

RESEARCH

Open Access



Genetic susceptibility of human leukocyte antigen alleles in chronic inflammatory demyelinating polyneuropathy in Korean patients

Short title: HLA alleles and CIDP in Korea

Soonwook Kwon¹ , Jin Myoung Seok² , Hye Lim Lee³ , Yeon Hak Chung³ , Hyunjin Ju⁴ , Mi Young Jeon⁵ and Byoung Joon Kim^{5*}

Abstract

Background The pathogenesis of chronic inflammatory demyelinating polyneuropathy (CIDP) is still not fully understood, but HLA polymorphisms have been implicated in immunogenesis. In the present study, we aimed to identify HLA alleles susceptible to CIDP in the Korean population.

Methods We retrospectively analyzed 27 Korean patients with CIDP diagnosed at Samsung Medical Center between 2016 and 2022. Clinical features and nodal/paranodal antibodies were assessed. HLA-DRB1, DPB1, and DQB1 genotyping was performed using the Luminex-based oligonucleotide probe method. Autoimmune nodopathy (AN) was defined by the presence of anti-NF155, anti-contactin-1, or anti-CASPR1 antibodies confirmed by cell-based assay. Allele frequencies were compared with those from 173 healthy Korean controls. Statistical analyses included chi-square or Fisher's exact tests, Cohen's *h*, post-hoc power analysis, and Hochberg correction for multiple comparisons. Haplotype frequencies were estimated using the expectation-maximization algorithm.

Results The median age of the patients was 58 years, and 12 (44.4%) were female. Anti-NF155 antibodies were identified in 7 of 27 patients (25.9%). DRB1*04 frequency was significantly higher in patients compared to controls (27.8% vs. 2.6%, *p*-value < 0.001), with an odds ratio of 14.40 (95% CI 5.91–35.08). This association remained significant in both CIDP and AN subgroups after correction for multiple comparisons. In subgroup comparisons, DRB1*07, DRB1*15, and DQB1*04 were more frequent in AN than in CIDP, but the differences were not statistically significant.

Conclusion Our findings suggest that HLA-DRB1*04 is more frequent in Korean patients with CIDP and AN compared to healthy controls. Further studies with larger cohorts are warranted to validate these observations.

Keywords Chronic inflammatory demyelinating polyneuropathy, Human leukocyte antigen, Genetic susceptibility, Paranodal antibody

*Correspondence:
Byoung Joon Kim
bjmyo.kim@samsung.com

Full list of author information is available at the end of the article



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated neuropathy with chronic progressive or relapsing courses by a chronic progressive or relapsing course lasting more than eight weeks [1]. The typical clinical presentation involves symmetric motor and sensory deficits with both proximal and distal muscle weakness and hyporeflexia. However, CIDP exhibits considerable heterogeneity, and atypical variants such as acute or subacute onset, asymmetric involvement, and purely motor, sensory, or focal forms have also been described.

Recently, the second revision of the EFNS/PNS guidelines suggested a new category of autoimmune neuropathies (AN) that are clinically and pathophysiologically distinct from CIDP in the presence of antibodies targeting nodal and paranodal proteins [2]. Identified target antigens include neurofascin-155 (NF155), NF186, contactin-1 (CNTN1), contactin-associated protein 1 (CASPR1), and leucine-rich glioma inactivated protein 4 (LGI4) [3, 4]. These nodal-paranodal proteins are critical for the formation and maintenance of axoglial junctions, proper ion channel distribution, and the structural integrity of the nodes of Ranvier, thereby enabling saltatory conduction of action potentials [5]. Among them, anti-NF155 antibodies are associated with early-onset disease, distal-dominant sensorimotor neuropathy, sensory ataxia, and tremor, and tend to show a poor response to intravenous immunoglobulin (IVIg) but a favorable response to rituximab [4, 6]. Patients with antibodies against LGI4, CNTN1, or CASPR1 share clinical features with anti-NF155-positive patients, although they generally present at an older age [3, 6, 7].

The pathogenesis of CIDP remains incompletely understood. However, the activation of humoral and cellular autoimmunity to unknown antigens, which might be located in the nodal and paranodal regions, is the main mechanism [8]. While the precise mechanisms of antigen sensitization are still under investigation, human leukocyte antigen (HLA) class II molecules have been implicated in disease susceptibility. HLA class II is expressed on the surface of antigen-presenting cells (APCs), including macrophages, dendritic cells, and B cells and binds to CD4+ receptors on helper T cells [9]. Activated T cells secrete cytokines such as interleukin (IL)-4, and IL-6, which stimulate B cells and cross the blood-nerve barrier leading to macrophage-mediated demyelination.

Several studies have investigated the association between HLA polymorphism and susceptibility to CIDP (Supplementary Tables 1 and 2). In a Greece study, patients with CIDP ($n=40$) demonstrated a trend higher frequency of DRB1*11 and lower frequency of DRB1*15 allele compared to healthy controls ($n=90$), although these differences did not reach statistical significance

(41.3% vs. 28.9%, p -value 0.065; and 1.3% vs. 7.2%, p value 0.075) [10]. An Iranian study involving 50 CIDP patients and 49 controls revealed that DQB1*02 allele was associated with CIDP (odds ratio [OR] 4.82, 95% confidence interval [CI] 2.06–11.3) [11]. In a Tunisian population, DRB1*13 allele was more prevalent in CIDP patients than in controls (22.2% vs. 9.0%, p -value 0.03) [12]. More recently, studies from Spain and Japan have demonstrated a strong association between DRB1*15 allele and anti-NF155 AN [13, 14]. These findings suggest that HLA-related genetic susceptibility may differ between CIDP and its nodopathy variants.

In the present study, we aimed to identify HLA class II alleles associated with genetic susceptibility to CIDP in a Korean population. Furthermore, we investigated whether the pattern of HLA associations differed according to the presence of nodal-paranodal antibodies.

Methods

Subjects

We retrospectively enrolled 27 Korean patients with CIDP who visited the Samsung Medical Center from January 1, 2016, to August 31, 2022. The diagnosis of CIDP was established based on the diagnostic criteria of the 2010 EFNS/PNS guidelines, and all patients also fulfilled the clinical and electrophysiological criteria of the 2021 EFNS/PNS guidelines [2, 15]. Demographic data, including age, sex, as well as clinical characteristics were collected. The clinical characteristics included the clinical course, predominance of motor or sensory symptoms, pattern of proximal/distal dominance, asymmetry, and presence of ataxia, Romberg sign, and tremor. The clinical course was classified as acute (duration of symptom onset to nadir ≤ 4 weeks), subacute (4–8 weeks), or chronic (≥ 8 weeks) [16]. Medication history, including corticosteroids, immunosuppressants, and IVIg, and treatment response were also documented.

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. IRB 2015-04-086-001), and written informed consent was obtained from all participants.

Analyses of HLA-DRB1, DPB1, and DQB1 alleles and haplotypes

In this study, we analyzed HLA-DRB1, DPB1, and DQB1, which is HLA class II alleles that directly contact antigens and exhibit allele-specific polymorphisms. HLA genotyping was performed by sequence-specific oligonucleotide probe method with the the Luminex system (Luminex Corp., Austin, TX, USA), in combination with the WAK-Flow HLA Typing Kit (Wakunaga, Hiroshima, Japan).

According to the manufacturer's instructions, patients' genomic deoxyribonucleic acid (DNA) was extracted from ethylenediaminetetraacetic acid (EDTA)-treated

peripheral blood via a QIAamp DNA Blood Kit (Qia-gen, USA). Polymerase chain reaction (PCR) amplification of target HLA loci was carried out using biotinylated primers specific to each allele. The WAKFlow HLA typing kits are originally designed for allele determination in the Japanese population [17], and has also been validated for use in the Korean population [18]. The biotin-labeled PCR products were denatured and hybridized to complementary oligonucleotide probes bound to fluorescence-labeled microsphere beads. The hybrids were then labeled with phycoerythrin-conjugated streptavidin, and the fluorescence signal was detected using the Luminex system. Allele assignments were made using the WAK-Flow Typing software, based on the hybridization signal patterns.

Identification of antibodies to nodal-paranodal proteins

The presence of antibodies targeting paranodal proteins was assessed using a cell-based assay. Peripheral blood samples were centrifuged at 1,000 g for 10 min, and the serum was stored at -80°C until analysis. Plasmid DNAs encoding green fluorescent protein-tagged human neurofascin-155 (NM_001160331), contactin (NM_001843), and caspr-1 (NM_003632) plasmid DNA (OriGene Technologies, Rockville, USA) were transfected into human embryonic kidney 293 cells using Lipofectamine 3000 (ThermoFisher Scientific, Waltham, MA, USA). The transfected cells were incubated with patient sera diluted at 1:20 for 60 min. Anti-human IgG4 antibody (1:500 dilution) was applied, followed by an Alexa-fluor 594 fluorescence-conjugated secondary antibody (ThermoFisher Scientific, Waltham, MA, USA). The number of cells with double-stained cells and their fluorescence intensity were measured under a fluorescence microscope (80i, Nikon, Japan). Antibody reactivity was semi-quantitatively graded by visual inspection on a scale from 0 (negative) to +4 (strongly positive). Patients were categorized into the AN group if they tested positive for any paranodal antibodies. Those who tested negative were categorized into the CIDP group.

Control group

As a control group, we used previously published data from a healthy Korean population [19]. A total of 173 genetically unrelated healthy Korean adults (346 alleles) were included. Genotyping was performed using next-generation DNA sequencing with long-range PCR, TruSight[®] HLA v2 kit, Illumina MiSeqDx platform system, and Assign[™] for TruSight[™] HLA software. The NGS results were validated by comparison with previously obtained results using Sanger sequencing, demonstrating the accuracy of NGS [20]. The study identified 31, 17, and 16 alleles of HLA-DRB1, HLA-DPB1, and HLA-DQB1, respectively (Supplementary Table 3).

Statistical analyses

Continuous data are presented as the median (interquartile range) for nonnormally distributed data. Categorical data are presented as numbers (percentages). Statistical analyses were performed using the chi-square test and Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables as appropriate. To assess the adequacy of the sample size and the robustness of observed differences in allele frequencies, post-hoc power analyses were conducted for each HLA allele comparison. Cohen's h was calculated as a measure of effect size for the difference in proportions, where values of 0.20, 0.50, and 0.80 indicate small, medium, and large effects, respectively. In this study, Cohen's $h \geq 0.50$ was considered to indicate a meaningful effect.

To adjust for multiple comparisons of HLA allele frequencies across groups, we applied the Hochberg step-up method to control the family-wise error rate. Adjusted p -values were calculated, and a threshold of $p < 0.05$ was considered statistically significant after correction.

Haplotype frequencies were inferred using the expectation-maximization (EM) algorithm implemented in the R package, 'haplo.stats' (version 1.6.0) [17, 21]. All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

Results

Demographic characteristics of patients with CIDP

The median age of all patients was 58 years (interquartile range 49.0–68.0), and twelve (44.4%) were female (Table 1). Antibodies to nodal-paranodal proteins were detected in seven patients, all of whom were positive for anti-NF155 antibodies (Fig. 1a–e). Among these, antibody titers were scored as +2 in three patients, +4 in two, and +1 and +3 in one patient each.

The proportion of female was higher in the AN group compared with the CIDP group (85.7% vs. 30.0%, p -value 0.024). Although the median age was lower in the AN group than in the CIDP group, but the difference was not statistically significant. Among all patients, five patients (18.5%) had an acute or subacute clinical onset, 19 (70.4%) presented sensorimotor symptoms, and 2 (7.4%) exhibited an asymmetric distribution (Table 1). Proximal-dominant weakness was observed in 3 (11.1%), ataxia in 10 (37.0%), tremor in 4 (13.8%), and a positive Romberg sign in 15 (51.7%). There were no significant differences between the CIDP and AN groups in terms of onset pattern, motor versus sensory predominance, proximal/distal distribution, or asymmetry. However, sensory ataxia and a positive Romberg sign were more frequently observed in the AN group (71.4% vs. 25.0%, and 85.7% vs. 45.0%, respectively).

Table 1 Demographic characteristics

	Total	AN	CIDP	P-value
Number (%)	27 (100)	7 (25.9)	20 (74.1)	
Median age (IQR)	58.0 (49.0–68.0)	53.5 (30.5–65.5)	61.0 (52.3–68.0)	0.114
Female (%)	12 (44.4)	6 (85.7)	6 (30.0)	0.024
Antibodies (%)	7 (29.6)	7 (100.0) [€]	0 (0)	
Clinical onset (%)				0.472
Acute	1 (3.7)	0 (0.0)	1 (5.0)	
Subacute	4 (14.8)	2 (28.6)	2 (10.0)	
Chronic	22 (81.5)	5 (71.4)	17 (85.0)	
Sensory/motor pattern (%)				0.118
Sensorimotor	19 (70.4)	3 (42.9)	16 (80.0)	
Sensory dominant	7 (25.9)	4 (57.1)	3 (15.0)	
Motor dominant	1 (3.7)	0 (0.0)	1 (5.0)	
Asymmetry (%)	2 (7.4)	0 (0.0)	2 (10.0)	1.000
Weakness pattern (%)				0.118
Proximal dominant	3 (11.1)	1 (14.3)	2 (10.0)	
Distal dominant	19 (70.4)	3 (42.9)	16 (80.0)	
Proximal=Distal	1 (3.7)	1 (14.3)	0 (0.0)	
No weakness	4 (13.8)	2 (28.6)	2 (10.0)	
Ataxia (%)	10 (37.0)	5 (71.4)	5 (25.0)	0.065
Tremor (%)	4 (13.8)	1 (14.3)	3 (15.0)	1.000
Romberg sign (%)	15 (51.7)	6 (85.7)	9 (45.0)	0.091
Treatment (%) ^{square}				
Steroid	23 (85.2)	6 (85.7)	17 (85.0)	0.731
Immunosuppressants [‡]	14 (51.9)	3 (42.9)	11 (55.0)	0.454
IVIg	18 (66.7)	4 (57.1)	14 (70.0)	0.653
Treatment response to IVIg (%)				0.319
Good	12 (44.4)	4 (57.1)	7 (35.0)	
Partial	8 (29.6)	1 (14.3)	8 (40.0)	
Poor	5 (18.5)	1 (14.3)	4 (20.0)	

Data are presented as number (%) for categorical variables

AN Autoimmune nodopathy, CIDP Chronic inflammatory demyelinating polyradiculoneuropathy, IQR Interquartile range, IVIg Intravenous immunoglobulin

€All detected antibodies were anti-neurofascin-155 antibodies

squareTwo patients with seronegative CIDP received rituximab

‡Immunosuppressants included azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide

Twenty-three (85.2%) patients were treated with corticosteroids, 14 (51.9%) with immunosuppressants, and 18 (66.7%) with IVIg (Table 1). Among those who received IVIg, 8 (29.6%) showed a partial response to IVIg, while 5 (18.5%) had a poor response. One patient in the AN group were treated IV cyclophosphamide, and two in the CIDP group were administrated either rituximab or cyclophosphamide due to an inadequate response to IVIg.

Frequencies of each HLA-DRB1, DPB1, and DQB1 alleles and haplotype

Allele and haplotype frequencies are summarized in Tables 2 and 3. A total of 20 DRB1, 12 DPB1, and 14 DQB1 alleles were identified (Table 2). Among DRB1 alleles, DRB1*04:05 (13.0%) was most frequent, followed by DRB1*13:02 (11.1%) and DRB1*08:03 (9.3%). Two

patients were homozygous for DRB1 allele (one each for DRB1*04:05 and DRB1*13:02).

In DPB1 alleles, DPB1*05:01 (33.3%) and DPB1*02:01 (27.8%) were most frequent, with five patients showing homozygosity (three for DPB1*05:01 and two for DPB1*02:01). For DQB1 alleles, DQB1*03:01, DQB1*04:01, and DQB1*06:01 were each observed in 13.0% of patients. One patient had homozygous for DQB1*04:01, and one patient showed no detectable allele pattern in DQB1 typing.

Haplotype analysis using the EM algorithm identified eight haplotypes observed in more than twice (Supplementary Table 4). The most common haplotypes were DRB1*04:05-DPB1*05:01-DQB1*04:01 and DRB1*13:02-DPB1*04:01-DQB1*06:04. One patient with anti-NF155 antibody had homozygosity across all three loci.

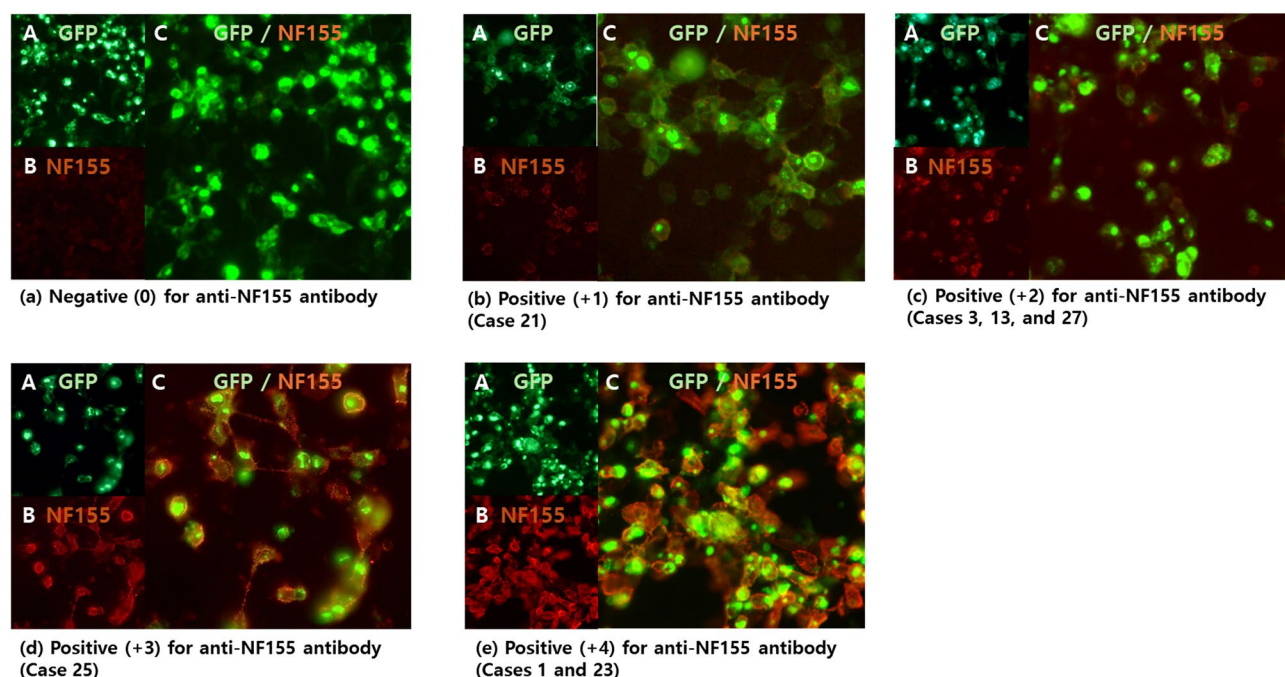


Fig. 1 The results of the cell-based assays for antibodies to neurofascin-155. **a-e** Panel A of each figure showed the green fluorescent protein (GFP) stain of HEK293 cells with GFP-tagged human neurofascin-155. The gene-transfected cells were incubated with patient sera and stained by the fluorescence-conjugated secondary antibody (Panel B). Panel C of each figure showed the merged image. The positivity of antibodies was confirmed by visual inspection (0: negative (a), +1 ~ +4: positive (b ~ e)) GFP, green fluorescent protein; NF155, neurofascin-155

Comparison of the HLA allele frequencies and odds ratios

Initially, HLA analysis was conducted at the second-field resolution. However, due to the limited sample size, all post-hoc analyses yielded small effect sizes (Cohen's $h < 0.5$), indicating insufficient power to detect meaningful differences. Therefore, subsequent analyses were performed at the first-field resolution.

The frequency of DRB1*04 was significantly higher in the patient group compared to the control group (27.8% vs. 2.6%, p -value < 0.001), with an OR of 14.40 (95% CI, 5.91–35.08; Table 3). The effect size, measured by Cohen's h , was 0.79, and the post-hoc power was 1.00, indicating a large and robust effect.

In subgroup analyses, the frequency of DRB1*04 remained significantly higher in the CIDP group than in the control group (OR, 14.20; 95% CI, 5.44–37.06; Supplementary Table 4), and in the AN group compared to the control group (OR, 14.98; 95% CI, 3.94–56.93; Supplementary Table 5). No other alleles showed statistically significant differences in frequency compared to the control group after correction for multiple comparisons using the Hochberg method.

In a comparison between the CIDP and AN subgroups, the frequencies of DRB1*07, DRB1*15, and DQB1*04 were more than two-fold higher in the AN group than in the CIDP group; however, these differences did not reach statistical significance.

Discussion

In this study, we analyzed the distribution of HLA class II alleles in Korean patients with CIDP and AN, and compared them with a healthy control group. Among the alleles analyzed, DRB1*04 was significantly more frequent in patient group than in control group. This association remained significant after correction for multiple comparisons and was consistently observed in both CIDP and AN groups. No other DRB1, DPB1, or DQB1 alleles showed statistically significant differences after correction. Additionally, a direct comparison between the CIDP and AN groups revealed a significantly higher frequency of DRB1*07 in the AN group.

In the present study, seven patients (25.9%) were positive for anti-NF155 antibody, which is a higher frequency than previously reported in Western populations (2.6–10%) [4, 6, 22] and comparable to frequencies reported in the East Asian populations (18–21%) [23, 24]. Other paranodal antibodies, anti-CNTN1 and anti-CASPR1 antibodies, were not detected. Although there are no prior reports on the prevalence of these antibody in Korea, studies from other countries have reported low frequencies (anti-CNTN1 antibody: 1–7%, and anti-CASPR1 antibodies: 1–3%) [1]. In our study, AN group were relatively younger and more likely to be female compared to those in the CIDP group. Previous studies have shown that while CIDP can occur at any age, its prevalence increased with age, particularly in individuals

Table 2 The frequency of HLA-DRB1, DPB1, and DQB1 alleles

Case	Sex	Antibody	DRB1		DPB1		DQB1	
1	F	NF155	DRB1*14:03	DRB1*15:01	DPB1*02:01	DPB1*05:01	DQB1*03:01	DQB1*06:02
2	F	No	DRB1*04:05	DRB1*13:02	DPB1*04:01	DPB1*05:01	DQB1*03:02	DQB1*06:04
3	F	NF155	<i>DRB1*04:05</i>	<i>DRB1*04:05</i>	<i>DPB1*05:01</i>	<i>DPB1*05:01</i>	<i>DQB1*04:01</i>	<i>DQB1*04:01</i>
4	F	No	<i>DRB1*13:02</i>	<i>DRB1*13:02</i>	DPB1*04:01	DPB1*05:01	DQB1*06:04	DQB1*06:09
5	F	No	DRB1*09:01	DRB1*14:01	<i>DPB1*05:01</i>	<i>DPB1*05:01</i>	DQB1*03:03	DQB1*05:03
6	M	No	DRB1*03:01	DRB1*08:03	DPB1*02:01	DPB1*03:01	DQB1*02:01	DQB1*06:01
7	M	No	DRB1*12:01	DRB1*13:02	DPB1*02:01	DPB1*03:01	DQB1*03:01	DQB1*06:09
8	M	No	DRB1*13:02	DRB1*15:02	DPB1*04:01	DPB1*09:01	DQB1*06:01	DQB1*06:04
9	F	No	DRB1*08:02	DRB1*11:01	DPB1*05:01	DPB1*17:01	DQB1*02:02	DQB1*04:01
10	M	No	DRB1*04:05	DRB1*08:03	DPB1*04:02	DPB1*05:01	DQB1*03:01	DQB1*04:02
11	M	No	DRB1*04:05	DRB1*04:06	DPB1*02:01	DPB1*05:01	DQB1*04:01	DQB1*06:01
12	M	No	DRB1*04:05	DRB1*14:05	<i>DPB1*02:01</i>	<i>DPB1*02:01</i>	DQB1*03:02	DQB1*04:01
13	F	NF155	DRB1*01:01	DRB1*15:02	<i>DPB1*05:01</i>	<i>DPB1*05:01</i>	DQB1*04:01	DQB1*05:03
14	M	No	DRB1*12:01	DRB1*14:01	DPB1*05:01	DPB1*09:01	No Pattern	No Pattern
15	M	No	DRB1*01:01	DRB1*13:02	DPB1*02:01	DPB1*06:01	DQB1*03:03	DQB1*05:03
16	F	No	DRB1*04:06	DRB1*15:01	<i>DPB1*02:01</i>	<i>DPB1*02:01</i>	DQB1*05:01	DQB1*06:09
17	M	No	DRB1*08:03	DRB1*14:03	DPB1*02:01	DPB1*05:01	DQB1*03:02	DQB1*06:02
18	M	No	DRB1*04:06	DRB1*08:03	DPB1*05:01	DPB1*17:01	DQB1*03:01	DQB1*06:01
19	M	No	DRB1*01:01	DRB1*11:01	DPB1*02:01	DPB1*02:01	DQB1*03:02	DQB1*06:01
20	M	No	DRB1*04:01	DRB1*04:05	DPB1*03:01	DPB1*38:01	DQB1*03:01	DQB1*05:01
21	F	NF155	DRB1*10:01	DRB1*15:02	DPB1*04:02	DPB1*14:01	DQB1*03:02	DQB1*04:01
22	M	No	DRB1*01:01	DRB1*15:01	DPB1*02:01	DPB1*09:01	DQB1*05:01	DQB1*06:01
23	F	NF155	DRB1*04:10	DRB1*07:01	DPB1*02:02	DPB1*05:01	DQB1*05:01	DQB1*06:02
24	F	No	DRB1*04:01	DRB1*15:01	DPB1*03:01	DPB1*13:01	DQB1*02:02	DQB1*04:02
25	F	NF155	DRB1*07:01	DRB1*08:03	DPB1*02:01	DPB1*04:01	DQB1*03:01	DQB1*06:02
26	M	No	DRB1*04:01	DRB1*12:01	DPB1*05:01	DPB1*13:01	DQB1*02:02	DQB1*06:01
27	M	NF155	DRB1*04:03	DRB1*07:01	DPB1*02:01	DPB1*05:01	DQB1*03:01	DQB1*03:03

The haplotype was written in bold and italic

F Female, HLA Human leukocyte antigen, NF155 Neurofascin-155

in their 50s to 60s [25]. In contrast, the onset of AN has been reported at a younger age (27–67 years), which is consistent with our finding. Regarding sex ratio, male predominance has been commonly reported for both CIDP (1.4–4.4:1) and AN (1.6–2:1) [23–26]. Although our study also showed a higher male ratio in the total patients and CIDP subgroup, the AN group showed a female predominance, which contrasts with previous reports. The acute onset and a high frequency of sensory ataxia were observed, consistent with previous studies. However, tremor and poor response to IVIg, commonly reported in AN, were not seen in our study. These differences may be due to the limited sample size and retrospective design. The clinical features of our anti-NF155 antibody-positive patients showed general similarity to those reported in a recent Korean study. In that study, all patients exhibited sensory ataxia, approximately half had tremor, and distal-dominant weakness was the predominant motor pattern [26]. However, both studies included a limited number of patients, and therefore, caution is warranted in generalizing the clinical phenotype of patients with autoimmune nodopathy. Large cohort

studies in Korean populations are warranted to validate these findings.

In the HLA allele analysis, the frequency of DRB1*04 was higher in the patient group compared to the control group, and this trend was consistently observed in both the CIDP and AN subgroups. Previous studies have reported considerable heterogeneity in the HLA alleles associated with CIDP. Various alleles have been proposed to be associated with CIDP: Aw30 and B8 [27], B7 and Cw7 [28], Dw3 [29], DR2 [30], DRB1*13 [12], DRB1*03 and DRB1*10 [31], and DQB1*02 (Supplementary Table 1) [11]. However, studies from Tunisia, Greek, and the Netherlands reported no specific alleles significantly associated with CIDP [10, 12, 32].

The association between DRB1*04 and autoimmune diseases has been reported. Specifically, DRB1*04:01 is a known susceptibility allele for rheumatoid arthritis (RA) and type 1 diabetes mellitus (T1DM) [33]. In RA, the P4 pocket of DRB1*04:01 preferentially binds to the citrullinate peptide [34], leading to the activation of autoreactive T cells and correlating with disease markers [35]. In T1DM, DRB1*04:01 is thought to facilitate presentation of pancreatic islet autoantigens, such as insulin or

Table 3 Comparison of the HLA allele frequencies and odds ratios

Allele	Patients (Alleles 54)	Controls (Alleles 346)	OR (95% CIs)	Adjusted p-value	Cohen's h	Post-hoc Power
HLA-DRB1 alleles						
DRB1*01	4 (7.4%)	20 (5.8%)	1.30 (0.43–3.97)	1.000	0.07	0.08
DRB1*03	1 (1.9%)	8 (2.3%)	0.80 (0.10–6.50)	1.000	–0.03	0.06
DRB1*04	15 (27.8%)	9 (2.6%)	14.40 (5.91–35.08)	<0.001	0.79	1.00
DRB1*07	3 (5.6%)	27 (7.8%)	0.69 (0.20–2.38)	1.000	–0.09	0.10
DRB1*08	6 (11.1%)	49 (14.2%)	0.76 (0.31–1.87)	1.000	–0.09	0.10
DRB1*09	1 (1.9%)	19 (5.5%)	0.32 (0.04–2.48)	1.000	–0.20	0.31
DRB1*10	1 (1.9%)	2 (0.9%)	3.25 (0.29–36.42)	1.000	0.12	0.14
DRB1*11	2 (3.7%)	15 (4.3%)	0.85 (0.19–3.82)	1.000	–0.03	0.06
DRB1*12	3 (5.6%)	29 (8.4%)	0.64 (0.19–2.19)	1.000	–0.11	0.13
DRB1*13	6 (11.1%)	37 (10.7%)	1.04 (0.42–2.61)	1.000	0.01	0.05
DRB1*14	5 (9.3%)	35 (10.1%)	0.91 (0.34–2.43)	1.000	–0.03	0.06
DRB1*15	7 (13.0%)	35 (10.1%)	1.32 (0.56–3.15)	1.000	0.09	0.10
HLA-DQB1 alleles						
DQB1*02	4 (7.4%)	34 (9.8%)	0.73 (0.25–2.16)	1.000	–0.09	0.10
DQB1*03	15 (27.8%)	120 (34.7%)	0.72 (0.38–1.37)	1.000	–0.15	0.20
DQB1*04	9 (16.7%)	35 (10.1%)	1.78 (0.80–3.94)	0.485	0.19	0.30
DQB1*05	7 (13.0%)	53 (15.3%)	0.82 (0.35–1.92)	1.000	–0.07	0.08
DQB1*06	17 (31.5%)	104 (30.1%)	1.07 (0.58–1.98)	1.000	0.03	0.06
HLA-DPB1 alleles						
DPB1*02	16 (29.6%)	105 (30.4%)	0.97 (0.52–1.81)	1.000	–0.02	0.05
DPB1*03	4 (7.4%)	16 (4.6%)	1.65 (0.53–5.14)	1.000	0.12	0.14
DPB1*04	6 (11.1%)	51 (14.7%)	0.72 (0.29–1.78)	1.000	–0.11	0.13
DPB1*05	18 (33.3%)	118 (34.1%)	0.97 (0.53–1.77)	1.000	–0.02	0.05
DPB1*06	1 (1.9%)	0 (0.0%)	–	0.270	0.27	0.52
DPB1*09	3 (5.6%)	11 (3.2%)	1.79 (0.48–6.64)	1.000	0.12	0.14
DPB1*13	2 (3.7%)	20 (5.8%)	0.63 (0.14–2.76)	1.000	–0.10	0.11
DPB1*14	1 (1.9%)	8 (2.3%)	0.80 (0.10–6.50)	1.000	–0.03	0.06
DPB1*17	2 (3.7%)	11 (3.2%)	1.17 (0.25–5.43)	1.000	0.03	0.06
DPB1*38	1 (1.9%)	1 (0.3%)	6.51 (0.40–105.65)	1.000	0.17	0.23

OR Odds ratio, CI Confidence intervals

glutamic acid decarboxylase, to CD4⁺ T cells, thereby contributing to loss of self-tolerance and autoimmune β -cell destruction [36].

Compared to the CIDP subgroup, DRB1*07, DRB1*15, and DQB1*04 were more frequently observed in the AN subgroup; however, these differences were not statistically significant. Recently, a study from Spain that included 13 AN patients with anti-NF155 found a strong association with DRB1*15, which was more frequent in the AN group than in both the general population (77% vs. 17%) and CIDP (77% vs. 14%; Supplementary Table 2) [14]. DRB1*15:01 and DRB1*15:02 showed particularly high ORs. A Japanese study also reported that DRB1*15:01 was more common in anti-NF155 AN than in controls (31.8% vs. 8.0%) and identified it as a susceptibility allele (OR 5.4, 95% CI 2.71–10.59) [23]. In our study, DRB1*15 did not show a significant difference in frequency between the patient group and controls, nor between the CIDP subgroup and controls. Although the frequency of DRB1*15 was relatively higher in the AN subgroup (21.4%) compared to both the CIDP group (10.0%) and the control group (10.1%), this difference did not reach statistical significance. This result may have been influenced by the small sample size.

The mechanisms involved in HLA polymorphisms and autoimmune diseases are not clearly understood. One possible hypothesis is that specific HLA II alleles may promote selective activation of CD4⁺ T cells, influencing T cell differentiation and immune responses [13, 37]. Another possibility is that these alleles easily impair immunologic tolerance, leading to autoimmunity through recognition of self-antigens. For instance, DRB1*15:01 allele which is well-known as a risk factor of multiple sclerosis in individuals with a high Epstein-Barr virus (EBV) nuclear antigen 1-IgG titers [38]. Similar EBV dysregulation has been observed in patients with CIDP [39], suggesting a potential role of HLA polymorphism in it immunopathogenesis.

To elucidate the immunopathogenic role of HLA alleles in CIDP, further studies are warranted to characterize epitope structures and potential target antigens. Although both humoral and cellular immunity implicated, disease-specific antibodies remain largely unidentified in CIDP. Given that HLA polymorphisms may influence T cell-mediated immune responses, including the expansion of T helper 17 cells in the serum and cerebrospinal fluid of patients with CIDP, comprehensive profiling of immune cell subsets and cytokine signatures according to HLA genotypes may provide further insights [40, 41].

This study has several limitations. First, it was a retrospective study conducted at a single tertiary center, which may introduce selection bias. Second, the sample size was relatively small, primarily due to the rarity of CIDP;

the age-adjusted prevalence in South Korea was reported to be approximately 1.16 per 100,000 persons in 2020 [42]. Third, although HLA typing was performed up to the second-field resolution, comparisons with the control group were restricted to the first-field level to improve statistical power [43]. Fourth, due to the retrospective design and limited availability of stored serum samples, we were unable to validate antibody findings using ELISA in addition to the cell-based assay, which may have limited the comprehensive confirmation of autoantibody status. In addition, among the paranodal antibodies, only NF155 antibodies were detected. Although anti-CNTN1 and anti-CASPR1 antibodies were not found, their reported prevalence in CIDP is very low, which may explain their absence in our cohort [1]. Lastly, we used an indirect immunofluorescence method involving an unconjugated anti-human IgG4 antibody followed by a fluorescence-conjugated secondary antibody. While this approach enhances sensitivity through signal amplification, it may also increase the risk of cross-reactivity or non-specific binding.

In conclusion, this study suggests that DRB1*04 allele may be associated with CIDP in the Korean population. While the frequency of specific alleles such as DRB1*04 was consistently higher in both CIDP and AN subgroups compared to controls, differences in HLA allele distribution between CIDP and AN subgroups could not be confirmed, likely due to the small sample size. Larger, multicenter studies with high-resolution genotyping are warranted to validate these findings and further explore potential immunogenetic differences between CIDP and AN.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12883-025-04312-3>.

Supplementary Material 1.

Acknowledgements

We are grateful to researchers who have previously published excellent work on the distribution of HLA alleles in Koreans.

Potential conflicts of interest

All authors report no disclosures relevant to the manuscript.

Authors' contributions

Soonwook Kwon: Formal analysis, Investigation, Data Curation, Writing - Original Draft, Funding acquisition; Jin Myoung Seok: Formal analysis, Investigation, Writing - Review & Editing; Hye Lim Lee: Investigation, Writing - Review & Editing; Yeon Hak Chung: Investigation, Writing - Review & Editing; Hyunjin Ju: Investigation, Writing - Review & Editing; Mi Young Jeon: Writing - Review & Editing, Visualization; Byoung Joon Kim: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision.

Funding

This research was supported by INHA UNIVERSITY HOSPITAL Research Grant (No. 2023-33-019 to Soonwook Kwon).

Data availability

Data is provided within the manuscript and supplementary tables.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved on 13-Oct-2021 by the Institutional Review Board of Samsung Medical Center (No. IRB 2015-04-086-001). Informed consent was obtained from all subjects involved in this study.

Consent for publication

All subjects involved in this study gave written informed consent for their personal or clinical details along with any identifying images.

Competing interests

The authors declare no competing interests.

Author details

¹Department of Neurology, Inha University Hospital, Inha University College of Medicine, Incheon, South Korea

²Department of Neurology, Soonchunhyang University Hospital Cheonan, Soonchunhyang University College of Medicine, Cheonan, Republic of Korea

³Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea

⁴Department of Neurology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, South Korea

⁵Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea

Received: 21 April 2025 / Accepted: 30 June 2025

Published online: 29 July 2025

References

- Bunschoten C, Jacobs BC, Van den Bergh PYK, Cornblath DR, van Doorn PA. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *Lancet Neurol*. 2019;18:784–94.
- Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European academy of neurology/peripheral nerve society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task Force-Second revision. *Eur J Neurol*. 2021;28:3556–83.
- Zhang X, Kira JI, Ogata H et al. Anti-LGI4 antibody is a novel Juxta-axonal autoantibody for chronic inflammatory demyelinating polyneuropathy. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(2):e200081.
- Devaux JJ, Miura Y, Fukami Y, et al. Neurofascin-155 IgG4 in chronic inflammatory demyelinating polyneuropathy. *Neurology*. 2016;86:800–7.
- Gao Y, Kong L, Liu S, Liu K, Zhu J. Impact of neurofascin on chronic inflammatory demyelinating polyneuropathy via changing the node of Ranvier function: A review. *Front Mol Neurosci*. 2021;14:779385.
- Cortese A, Lombardi R, Briani C et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: clinical relevance of IgG isotype. *Neurol Neuroimmunol Neuroinflamm*. 2019;7(1):e639.
- Miura Y, Devaux JJ, Fukami Y, et al. Contactin 1 IgG4 associates to chronic inflammatory demyelinating polyneuropathy with sensory ataxia. *Brain*. 2015;138:1484–91.
- Dimachkie MM, Barohn RJ. Chronic inflammatory demyelinating polyneuropathy. *Curr Treat Options Neurol*. 2013;15:350–66.
- Dalakas MC. Medscape. Advances in the diagnosis, pathogenesis and treatment of CIDP. *Nat Rev Neurol*. 2011;7:507–17.
- Anagnostouli MC, Acquaviva T, Artemiadis AK, et al. HLA-DRB1* alleles genotyping in chronic inflammatory demyelinating polyneuropathy in Greek patients. *J Peripher Nerv Syst*. 2014;19:187–9.
- Ghafari-Fard S, Akbari MT, Houlden H, et al. Distribution of HLA alleles and genotypes in patients with chronic inflammatory demyelinating polyneuropathy. *J Mol Neurosci*. 2022;72:574–84.
- Mrad M, Fekih-Mrissa N, Mansour M, et al. Association of HLA-DR/DQ polymorphism with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in Tunisian patients. *Transfus Apher Sci*. 2013;49:623–6.
- Ogata H, Isobe N, Zhang X, et al. Unique HLA haplotype associations in IgG4 anti-neurofascin 155 antibody-positive chronic inflammatory demyelinating polyneuropathy. *J Neuroimmunol*. 2020;339:577139.
- Martinez-Martinez L, Lleixa MC, Boera-Carnicero G, et al. Anti-NF155 chronic inflammatory demyelinating polyradiculoneuropathy strongly associates to HLA-DRB15. *J Neuroinflammation*. 2017;14:224.
- Van den Bergh PY, Hadden RD, Bouche P, et al. European federation of neurological societies/peripheral nerve society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European federation of neurological societies and the peripheral nerve society - first revision. *Eur J Neurol*. 2010;17:356–63.
- Ruts L, Drenth J, Jacobs BC, van Doorn PA, Dutch GBSSG. Distinguishing acute-onset CIDP from fluctuating Guillain-Barre syndrome: a prospective study. *Neurology*. 2010;74:1680–6.
- Ikeda N, Kojima H, Nishikawa M, et al. Determination of HLA-A, -C, -B, -DRB1 allele and haplotype frequency in Japanese population based on family study. *Tissue Antigens*. 2015;85:252–9.
- Park H, Lee YJ, Song EY, Park MH. HLA-A, HLA-B and HLA-DRB1 allele and haplotype frequencies of 10 918 Koreans from bone marrow donor registry in Korea. *Int J Immunogenet*. 2016;43:287–96.
- Baek IC, Choi EJ, Shin DH, Kim HJ, Choi H, Kim TG. Allele and haplotype frequencies of human leukocyte antigen-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, and -DPB1 by next generation sequencing-based typing in Koreans in South Korea. *PLoS One*. 2021;16:e0253619.
- Shin DH, Baek IC, Kim HJ, et al. HLA alleles, especially amino-acid signatures of HLA-DPB1, might contribute to the molecular pathogenesis of early-onset autoimmune thyroid disease. *PLoS ONE*. 2019;14:e0216941.
- Schaid DJ, Sinnwell JP, Thibodeau SN. Robust multipoint identical-by-descent mapping for affected relative pairs. *Am J Hum Genet*. 2005;76:128–38.
- Burnor E, Yang L, Zhou H, et al. Neurofascin antibodies in autoimmune, genetic, and idiopathic neuropathies. *Neurology*. 2018;90:e31–8.
- Ogata H, Yamasaki R, Hiwatashi A, et al. Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. *Ann Clin Transl Neurol*. 2015;2:960–71.
- Zhang X, Zheng P, Devaux JJ, et al. Chronic inflammatory demyelinating polyneuropathy with anti-NF155 IgG4 in China. *J Neuroimmunol*. 2019;337:577074.
- Broers MC, Bunschoten C, Nieboer D, Lingsma HF, Jacobs BC. Incidence and prevalence of chronic inflammatory demyelinating polyradiculoneuropathy: A systematic review and Meta-Analysis. *Neuroepidemiology*. 2019;52:161–72.
- Lyou HJ, Chung YH, Kim MJ, et al. Clinical features of autoimmune neuropathy with Anti-Neurofascin-155 antibodies in South Koreans. *J Clin Neurol*. 2024;20:186–93.
- Stewart GJ, Pollard JD, McLeod JG, Wolnizer CM. HLA antigens in the Landry-Guillain-Barre syndrome and chronic relapsing polyneuritis. *Ann Neurol*. 1978;4:285–9.
- Vaughan RW, Adam AM, Gray IA, et al. Major histocompatibility complex class I and class II polymorphism in chronic idiopathic demyelinating polyradiculoneuropathy. *J Neuroimmunol*. 1990;27:149–53.
- Adams D, Festenstein H, Gibson JD, et al. HLA antigens in chronic relapsing idiopathic inflammatory polyneuropathy. *J Neurol Neurosurg Psychiatry*. 1979;42:184–6.
- McCombe PA, Csurhes PA, Greer JM. Studies of HLA associations in male and female patients with Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *J Neuroimmunol*. 2006;180:172–7.
- Cotti Piccinelli S, Carella G, Frassi M, et al. Human leukocyte antigens class II in CIDP spectrum neuropathies. *J Neurol Sci*. 2019;407:116533.
- van Doorn PA, Schreuder GM, Vermeulen M, d'Amaro J, Brand A. HLA antigens in patients with chronic inflammatory demyelinating polyneuropathy. *J Neuroimmunol*. 1991;32:133–9.
- Cruz-Tapias P, Perez-Fernandez OM, Rojas-Villarraga A, Rodriguez-Rodriguez A, Arango MT, Anaya JM. Shared HLA class II in six autoimmune diseases in Latin America: A Meta-Analysis. *Autoimmune Dis*. 2012;2012:569728.
- Scully SW, Petersen J, Law SC, et al. A molecular basis for the association of the HLA-DRB1 locus, citrullination, and rheumatoid arthritis. *J Exp Med*. 2013;210:2569–82.

35. Larid G, Pancarte M, Offer G, et al. In rheumatoid arthritis patients, HLA-DRB1*04:01 and rheumatoid nodules are associated with ACPA to a particular fibrin epitope. *Front Immunol.* 2021;12:692041.
36. Yang J, James EA, Sanda S, Greenbaum C, Kwok WW. CD4+T cells recognize diverse epitopes within GAD65: implications for repertoire development and diabetes monitoring. *Immunology.* 2013;138:269–79.
37. Tubo NJ, Jenkins MK. TCR signal quantity and quality in CD4(+) T cell differentiation. *Trends Immunol.* 2014;35:591–6.
38. Sundstrom P, Nystrom L, Jidell E, Hallmans G. EBNA-1 reactivity and HLA DRB1*1501 as statistically independent risk factors for multiple sclerosis: a case-control study. *Mult Scler.* 2008;14:1120–2.
39. Lunemann JD, Tackenberg B, Stein A, et al. Dysregulated Epstein-Barr virus infection in patients with CIDP. *J Neuroimmunol.* 2010;218:107–11.
40. De Almeida DE, Ling S, Pi X, Hartmann-Scruggs AM, Pumpens P, Holoshitz J. Immune dysregulation by the rheumatoid arthritis shared epitope. *J Immunol.* 2010;185:1927–34.
41. Chi LJ, Xu WH, Zhang ZW, Huang HT, Zhang LM, Zhou J. Distribution of Th17 cells and Th1 cells in peripheral blood and cerebrospinal fluid in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst.* 2010;15:345–56.
42. Jung S, Jung G, Kim D, Oh J, Choi K. Epidemiology of chronic inflammatory demyelinating polyneuropathy in South Korea: A Population-Based study. *J Clin Neurol.* 2023;19:558–64.
43. Janeway CA Jr, Walport TP, et al. M, immunobiology: the immune system in health and disease. 5th ed. New York: Garland Science; 2001.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.