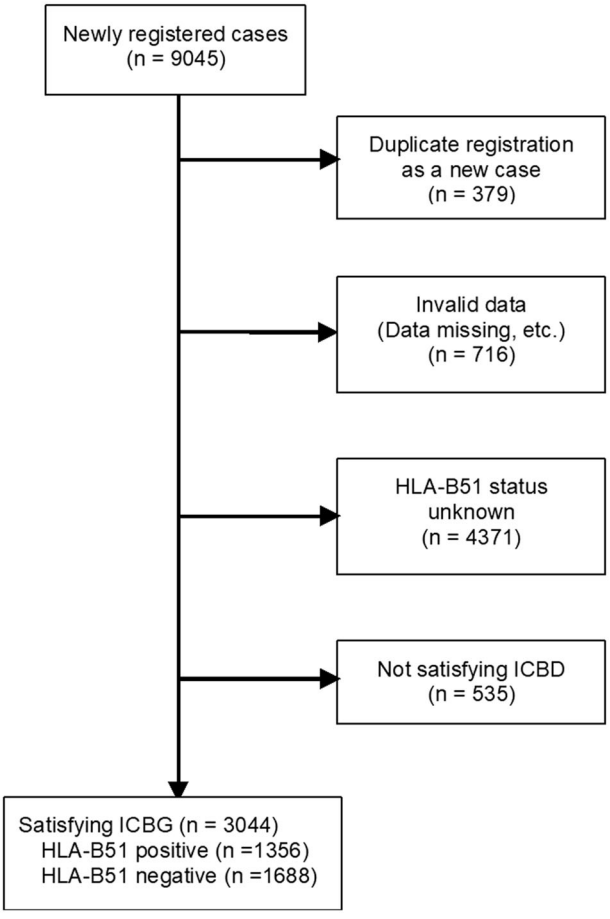

Figure 1. Flow chart of patients screening. ICBD: International Criteria for Behçet's Disease.

Background patient characteristic

Patients were registered from all prefectures of Japan: 39 (1.3%) from Hokkaido, 2575 (84.6%) from Honshu, 139 (4.6%) from Shikoku, and 291 (9.6%) from Kyushu.

Among the 3044 patients with BD who satisfied ICBD, the median age was 38 years old (IQR 29–48) and the median duration between onset to registration was 1 year (IQR 0–3 years). A total of 149 patients had a family history of BD (Table 1).

Data of each manifestation were obtained for more than 90% of cases except for vascular lesion, of which 485 (15.9%) of cases were not evaluated for and pathergy test, of which 962 (31.6%) of cases were not evaluated for.

The prevalence for each manifestation greatly varied. For example, while oral ulcer was observed for 98.5% of cases, the prevalence of epididymitis and vascular lesion were 8.8% and 13.6%, respectively (Table 1).

In our cohort of 3044 cases, 1356 (44.5%) cases had HLA-B51-positive status and 1688 cases (55.5%) had negative status.

Comparison of symptoms between HLA-B51-positive and -negative cases

Based on the analysis of all 3044 patients, HLA-B51-positive patients were more frequently men (OR 1.32, 95%CI 1.14–1.52; $p < .001$). Patients with HLA-B51 were significantly older than those without HLA-B51 ($p = .022$); however, the median age difference between 37 year and 38 years does not seem clinically important. Median ICBD score was 5 out of 10 in both groups ($p = .0504$) (Table 1).

HLA-B51 cases had higher risk for ocular lesion (OR 1.59, 95%CI 1.37–1.84; $p < .001$) and lower risk for genital ulceration (OR 0.72, 0.62–0.84; $p < .001$) and gastrointestinal symptom (OR 0.65, 0.55–0.77; $p < .001$) (Table 1). Data for iridocyclitis and Retinal uveitis are compatible those for ocular lesions (Table 2). Stomachache and bloody stool were less prevalent with HLA-positive cases as for gastrointestinal symptoms (Table 2).

No significant difference was observed for other organ involvements such as oral ulceration (OR 0.64, 95%CI: 0.35–1.16; $p = .140$) and skin lesion (OR 1.19, 95%CI: 0.97–1.46; $p = .098$) (Table 1).

Subgroup analysis

Figure 2 shows results from stratified analysis of ocular lesion, genital ulceration, and gastrointestinal lesion. The analysis using the data of all patients revealed that HLA-B51 affected the risk of three organ involvements namely, ocular lesion, genital ulceration, and gastrointestinal symptom. For sensitivity analyses, the effects of HLA-B51 positivity on the three manifestations were checked based on subgroups (Figure 2).

HLA-B51 had a significant effect on ocular lesions and gastrointestinal symptom in all subgroups. On the other hand, HLA-B51 was not related to genital ulceration in the cases with an ICBD score of six or higher.

HLA-B51 tended to more largely affect the risk of the three manifestations for men compared to that for women.

HLA-A26 and ocular lesion

As a previous study demonstrated that HLA-A26 is associated with ocular lesions, the prevalence of ocular lesions among HLA-A26-positive patients were assessed (Table 3). The prevalence was 53.6% for ocular lesion, 40.6% for iridocyclitis, and 45.6% for retinal uveitis, which were significantly higher than those in the population regardless of HLA status.

Discussion

In this study, we used a large dataset supported by the MHLW of Japan and observed a strong association between ocular manifestation and HLA-B51 and a protective association between genital ulceration and gastrointestinal lesion. To the best of our knowledge, this is the largest single study to assess the impact of HLA-B51 on each BD symptom. The simplicity, straightforward analysis, size of the database, focus on HLA-B51, and use of a uniform questionnaire are strength of our analysis.

There are some reports that mentioned the association between HLA-B51 and ocular manifestation. Ocular lesion is the key involvement in BD as it greatly deteriorates patient quality of life. For ICBD score, ocular lesions, oral aphthous ulcer and genital ulceration are each assigned two points, while skin lesions, central nervous system involvement and vascular manifestations are assigned one point each [2]. Maldini et al. conducted a meta-analysis using the data of 5790 patients from 47 publications and estimated the association between HLA-B51/B5 and each clinical manifestation. In that report, they revealed that HLA-B51/B5 is related to eye involvement with relative risk of 1.13 (95%CI: 1.06–1.21; $p < .0005$), but other clinical manifestations did not show any association [16]. Another recent meta-analysis by Horie et al. using the data of 1076 patients from 16 studies concluded that HLA-B51 is a stronger risk factor of ocular lesions (OR 1.76, $p = .000057$) compared to the estimation by Maldini et al. [17]. Maldini et al. [17] might mitigate the influence of HLA-B51 by including HLA-B subtype other than B-51. Horie et al. also suggested that the association between HLA-B51 and ocular lesion became stronger towards the east along the Silk Road [17]. They speculated that the environmental factor might be more influential in patients with BD in western countries. In addition, Horie et al. suggested that atmospheric aerosol particles could be influential for the onset of diseases. For example, unidentified particles from the Sahara Desert on westerlies and air pollutant in postwar Japan. Our result from Japanese data showing a strong relationship between HLA-B51 and ocular involvement with OR of 1.58 is compatible with the data by Horie et al., which used data from 12 countries along the Silk Road. Our subgroup analysis also replicated this conclusion (Figure 2; Tables 2 and 3). Nishiyama

Table 1. Demographic and clinical profiles of the patients.

	Total	HLA-B51 positive	HLA-B51 negative	Comparison
N	3044	1356	1688	
Age at registration (year)				
Median (IQR)	38 (29–48)	38 (30–49)	37 (29–46)	$p = .022$
Duration since onset (year)				
Median (IQR)	1 (0–3)	1 (0–3)	1 (0–3)	$p = .94$
Sex (OR men/women)				
Men	1334 (43.8%)	645 (47.6%)	689 (40.8%)	OR 1.32 (1.14–1.52)
Women	1710 (56.2%)	711 (52.4%)	999 (59.2%)	$p < .001$
Family history				
Yes	149 (4.9%)	70 (5.2%)	79 (4.7%)	OR 1.14 (0.82–1.59)
No	2441 (80.2%)	1066 (78.6%)	1375 (81.5%)	$p = .44$
Unclear	454 (14.9%)	220 (16.2%)	234 (13.9%)	
Prevalence	5.8%	6.2%	5.4%	
Oral ulceration				
Yes	2982 (98.0%)	1327 (97.9%)	1655 (98.0%)	OR 0.64 (0.35–1.16)
No	45 (1.5%)	25 (1.8%)	20 (1.2%)	$p = .140$
Unclear	17 (0.6%)	4 (0.3%)	13 (0.8%)	
Prevalence	98.5%	98.2%	98.8%	
Skin lesion				
Yes	2568 (84.4%)	1160 (85.5%)	1408 (83.4%)	OR 1.19 (0.97–1.46)
No	435 (14.3%)	178 (13.1%)	257 (15.2%)	$p = .098$
Unclear	41 (1.3%)	18 (1.3%)	23 (1.4%)	
Prevalence	85.5%	86.7%	84.6%	
Ocular lesion				
Yes	1252 (41.1%)	642 (47.3%)	610 (36.1%)	OR 1.59 (1.37–1.84)
No	1725 (56.7%)	686 (50.6%)	1039 (61.6%)	$p < .001$
Unclear	67 (2.2%)	28 (2.1%)	39 (2.3%)	
Prevalence	42.1%	48.3%	37.0%	
Genital ulceration				
Yes	2037 (66.9%)	846 (62.4%)	1191 (70.6%)	OR 0.72 (0.62–0.84)
No	913 (30.0%)	453 (33.4%)	460 (27.3%)	$p < 0.001$
Unclear	94 (3.1%)	57 (4.2%)	37 (2.2%)	
Prevalence	69.1%	65.1%	72.1%	
Positive pathergy test				
Yes	687 (22.6%)	317 (23.4%)	370 (21.9%)	OR 1.18 (0.98–1.42)
No	1395 (45.8%)	588 (43.4%)	807 (47.8%)	$p = .078$
Unclear	962 (31.6%)	451 (33.3%)	511 (30.3%)	
Prevalence	33.0%	35.0%	31.4%	
Arthritis				
Yes	1503 (49.4%)	668 (49.3%)	835 (49.5%)	OR 1.01 (0.87–1.17)
No	1387 (45.6%)	614 (45.3%)	773 (45.8%)	$p = .89$
Unclear	154 (5.1%)	74 (5.5%)	80 (4.7%)	
Prevalence	52.0%	52.1%	51.9%	
Epididymitis (male only)				
Yes	107 (8.0%)	58 (9.0%)	49 (2.9%)	OR 1.33 (0.89–1.98)
No	1107 (83.0%)	522 (80.9%)	585 (34.7%)	$p = .160$
Unclear	120 (9.0%)	65 (10.1%)	55 (3.3%)	
Prevalence	8.8%	10.0%	7.7%	
Gastrointestinal symptom				
Yes	848 (27.9%)	311 (22.9%)	537 (31.8%)	OR 0.65 (0.55–0.77)
No	2074 (68.1%)	980 (72.3%)	1094 (64.8%)	$p < .001$
Unclear	122 (4.0%)	65 (4.8%)	57 (3.4%)	
Prevalence	29.0%	24.1%	32.9%	
Vascular lesion				
Yes	347 (11.4%)	144 (10.6%)	203 (12.0%)	OR 0.92 (0.73–1.16)
No	2212 (72.7%)	962 (70.9%)	1250 (74.1%)	$p = .48$
Unclear	485 (15.9%)	250 (18.4%)	235 (13.9%)	
Prevalence	13.6%	13.0%	14.0%	
Neurological manifestation				
Yes	776 (25.5%)	353 (26.0%)	423 (25.1%)	OR 1.07 (0.91–1.26)
No	2169 (71.3%)	949 (70.0%)	1220 (72.3%)	$p = .42$
Unclear	99 (3.3%)	54 (4.0%)	45 (2.7%)	
Prevalence	26.3%	27.1%	25.7%	
ISG				
Yes	2510 (82.5%)	1123 (82.8%)	1387 (82.2%)	OR 1.05 (0.87–1.27)
No	534 (17.5%)	233 (17.2%)	301 (17.8%)	$p = .611$
BD 2010 Japan criteria				
Yes	2866 (94.2%)	1282 (94.5%)	1584 (93.8%)	OR 1.14 (0.84–1.55)
No	178 (5.8%)	74 (5.5%)	104 (6.2%)	$p = .40$
ICBD score				
Median (IQR)	5 (5–6)	5 (5–6)	5 (5–6)	$p = .0504$
Score = 4	459 (15.1%)	190 (14.0%)	269 (15.9%)	
Score = 5	1278 (42.0%)	565 (41.7%)	713 (42.2%)	
Score = 6	709 (23.3%)	315 (23.2%)	394 (23.3%)	

(*continued*)

Table 1. Continued.

	Total	HLA-B51 positive	HLA-B51 negative	Comparison
Score = 7	402 (13.2%)	190 (14.0%)	212 (12.6%)	
Score = 8	145 (4.8%)	69 (5.1%)	76 (4.5%)	
Score = 9	44 (1.4%)	23 (1.7%)	21 (1.2%)	
Score = 10	7 (0.2%)	4 (0.3%)	3 (0.2%)	

ICBD: International Criteria for Behçet's Disease. ISG: International Study Group for Behçet's Disease. Prevalence was calculated by 'Yes/(Yes + No)' ignoring 'Unclear.' IQR: interquartile range. OR: odds ratio accompanied with 95% confidence interval using 'HLA-B51 negative' as reference. For continuous and categorical variables comparison, Mann–Whitney test and Cochran–Armitage test were used.

Table 2. Detailed ocular and gastrointestinal symptoms.

	Total	HLA-B51 positive	HLA-B51 negative	
N	3044	1356	1688	Comparison
Iridocyclitis				
Yes	917 (30.1%)	482 (35.5%)	435 (25.8%)	OR 1.63
No	1985 (65.2%)	804 (59.3%)	1181 (70.0%)	(1.39–1.91)
Unclear	142 (4.7%)	70 (5.2%)	72 (4.3%)	$p < .001$
Prevalence	31.6%	37.5%	26.9%	
Retinal uveitis				
Yes	930 (30.6%)	482 (35.5%)	448 (26.5%)	OR 1.56
No	1998 (65.6%)	816 (60.2%)	1182 (70.0%)	(1.33–1.82)
Unclear	116 (3.8%)	58 (4.3%)	58 (3.4%)	$p < .001$
Prevalence	31.8%	37.1%	27.5%	
Stomachache				
Yes	730 (24.0%)	267 (19.7%)	463 (27.4%)	OR 0.66
No	2168 (71.2%)	1010 (74.5%)	1158 (68.6%)	(0.56–0.78)
Unclear	146 (4.8%)	79 (5.8%)	67 (4.0%)	$p < .001$
Prevalence	25.2%	20.9%	28.6%	
Overt or occult bloody stool				
Yes	465 (15.3%)	150 (11.1%)	315 (18.7%)	OR 0.56
No	2208 (72.5%)	1018 (75.1%)	1190 (70.5%)	(0.45–0.69)
Unclear	371 (12.2%)	188 (13.9%)	183 (10.8%)	$p < .001$
Prevalence	17.4%	12.8%	20.9%	

Prevalence was calculated by 'Yes/(Yes + No)' ignoring 'Unclear.' OR: odds ratio accompanied with 95% confidence interval using 'HLA-B51 negative' as reference.

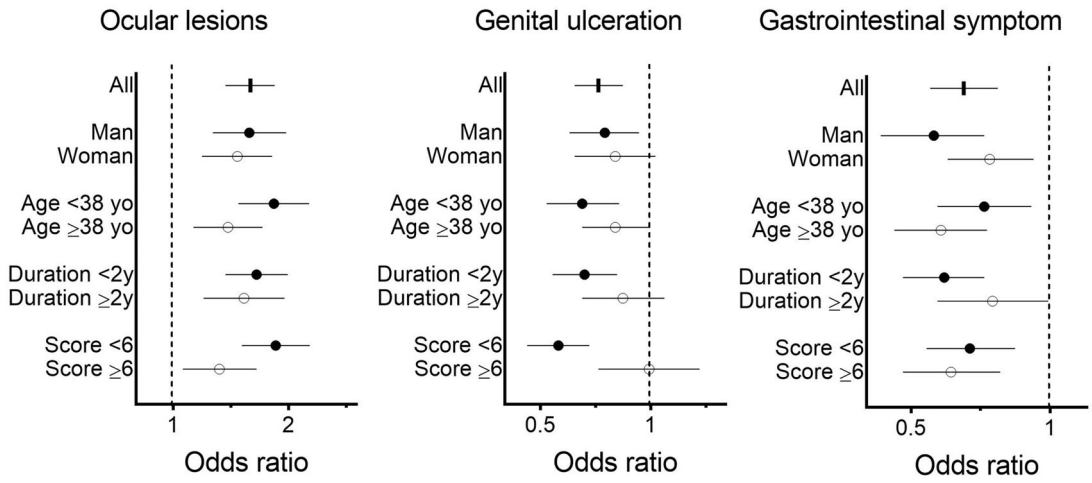

Figure 2. Sensitivity analysis. A bar indicates 95% confidence interval. Score: International Criteria for Behçet's Disease.

Table 3. Ocular lesions observed in HLA-A26-positive patients.

	Ocular lesions	Iridocyclitis	Retinal uveitis
Yes	158 (52.1%)	117 (38.6%)	134 (44.2%)
No	137 (45.2%)	171 (56.4%)	160 (52.8%)
Unclear	8 (2.6%)	15 (5.0%)	9 (3.0%)
Prevalence	53.6%	40.6%	45.6%
Population proportion	42.1%	31.6%	31.8%
p	<.001	.002	<.001

Data for 303 HLA-A26-positive patients are presented.
p-value is for hypothesis testing for the population proportion. Hypothesis is derived from 3044 cases regardless of HLA status presented in Tables 1 and 2.

et al. conducted a study of 83 familial occurrences of Behcet's disease and found that HLA-B51 positive is a risk factor for ocular lesion and protective factor for genital ulcer [18].

Genital ulceration is another major symptom of BD. The report by Maldini et al. [16] estimated that HLA-B51/B5 is a weak risk factor for genital ulceration (relative risk 1.07, $p = .03$) based on 30 reports with 1303 patients. However, the link between HLA-B51 and genital ulceration has not been evaluated in a sufficiently large cohort. The reason why HLA-

B51 is a preventive factor only in patients with lower ICBD score is not clear (Figure 2).

The OR for gastrointestinal symptoms was 0.72 using HLA-B51-negative cases as reference in our study. Although some diagnostic criteria ignore gastrointestinal manifestation, gastrointestinal symptom is regarded as one of the key minor symptoms of BD in other diagnostic criteria. Ileocecal ulceration and small bowel lesions are difficult to assess. However, colonoscopy and capsule endoscopy are easily available in tertiary hospitals [19]. Scrutinized evaluation of gastrointestinal manifestation may lead to a better understanding of the disease.

Menthon et al. conducted a meta-analysis using data of 4800 patients with BD from 78 independent studies and estimated the prevalence of HLA B51 positivity. The estimated prevalence of HLA B51 was 55.0% for East Asian, 63.5% for population in the Middle East and the North Africa, 60.6% for Southern European, 39.0% in people in the Northern and Eastern Europe, and 34.2% for North American. If our data of 3044 cases had been included in their meta-analysis, the estimated prevalence of HLA-B51 in the East Asian would have been greatly decreased [20].

We thought to assess the influence of HLA-A26 on the ocular lesion because Kaburaki et al. reported that HLA-A*2601 was significantly associated with poor visual prognosis corresponding to visual acuity of 0.1 or less in the worse eye [21]. Our data suggest that HLA-A26 greatly increase the risk of both iridocyclitis and retinal uveitis. The analytic format of ours is different from Kaburaki's; however, the results are compatible.

We should comment on a few limitations of the current study. First, most of the patients in our database are early-phase patients, thus it is not clear if HLA-B51 has a similar impact for late-phase patients with BD. Second, the data are derived from Japan only. The impact of HLA-B51 on each manifestation may be varied among races [17]. Third, we extracted the patients diagnosed by ICBD, which does not include gastrointestinal symptoms, from the patients previously diagnosed by the criteria of the Behçet's Disease Research Committee of Japan. In addition, only 40% of patients registered in the original database were checked for HLA-B51. These facts may have introduced a strong selection bias. Fourth, the reliability of our database might be questionable, as a doctor might count a clinical symptom without careful exams.

In conclusion, HLA-B51 is associated with a higher risk of ocular lesion and a lower risk of genital ulceration and gastrointestinal symptoms. These findings may have clinical implications not only on the choice of therapy but also for speculation of disease course. These results of this study may facilitate understanding of the etiology and characteristics of BD.

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Conflict of interest

None.

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Ⅰ 主 論 文

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Ⅱ 副 論 文

なし

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