Association study of HLA-A and HLA-B alleles with clinical manifestations of Behçet's disease in a Japanese population

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Background and Aim

- It is well established that Behçet's disease (BD) is strongly associated with HLA-B*51 in many different ethnic groups.
- HLA-A*26, also is strongly associated with BD in several ethnic groups, particularly in people of northeast Asian ancestry. Additionally, some other HLA-A and -B alleles, including B*15, B*27, and B*57, are reportedly associated with BD risk.
- Moreover, it has been suggested that some HLA-A and -B alleles are associated with specific clinical manifestations of BD.
- In this study, we investigated the association of HLA-A and -B alleles with clinical manifestations of BD in a Japanese patients.

Materials and Methods

- A total of 608 Japanese patients with BD and 2,955 Japanese healthy controls were enrolled in this study.
- For the genotyping of the HLA-A and -B alleles, we performed HLA imputation using SNP2HLA with the genotypes of approximately 8,000 SNPs in the HLA region from our existing genome-wide association studies.

Results

- HLA-B*51 showed the most significant association with BD ($Pc=1.2x10^{-54}$, odds ratio [OR]=3.73). Among HLA-A alleles, HLA-A*26 showed the most significant association with BD ($Pc=1.1x10^{-10}$, OR=1.85), and the association between A*26 and BD was stronger in B*51-negative cases ($Pc=6.0x10^{-15}$, OR=2.51) (Table 1).
- B*59, B*39, B*55, and A*31 were also significantly associated with the risk of BD, and B*56, B*67, B*52, B*54, B*44, A*33, and A*11 were protective alleles (Table 1).
- The allele frequency of B*51 was significantly increased in male cases (31.8%) compared to female cases (22.4%) (OR=1.62). In contrast, no significant gender differences were found in the allele frequencies of other HLA-A and -B alleles (Table 2).
- B*51 showed no significant association with specific clinical manifestations, whereas A*26 was significantly associated with ocular (OR=2.96) and neurological (OR=3.13) lesions, with higher ORs in B*51-negative cases (OR=4.42 and 4.85, respectively). (Table 3).
- In other alleles, B*35 significantly increased the risk of ocular lesions (OR=4.44), with a greater OR in the B*51-negative cases (OR=7.25). In addition, A*02 was significantly associated with the risk of arthritis (OR=1.99), B*15 with epididymitis (OR=4.58), and A*24 with vascular lesions (OR=3.93) in the B*51-negative cases (Table 3).

Table 1. Significant association between BD and HLA-A/B alleles

		All subjects (BD:Controls=608:2955)					B*51-negative (BD:Controls=314:2444)				
		Allele Freq., %					Allele Freq., %				
HLA allele		Cases	Ctrls	P	Pc	OR	Cases	Ctrls	P	Pc	OR
Risk allele											
HLA-B	B*51	27.8	9.1	4.5E-56	**1.2E-54**	3.73					
	B*59	1.5	0.0	2.4E-15	**6.4E-14**	-	1.8	0.0	5.0E-12	**1.4E-10**	-
	B*39	4.6	1.1	2.8E-14	**7.6E-13**	4.54	7.3	1.3	3.1E-17	**8.3E-16**	6.57
	B*55	2.5	0.4	2.7E-11	**7.3E-10**	6.65	3.8	0.5	3.5E-12	**9.3E-11**	9.47
HLA-A	A*26	18.3	10.8	1.1E-11	**1.1E-10**	1.85	23.6	11.1	6.0E-16	**6.0E-15**	2.51
	A*31	11.2	8.4	0.0037	**0.037**	1.36	4.5	5.9	0.16	1	0.76
Protective allele											
HLA-B	B*56	0.7	5.3	1.2E-16	**3.2E-15**	0.13	1.0	6.1	1.9E-10	**5.2E-09**	0.15
	B*67	0.8	3.3	4.3E-08	**1.2E-06**	0.24	1.1	3.6	1.0E-04	**0.0028**	0.29
	B*52	7.2	11.9	5.1E-07	**1.4E-05**	0.57	8.9	13.2	0.0016	**0.042**	0.65
	B*54	3.6	7.4	9.4E-07	**2.5E-05**	0.49	5.3	8.1	0.012	0.33	0.65
	B*44	4.6	7.4	2.6E-04	**0.0070**	0.60	5.7	8.1	0.029	0.77	0.69
HLA-A	A*33	4.7	8.1	1.7E-05	**1.7E-04**	0.56	4.6	8.8	1.2E-04	**0.0012**	0.50
	A*11	6.2	9.2	8.1E-04	**0.0081**	0.67	7.8	9.3	0.23	1	0.83

Table 2. Significant HLA-A/B allele differences between male and female BD patients

HLA-B						HLA-A					
	Allele Freq., %						Allele Freq., %				
Allele	Males (n=349)	Females (n=259)	P	Pc	OR	Allele	Males (n=349)	Females (n=259)	P	Pc	OR
B*51	31.8	22.4	3.2E-04	**0.0087**	1.62	A*11	4.7	8.1	0.013	0.13	0.55
B*54	2.6	5.0	0.0083	0.22	0.43	A*26	17.2	19.9	0.24	1	0.83

Table 3. Significant associations between HLA-A/B alleles and clinical manifestations of BD

		All patients					B*51-negative patients				
		Allele Freq., %					Allele Freq., %				
Symptom	HLA allele	Carriers	Non-carriers	P	Pc	OR	Carriers	Non-carriers	P	Pc	OR
Ocular lesions		n=469:117					n=232:69				
	B*35	7.5	2.1	2.8E-04	**0.0077**	4.44	13.1	2.9	2.0E-05	**5.4E-04**	7.25
	A*26	20.8	9.8	3.9E-06	**3.9E-05**	2.96	27.8	10.9	1.0E-06	**1.0E-05**	4.42
	B*54	2.5	9.0	6.6E-04	**0.018**	0.30	3.4	12.3	0.0084	0.23	0.33
	A*31	10.1	17.5	9.3E-04	**0.0093**	0.48	4.3	5.8	0.39	1	0.65
Skin lesions		n=488:98					n=241:60				
	B*61	0.2	3.6	0.0011	**0.029**	0.16	0.4	5.8	0.0020	0.055	0.17
Arthritis		n=226:360					n=107:194				
	A*02	22.3	21.1	0.46	1	1.12	29.0	18.0	0.0010	**0.010**	1.99
	A*26	15.0	20.8	0.0039	**0.039**	0.61	18.7	26.8	0.011	0.11	0.55
Epididymitis		n=35:296					n=12:137				
	B*15	14.3	10.1	0.32	1	1.45	41.7	12.8	0.0013	**0.036**	4.58
Intestinal lesions		n=97:489					n=53:248				
	A*26	12.4	19.8	0.0026	**0.026**	0.49	14.2	26.0	0.0013	**0.013**	0.36
Vascular lesions		n=26:560					n=16:285				
	A*24	50.0	35.0	0.027	0.27	1.96	62.5	33.3	5.4E-04	**0.0054**	3.93
Neurological lesions		n=38:548					n=21:280				
	A*26	34.2	17.5	1.7E-04	**0.0017**	3.13	42.9	22.5	4.5E-04	**0.0045**	4.85

- All association analyses were carried out under an additive model, including age and sex as covariates.
- The obtained P-values were corrected for multiple testing with the Bonferroni correction.

Conclusions

- This study suggests that some HLA-A and HLA-B alleles are important in the development of specific clinical manifestations of BD.
- To validate our findings, further studies with other independent cohorts are needed.