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HLA Association With AQP4-IgG-Positive Neuromyelitis Optica Spectrum Disorder in the Korean Population

Jae-Won Hyun,[1] Sinae Kim,[2] Jangsup Moon,[3,4] Na Young Park,[1] You-Ri Kang,[1] Ki Hoon Kim,[1,5] Su-Hyun Kim,[1] and Ho Jin Kim[1]

Correspondence
Dr. Kim
hojinkim@ncc.re.kr

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Abstract

Background and Objectives

Association of human leukocyte antigen (HLA) with anti-aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder (AQP4-IgG NMOSD) has been reported. However, this association in the Korean population has not been previously investigated. We aimed to evaluate whether specific HLA subtypes were associated with Korean patients with AQP4-IgG NMOSD and whether the HLA genotype is associated with specific clinical features.

Methods

We compared the HLA subtypes of 122 patients with AQP4-IgG NMOSD with those of 485 (HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1) and 173 (HLA-DPB1) healthy controls. In addition, we compared the clinical features of patients with and without specific HLA genotypes.

Results

The most significant risk allele for AQP4-IgG NMOSD was HLA-DRB1*03:01 (24 patients [19.67%], odds ratio [OR]: 3.997, p_c value = 0.0001). Susceptibility of AQP4-IgG NMOSD was significantly associated with the HLA-DRB1*03:01–DQB1*02:01 (23 patients [18.85%], OR: 3.792, p_c value = 0.0002) and DRB1*12:02–DQB1*03:01 (23 patients [18.85%], OR: 3.402, p_c value = 0.0009) haplotypes. Patients with the DRB1*12:02–DQB1*03:01 haplotype showed more frequent spinal involvement, a higher Expanded Disability Status Scale score at disease-onset nadir, and a shorter time to second attack than patients without this haplotype.

Discussion

In a Korean cohort of patients withAQP4-IgG NMOSD, the HLA-DRB1*12:02–DQB1*03:01 haplotype was associated with disease severity at onset. HLA-DRB1*03:01, broadly reported as a significant susceptibility allele across diverse ethnic groups, showed a significant risk association in Korean patients with AQP4-IgG NMOSD.

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Supplementary Material

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an immunologic disease of the CNS, characterized by immune responses mediated by antibodies against the aquaporin-4 water channel.[1] Epidemiologic data show that NMOSD has a diverse ethnic distribution and is more prevalent in Asians and African ancestry than in Caucasians, suggesting that genetic factors and ethnicity may contribute to its pathogenesis.[2,3] Human leukocyte antigen (HLA), a part of the major histocompatibility complex, plays a role in antigen presentation, which is directly

[1]Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea; [2]Biostatistics Collaboration Team, Research Core Center, Research Institute and Hospital of National Cancer Center, Goyang, Korea; [3]Department of Genomic Medicine, Seoul National University Hospital, Korea; [4]Department of Neurology, Seoul National University Hospital, Korea; and [5]Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea.

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Glossary

AQP4-IgG = aquaporin-4 immunoglobulin G; **EDSS** = Expanded Disability Status Scale; **HLA** = human leukocyte antigen; **IST** = immunosuppressive therapy; **NCC** = National Cancer Center; **NMOSD** = neuromyelitis optica spectrum disorder; **OR** = odds ratio.

involved in the immune process.[4] Associations between HLA genotyping and various autoimmune diseases, including NMOSD, have been described.[5,6]

Although HLA associations can vary between different ethnic groups, HLA associations in Korean patients with anti-aquaporin-4 immunoglobulin G-positive NMOSD (AQP4-IgG NMOSD) have not been previously investigated. In addition, some previous studies did not separately analyze patients with NMOSD without AQP4-IgG, who were recently classified into other disease groups, such as myelin oligodendrocyte glycoprotein antibody–associated diseases.[5,6] Finally, association of HLA genotypes and specific clinical features is not fully elucidated in AQP4-IgG NMOSD.

In this study, we aimed to investigate HLA association in a cohort of Korean patients with AQP4-IgG NMOSD. In addition, we explored whether HLA genotypes are associated with specific clinical features in AQP4-IgG NMOSD.

Methods

Study Participants

From 2015 to 2024, this study enrolled participants from a cohort of demyelinating diseases of the CNS at the National Cancer Center (NCC) who (1) were Korean, (2) met the 2015 diagnostic criteria for NMOSD,[7] and (3) were seropositive for AQP4-IgG tested by in-house live cell–based assays.[8] We reviewed the demographic and clinical characteristics of the participants, focusing on the clinical features at disease onset before immunosuppressive therapy (IST) to minimize treatment effects; these features included the initial lesion location, Expanded Disability Status Scale (EDSS) score at nadir at onset, and time to second attack in patients not treated with IST after first attack.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Institutional Review Board of the NCC (no. NCC 2023-0252), and written informed consent was collected from all enrolled participants.

HLA Genotyping

Genomic DNA was extracted from the peripheral whole blood of patients with AQP4-IgG NMOSD, and HLA genotyping was performed. The genotypes of the HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, and HLA-DPB1 loci of each patient were investigated using direct DNA sequence analysis at the four-digit allele level following established protocols (Biowithus, Seoul, South Korea).[9] The previously described frequencies of HLA genotyping (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1) and haplotype (a series of HLA alleles in the chromosome) in the Korean population (n = 485) were used as the values of healthy controls, which were analyzed using sequence-specific oligonucleotide probes.[10] The frequencies of the HLA-DPB1 genotype in the Korean population (n = 173) were used as the values of healthy controls, which were analyzed using next-generation sequencing–based typing.[11] All participants with AQP4-IgG NMOSD and healthy control groups originated from Korean general population.

Statistical Analyses

HLA genotypes were compared between patients with AQP4-IgG-positive NMOSD (n = 122) and healthy controls (485 with HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 and 173 with HLA-DPB1). In addition, clinical features were compared between patients with and without a specific HLA genotype.

Comparison of HLA allele or haplotype frequencies between the patients with AQP4-IgG NMOSD and healthy control groups was performed using the χ^2 test (or Fisher exact test). Odds ratios (ORs) and 95% CIs were used to describe the association between the HLA data and AQP4-IgG NMOSD. Bonferroni correction for multiple comparisons was used to compare the alleles and haplotypes. The p values estimated using the Fisher exact test were corrected by multiplying the total number of alleles previously detected for each locus: HLA-A (24), HLA-B (44), HLA-C (22), HLA-DRB1 (33), HLA-DQB1 (15), and HLA-DPB1 (16) alleles.[9-11] To define heterogeneity in disease risk at the primary disease gene, the relative predispositional effect (RPE) method was performed.[12] Groups with and without significant HLA haplotypes were compared using the χ^2 test (or the Fisher exact test) for categorical variables and the Mann-Whitney U test (or Student t test) for continuous variables, as appropriate. Corrected p values under 0.05 (2-tailed) were considered statistically significant. Statistical analyses were performed using R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

Data Availability

Anonymized data not described within this article can be made available on appropriate request from any qualified researcher.

Results

The demographics and clinical characteristics of 122 patients with AQP4-IgG NMOSD are summarized in Table 1. The

Table 1 Characteristics of 122 Korean Patients With AQP4-IgG NMOSD

Female, n (%)	110 (90.16)
Onset age, y, median (IQR)	33 (24–42)
Disease duration, y, median (IQR)	18.5 (13.4–22.5)
Onset lesion location[a], n (%)	
Optic nerve	51 (41.80)
Spine	50 (40.98)
Brain (APS)	25 (20.49)
EDSS score at nadir at onset, median (range)	3.0 (1.0–9.5)
Nonconverted visual function score at nadir at onset, median (range)	4.0 (1.0–6.0)
Time to first relapse, mo, median (IQR)[b]	6.1 (3.0–19.5)
Current EDSS, median (range)	3.0 (0.0–7.5)
Current maintenance treatment, n (%)	
Rituximab	90 (73.77)
Mycophenolate mofetil	22 (18.03)
Azathioprine	6 (4.92)
Others (IL-6 receptor or complement inhibitor, etc)	4 (3.28)

Abbreviations: APS = area postrema syndrome; AQP4-IgG = aquaporin-4 immunoglobulin G; EDSS = Expanded Disability Status Scale; IQR = interquartile range; NMOSD = neuromyelitis optica spectrum disorder.
[a] The multifocal involvement onset lesion location is separately counted.
[b] Except 5 patients treated with immunosuppressive therapy after first attack.

distribution of significant HLA alleles and haplotypes in AQP4-IgG NMOSD is shown in Table 2. In HLA genotyping analysis of four-digit alleles, alleles of HLA class II subtypes were associated with AQP4-IgG NMOSD and the frequencies of HLA-DRB1*03:01, 12:02, and HLA-DQB1*02:01, 03:01 alleles were significantly higher in patients with AQP4-IgG NMOSD than in healthy controls. HLA-DRB1*03:01 was the most susceptible locus for AQP4-IgG NMOSD (24 patients (19.67%), OR 3.997 [95% CI 2.222–7.191, p value corrected 0.0001]). After RPE analysis, the results remained significant. In haplotype analysis, 23 (18.85%) of the 122 patients with AQP4-IgG NMOSD had DRB1*03:01–DQB1*02:01 or DRB1*12:02–DQB1*03:01 2-locus haplotypes, respectively. Two of them had both haplotypes DRB1*03:01–DQB1*02:01 and DRB1*12:02–DQB1*03:01. By contrast, the frequencies of the DRB1*03:01–DQB1*02:01 and DRB1*12:02–DQB1*03:01 haplotypes were 5.77% and 6.39% in healthy controls, respectively, indicating a significant association between each haplotype and AQP4-IgG NMOSD (OR 3.792 (95% CI 2.096–6.86), p value corrected 0.0002; OR 3.402 (95% CI 1.902–6.086), p value corrected 0.0009), respectively. The protective alleles were HLA-DPB1*02:01, HLA-DQB1*03:03, HLA-DRB1*09:01, and HLA-DPB1*13:01. In addition, a significant protective haplotype was HLA-DRB1*09:01-DQB1*03:03.

A comparative analysis of clinical features found that patients with the HLA-DRB1*12:02-DQB1*03:01 haplotype (n = 23) showed more frequent spinal involvement and had higher EDSS scores at disease-onset nadir and a shorter time to the second attack compared with patients without the haplotype (n = 99) (Table 3). Among 51 patients who presented with optic neuritis at onset, those with the HLA-DRB1*12:02-DQB1*03:01 haplotype showed higher visual functional scores and proportion of blindness (at least one eye) at disease-onset nadir than those without this haplotype. A comparison of patients with AQP4-IgG NMOSD with each susceptible haplotype found that the EDSS score at disease-onset nadir was higher in 21 patients with the HLA-DRB1*12:02-DQB1*03:01 haplotype than in 21 patients with the HLA-DRB1*03:01-DQB1*02:01 haplotype (eTable 1). Among 16 patients who presented with optic neuritis at onset, higher visual functional scores and proportion of blindness at disease-onset nadir were found in patients with the HLA-DRB1*12:02-DQB1*03:01 haplotype than in patients with the HLA-DRB1*03:01-DQB1*02:01 haplotype. However, the clinical characteristics of patients with and without the HLA-DRB1*03:01–DQB1*02:01 haplotype were not significantly different (eTable 2).

Discussion

HLA-DRB1*03:01 allele and HLA-DRB1*03:01–DQB1*02:01 haplotypes are the most common risk loci for AQP4-IgG-positive NMOSD in the Korean population. Greater disease severity at onset was found in patients with the HLA-

Table 2 Associations of 4-Digit HLA Alleles or Haplotypes With AQP4-IgG NMOSD

HLA allele/haplotype	Phenotype frequency			AQP4 vs healthy controls		
	AQP4 (n = 122)	Healthy controls (n = 485)	Healthy controls (n = 173 in DPB1)	OR (95% CI)	Raw *p* value	Bonferroni corrected *p*
Risk allele, n (%)						
DRB1*03:01	24 (19.67)	28 (5.77)	—	3.997 (2.222–7.191)	<0.0001	0.0001
DQB1*02:01	23 (18.85)	28 (5.77)	—	3.792 (2.096–6.86)	<0.0001	0.0001
DRB1*12:02	23 (18.85)	31 (6.39)	—	3.402 (1.902–6.086)	<0.0001	0.0012
DQB1*03:01	58 (47.54)	121 (24.95)	—	2.726 (1.808–4.11)	<0.0001	<0.0001
DRB1*03:01-DQB1*02:01 haplotype	23 (18.85)	28 (5.77)	—	3.792 (2.096–6.86)	<0.0001	0.0002
DRB1*12:02-DQB1*03:01 haplotype	23 (18.85)	31 (6.39)	—	3.402 (1.902–6.086)	<0.0001	0.0009
Protective allele, n (%)						
DPB1*02:01	33 (27.05)	—	87 (50.29%)	0.367 (0.223–0.603)	0.0001	0.0011
DQB1*03:03	11 (9.02)	104 (21.44)	—	0.363 (0.188–0.7)	0.0027	0.0483
DRB1*09:01	5 (4.10)	86 (17.73)	—	0.198 (0.079–0.5)	0.0003	0.0103
DPB1*13:01	2 (1.64)	—	20 (11.56%)	0.128 (0.014–0.544)	0.0030	0.0450
DRB1*09:01-DQB1*03:03 haplotype	5 (4.10)	86 (17.73)	—	0.198 (0.079–0.500)	0.0003	0.0071

Abbreviations: AQP4-IgG = aquaporin-4 immunoglobulin G; NMOSD = neuromyelitis optica spectrum disorder; OR = odds ratio.
%: percentage of individuals with the significant allele or haplotype in the entire group.

DRB1*12:02–DQB1*03:01 haplotype than in those without this haplotype.

This study revealed that the HLA-DRB1*12:02 and DQB1*03:01 subtypes were significant risk alleles. HLA-DQB1*03:01 was reported as a risk allele in a Mexican cohort with NMOSD[13]; however, associations between clinical findings and this allele in NMOSD were not thoroughly elucidated. Of interest, patients with the HLA-DRB1*12:02–DQB1*03:01 haplotype exhibited significantly higher disease severity at nadir and shorter interval to second attack compared with those without the haplotype. Because EDSS scores could be preferentially influenced by spinal involvement, we analyzed patients with optic neuritis at onset; patients carrying HLA-DRB1*12:02-DQB1*03:01 showed a greater severity of optic neuritis. These results suggest that the HLA-DRB1*12:02–DQB1*03:01 haplotype is associated with disease severity at onset in Korean patients with AQP4-IgG NMOSD. Considering that devastating neurologic deficits can occur with even a single attack of AQP4-IgG NMOSD, early use of high-efficacy therapies is recommended in clinical practice despite unresolved cost and safety issues.[14] The HLA-DRB1*12:02–DQB1*03:01 haplotype could be a potential marker for designing personalized therapeutic strategies. Further large-scale studies are warranted to confirm the predictive significance of the HLA-DRB1*12:02–DQB1*03:01 haplotype on disease severity at onset in patients with AQP4-IgG NMOSD.

HLA-DRB1*03:01 is a risk allele for NMOSD among diverse ethnic backgrounds, including French, Brazilian, Indian, and Dutch populations. This haplotype also showed the most significant risk association for Korean patients with AQP4-IgG NMOSD.[15-20] In this study, an odds ratio consistent with previous results (OR 3.99 vs 2.46–9.23) was observed in a larger cohort of patients with AQP4-IgG NMOSD than in previous cohorts (n = 122 vs 13–44).[15-20] The phenotype frequencies (PFs) of HLA-DRB1*03:01 were lower than those in previous studies (20% vs 25–54%; if only the allele frequency (AF) was published, the PF was speculated as 2×AF).[15-20] These results suggest that HLA-DRB1*03:01 would be a shared HLA genotype in AQP4-IgG NMOSD, although the PF could be diverse among ethnic groups. HLA-DRB1*03:01 has also been associated with other autoimmune diseases, such as celiac disease and Sjogren syndrome.[21] These autoimmune diseases could share similar immunologic pathogenesis; a subset of patients with NMOSD also have autoimmune comorbidities such as Sjogren syndrome or SLE.[22]

Previously, the HLA-DRB1*03:01 allele did not show a significant difference between disease and healthy groups (PF 0.6–23% vs 0–16%) in other Asian (Japanese and Han Chinese) populations.[23-25] Instead, HLA-DPB1*05:01, observed in 56–88% of Asian healthy controls[11,23-26] but only in 2.6%–5.3% of Caucasians,[27] was identified as a significant risk allele in Asian patients with NMOSD (PF = 82%–98%, OR: 2.38–7.10).[23-26] This allele was not significantly associated with Korean patients with AQP4-IgG NMOSD (PF = 82%, OR: 2.11). In addition, HLA-DRB1*16:02 (PF = 7–27%, OR:

Table 3 Comparison of Clinical Features of Patients With AQP4-IgG NMOSD With and Without HLA-DRB1*12:02-DQB1*03:01

	HLA-DRB1*12:02-DQB1*03:01 positive (n = 23)	HLA-DRB1*12:02-DQB1*03:01 negative (n = 99)	*p* Value
Female, n (%)	21 (91.30)	89 (89.90)	>0.9999
Onset age, y, median (IQR)	33 (24–46)	33 (24–39)	0.6094
Disease duration, y, median (IQR)	16.5 (13.3–22.5)	18.7 (13.3–22.5)	0.4076
Onset lesion location[a], n (%)			
Optic nerve	6 (26.09)	45 (45.45)	>0.9999[b]
Spine	15 (65.22)*	35 (35.35)	0.0015[b*]
Brain (including APS)	5 (21.74)	20 (20.20)	>0.9999[b]
EDSS score at nadir at onset, median (range)	4.0 (2.0–8.5)*	3.0 (1.0–9.5)	0.0010*
Nonconverted visual function score at nadir at onset, median (range) [total n = 51]	5.0* (4.0–6.0) [n = 6]	4.0 (1.0–6.0) [n = 45]	0.0260*
No light perception at nadir at onset	5/6 (83%)*	15/45 (33%)	0.0288*
Time to first relapse, mo, median, IQR [total n = 117][c]	4.0 (2.3–6.1)* [n = 21]	7.8 (3.0–20.4) [n = 96]	0.0495*
Current EDSS score, median (range)	3.5 (0.0–7.0)	3.0 (0.0–7.5)	0.3252
Current maintenance treatment, n (%)			0.7307
Rituximab	17 (73.91)	73 (73.74)	
Mycophenolate mofetil	4 (17.39)	18 (18.18)	
Azathioprine	2 (8.70)	4 (4.04)	
Others (IL-6 receptor or complement inhibitor)	0 (0.00)	4 (4.04)	

Abbreviations: APS = area postrema syndrome; AQP4-IgG = aquaporin-4 immunoglobulin G; EDSS = Expanded Disability Status Scale; NMOSD = neuromyelitis optica spectrum disorder; IQR = interquartile range.
[a] The multifocal involvement onset lesion location is separately counted.
[b] Corrected *p* value is calculated multiplying 3 because onset location had 3 categories.
[c] Except 5 patients treated with immunosuppressive therapy after first attack.

2.71–8.99 in NMOSD cohorts [n = 30–184]) was reported as a significant risk allele in a Han Chinese study and 2 of 3 Japanese studies.[23,24,26] The allele did not significantly associate with NMOSD in a Japanese cohort or the current Korean population (PF = 3.6%–5.7%, OR: 3.68–4.84).[25] The heterogeneity of HLA alleles susceptible to NMOSD, even in Asian populations, might explain these discrepancies.

HLA-DRB1*09:01 is a protective allele in Japanese and Han Chinese populations[23-26] and has been reported to be a protective allele in Korean patients with AQP4-IgG NMOSD. The risk/protective alleles significantly linked with Korean AQP4-IgG NMOSD (mainly HLA-DRB1 or HLA-DQB1) are in the HLA class II subtype associated with humoral immunity characterized by specific autoantibodies, compatible with the pathogenesis of NMOSD primarily mediated by AQP4-IgG.[1,4]

Possible unintentional biases limit this study because the data were collected from a single referral center. However, the single-center design suggests that the clinical features were consistently evaluated and recorded. In addition, a subset of healthy controls were genotyped using a low-resolution method, necessitating future detailed case-control investigations.

In conclusion, we found an association between AQP4-IgG NMOSD disease severity at onset and HLA-DRB1*12:02–DQB1*03:01 haplotype. We also identified a significant risk association between Korean patients with AQP4-IgG NMOSD and HLA-DRB1*03:01, which is a widely documented susceptibility allele in various ethnic groups.

Author Contributions

J.-W. Hyun: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S. Kim: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Moon: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. N.Y. Park: major role in the acquisition of data. Y.-R. Kang: major role in the acquisition of data; analysis or interpretation of data. K.H. Kim: major role in the acquisition of data. S.-H. Kim:

drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. H.J. Kim: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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