Review Article

The Genetics of Multiple Sclerosis and Neuromyelitis Optica in Japan

Satoshi Yoshimura*
Department of Neurology, Kyushu University, Japan

Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease with a substantial genetic component. Since the discovery of anti-aquaporin-4 (AQP4) antibodies, a specific biomarker for neuromyelitis optica (NMO), NMO has been classified as a distinct disease entity with a fundamentally different etiology from MS. Recent genetic studies have clarified the distinct and common genetic profiles of Japanese MS and NMO patients: HLA-DRB1*0405, HLA-DPB1*0301 and the IL-7RA rs6897932 CC genotypes were found to be MS susceptibility genes, whereas HLA-DRB1*0901, HLA-DPB1*0401 and the NOTCH4 rs422951 G alleles were found to be protective against MS. In contrast, HLA-DRB1*1602 and HLA-DPB1*0501 conferred susceptibility only to anti-AQP4 antibody-positive NMO, whereas HLA-DRB1*0901 was a common protective allele, irrespective of the presence or absence of anti-AQP4 antibody. HLA-DRB1*0405-positive MS patients show a younger age at onset, slower progression, fewer brain lesions and are cerebrospinal fluid IgG abnormality-negative. The recent increase in the numbers of MS patients in this subgroup could explain the decrease in age at onset, as shown by the fourth nationwide survey of Japanese MS patients. In contrast, HLA-DRB1*0405-negative Japanese MS patients show similar trends to Caucasians in terms of associations with HLA-DRB1*1501, brain lesions fulfilling Barkhof criteria and cerebrospinal fluid IgG abnormalities. Therefore, idiopathic central nervous system demyelinating disease in Japanese can be subclassified into HLA-DRB1*0405-positive and -negative MS, and anti-AQP4 antibody-positive and -negative NMO, in terms of genetic background and clinical features.

ABBREVIATIONS

MS: Multiple Sclerosis; OSMS: Opticospinal Multiple Sclerosis; NMO: Neuromyelitis Optica; AQP4: Aquaporin-4; NMOSD: Neuromyelitis Optica Spectrum Disorder; MHC: Major Histocompatibility Complex; HLA: Human Leukocyte Antigen; GWAS: Genome-Wide Association Studies; CMS: Conventional Multiple Sclerosis; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; Lescls: Longitudinally Extensive Spinal Cord Lesions; Obs: Oligoclonal Bands; PVL: Periventricular White Matter Lesions; SNP: Single-Nucleotide Polymorphism; PI: Progression Index; IL: Interleukin

INTRODUCTION

Multiple sclerosis (MS) is a clinically heterogeneous condition that is thought to be caused by a complex interplay between multiple genetic and environmental factors. MS is relatively rare in Asians, but when it occurs, selective and severe involvement of the optic nerve and spinal cord is characteristic [1]. This form, termed opticospinal MS (OSMS), accounts for 15–40% of cases in Japan and shows similar features to the relapsing form of neuromyelitis optica (NMO) in Westerners [2]. The nosological position of NMO has long been a matter of debate. However, the discovery of an IgG specific for NMO, initially designated NMO-IgG but now known to be an anti-aquaporin-4 (AQP4) antibody, suggested that NMO is a distinct disease entity with a fundamentally different etiology from MS [3,4]. The classification of NMO was recently expanded and the limited form of NMO is now named NMO spectrum disorder (NMOSD) [5]. Because NMO-IgG/anti-AQP4 antibody was identified in about 30 to 60% of patients with Japanese OSMS [6-9], OSMS in Asians is now postulated to be the same entity as NMO [5].

The first genetic factor related to MS was the major histocompatibility complex (MHC) in 1972 [10]. Until recently, despite many linkage analysis and association studies, only the human leukocyte antigen (HLA) class II region on chromosome 6p21 had been shown to be significantly associated with MS. In Caucasians of northern European descent, the DR15 haplotype (DRB1*1501-DQA1*0102-DQB1*0602) is strongly associated with MS risk [11], while the DR3 (DRB1*0301-DQA1*0501-DQB1*0201) and DR4 (DRB1*0405-DQA1*0501-DQB1 *0301) haplotypes...
confer susceptibility to MS in Sardinians [12]. MS-associated HLA class II genes were also identified in Japanese (discussed in detail below). The next significant step forward occurred in 2007 when new genes associated with MS were identified by genome-wide association studies (GWAS) [13]. GWAS of MS in Caucasians confirmed the HLA-DRB1*1501 allele as having the strongest association with MS risk, and identified close to 110 non-MHC associations, all of which have relatively modest individual effects (OR < 1.4) [14-16].

Four nationwide surveys of MS have been conducted in Japan, in 1972, 1982, 1989 and 2004. Recent epidemiological studies have revealed a four-fold increase in the estimated number of clinically definite MS patients in 2003 compared with 1972. Additionally, a shift in the peak age at disease onset from the early 30s in 1989 to the early 20s in 2003 (anticipation of age at onset) and a successive increase in the number of patients with conventional MS (CMS) showing involvement of multiple sites of the central nervous system (CNS), including the cerebrum and cerebellum, were observed [17]. This significant change may be caused by ill-defined environmental changes such as “Westernization”, while the reasons for the “earlier age at onset” are unknown.

Because Japanese populations are genetically homogeneous and geographically isolated, it is important to investigate changes in disease prevalence and phenotype over time to clarify how genetic or environmental factors affect the manifestation of MS. Here, I review Japanese MS and NMO genetic studies taking the epidemiological changes and characteristic features in Japanese MS cohorts into consideration.

**HLA associations with MS before the discovery of the anti-AQP4 antibody in Japanese**

In early HLA studies in Japanese MS patients, some associations of MS susceptibility with DP4 [18], DRB1*0301 and DR52 [19], and DR2 and DPB1*0602 [20] were found. However, if the appropriate correction (Bonferroni’s correction) is made in these studies, all of the results lose significance. In 1996, Kira et al. [1] first reported that there are two distinct phenotypes of MS in Japanese, conventional MS (CMS), which is indistinguishable from MS in western countries (disseminated lesions in the CNS), and optico-spinal MS (OSMS), which predominantly involves the optic nerve and spinal cord. Compared with CMS, OSMS has the following characteristic features in Asians [2]: (1) higher age at onset, (2) female preponderance, (3) frequent relapses, (4) greater disability due to severe optic nerve and spinal cord damage, (5) fewer brain MRI lesions, (6) longitudinally extensive spinal cord lesions (LESCS) extending over many vertebral segments on spinal cord MRI, (7) marked pleocytosis and neutrophilia in cerebrospinal fluid (CSF), and (8) absence of oligodendroglial bands (OBS) in CSF. Moreover, the association of HLA alleles with MS is also distinct between the two subtypes: HLA-DRB1*1501 is associated with the CMS phenotype [1], as seen in Caucasian patients with MS, while HLA-DPB1*0501 is associated with OSMS in Japanese [21]. The differences in immunogenetic backgrounds as well as clinical features including MRI findings between CMS and OSMS reinforce the notion that CMS and OSMS are distinct subtypes in Japanese MS.

In a combined series of MS patients from the islands of Kyushu and Hokkaido, the southernmost and northernmost islands of Japan, there was also a significant association of DPB1*0501 with OSMS, while DPB1*0301 was associated with CMS [22]. In contrast to these findings, logistic analysis, adjusted for sex and age, of patients with CMS, showed independent associations of the disease with DPB1*0301, DPB1*0501 and DRB1*1501, but the associations with DPB1*0501 and DRB1*1501 were only found in females and not in males. This finding suggests that a gender difference plays an important role in the associations of HLA alleles with MS in Japanese. Additionally, the DPB1*0301 allele was absent in OSMS patients, suggesting that DPB1*0301 may provide protection against the development of OSMS in Japanese.

Based on the above results, Fukazawa and colleagues verified the role of DPB1*0501 and DPB1*0301 in Japanese MS patients on Hokkaido (26 OSMS patients, 167 CMS patients and 156 controls) [23]. All (100%) OSMS patients were negative for DPB1*0301 while 32 (19%) of the 167 CMS patients were positive for the allele. Among DPB1*0301-negative individuals, the frequencies of DPB1*0501 in OSMS (85%) and CMS (82%) were similar, both being higher than the frequencies in controls (66%). Among DPB1*0301-positive individuals, the frequency of DPB1*0501 was low but similar in CMS (12/32; 38%) patients and controls (6/14; 43%). Periventricular white matter lesions (PVW) were noted in 31 of 32 (97%) DPB1*0301-positive CMS patients but in only 22 of 135 (16%) DPB1*0301-negative CMS patients and two of 26 (9%) OSMS patients. These findings indicate that DPB1*0301 plays an important role in the development of MS in general, but not in the development of OSMS. The strong association of DPB1*0501 with OSMS may be because of the over-representation of the DPB1*0301 allele among individuals in the CMS group. In addition, DPB1*0301 might be relevant to the development of periventricular lesions in Japanese patients with MS.

No association was found with HLA class I alleles (HLA-A and B genes) even if MS patients were clinically classified as having CMS or OSMS [24].

**Associations of HLA alleles with MS and NMO after the discovery of the anti-AQP4 antibody in Japanese**

After the discovery of the anti-AQP4 antibody that has high specificity for NMO, at first, we proceeded with genetic analyses when patients with idiopathic demyelinating diseases including MS and NMO were classified according to anti-AQP4 antibody status. We compared the prevalences of HLA-DRB1 and -DPB1 gene polymorphisms in anti-AQP4 antibody-positive and -negative patients (38 AQP4-positive and 32 AQP4-negative OSMS patients, 52 AQP4-negative CMS patients and 125 controls) [25]. The DPB1*0501 allele was shown to be associated only with anti-AQP4 antibody positivity, but not with anti-AQP4 antibody-negative OSMS or CMS in Japanese. This finding suggested that the emergence of the anti-AQP4 antibody is reinforced by the presence of the HLA-DRB1*0501 allele in Japanese.

Epistatic interactions between HLA-DRB1 alleles alter MS risk in Caucasians. We revealed the epistatic interactions of HLA-DRB1 alleles in Japanese MS patients [27]. AQP4-positive patients, B1 AQP4-negative patients and 127 controls] [26].
HLA-DRB1*09 and DRB1*01 were associated with a decreased risk of anti-AQP4 antibody-negative MS, while HLA-DRB1*12 was associated with an increased risk of anti-AQP4 antibody-positive MS. HLA-DRB1*09/15 decreased the risk of anti-AQP4 antibody-negative MS, whereas HLA-DRB1*12/15 increased the risk of anti-AQP4 antibody positive MS. These findings suggest that the ability of HLA-DRB1*09 to reduce the risk of anti-AQP4 antibody-negative MS may arise from an interaction with HLA-DRB1*15. By contrast, HLA-DRB1*12 increases susceptibility to anti-AQP4 antibody-positive MS, possibly via an interaction with HLA-DRB1*15. Epistatic interactions among HLA-DRB1 alleles were distinct depending on the presence or absence of anti-AQP4 antibody. In that study, furthermore, there was a significant association of HLA-DRB1*04 with MS, which only became evident after excluding two sets of patients: those who met the NMO criteria and those who had anti-AQP4 antibody but who did not fulfill the NMO criteria. The HLA-DRB1*04/04, HLA-DRB1*04/14, and HLA-DRB1*04/15 genotypes increased the risk of MS and this effect was especially pronounced in patients carrying HLA-DRB1*04 in both alleles.

Later genetic analyses were conducted in a relatively large cohort through the South Japan MS Genetics Consortium (SJMSGC). The first study was an attempt to identify HLA loci associated with MS in a Japanese population genotyped for 3534 MHC region single-nucleotide polymorphisms (SNPs) in cooperation with the University of California, San Francisco (UCSF) [27]. Using a logistic regression model, two SNPs (MHC Class III SNP rs422953 in the NOTCH4 gene and MHC Class II SNP rs3997849, susceptibility alleles A and G, respectively) were independently associated with MS susceptibility. Two more (MHC Class II SNP rs600895 and MHC Class I SNP rs2269704 in the NRM gene, susceptibility alleles G and G, respectively) were associated with anti-AQP4 antibody-negative MS susceptibility and a single SNP (MHC Class II SNP rs1694112, susceptibility allele G) was significant when contrasting anti-AQP4 antibody-positive and anti-AQP4 antibody-negative patients. No SNPs were significant when contrasting anti-AQP4 antibody-positive patients and controls. Haplotype analysis revealed a large susceptibility association, likely DRB1*04 or a locus included in the DRB1*04 haplotype but excluding DRB1*15:01, with anti-AQP4 antibody-negative MS.

Next, the largest ever genetic study in Japanese MS patients was performed by the SJMSGC (145 MS patients, 116 NMO patients including NMOSD and 367 controls) [28,29]. In this study, NMO was defined as cases fulfilling the 2006 revised criteria for NMO [30]. We regarded patients as having an NMOSD when the patients fulfilled two absolute criteria plus at least one supportive criterion, or one absolute criterion plus more than one supportive criterion from the 2006 NMO criteria [30], primarily because there seems to be considerable overlap between MS and NMO in Asians. We defined MS as fulfilling the McDonald criteria, but not meeting the above-mentioned NMO/NMOSD criteria. Primary progressive MS was excluded. The frequencies of DRB1*0405 and DPB1*0301 were significantly higher, and those of DRB1*0901 and DPB1*0401 were significantly lower in MS patients compared with healthy controls. In contrast, NMO patients showed a significantly lower frequency of DRB1*0901 and significantly higher frequencies of DRB1*1602 and DPB1*0501, which conferred susceptibility to anti-AQP4 antibody-positive NMO, but not to antibody-negative NMO compared with healthy controls. DRB1*0901 was a common protective allele, irrespective of the presence or absence of anti-AQP4 antibody. The proportions and absolute numbers of MS patients increased steadily with advancing year of birth (P < 0.0001 and P = 0.0701, respectively), whereas the reverse trend was seen for NMO [31]. Interestingly, in MS patients, the proportion and absolute number of patients with DRB1*0405 successively increased with advancing year of birth (p = 0.0013, and p = 0.0005, respectively), whereas such a trend was not observed among NMO patients (p > 0.05). These MS patients with the DRB1*0405 allele showed an earlier age of onset, a lower EDSS score, a lower Progression Index (PI) and a lower frequency of brain MRI lesions that met the Barkhof criteria compared with patients without this allele. DRB1*0405-positive MS patients also tended to have lower frequencies of CSF OBs and/or increased IgG indexes compared with DRB1*0405-negative MS patients. Among individuals lacking the DRB1*0405 allele, the frequency of the DRB1*1501 allele was significantly higher, whereas that of the DRB1*0901 allele was significantly lower compared with healthy controls. These results showed that, among patients without the DRB1*0405 allele, DRB1*1501 was also a major susceptibility allele in Japanese MS patients. Additionally, among patients without DRB1*0405, the presence of DRB1*1501 was significantly associated with CSF OBs/increased IgG index.

Non-HLA associations with MS and NMO

The search for MS-associated non-HLA genetic factors started with a hypothesis-based candidate-gene approach. Many candidate-gene studies were performed in Japanese populations [32-38], and some gene polymorphisms were found to be associated with MS such as the vitamin D receptor gene, estrogen receptor gene, osteopontin gene, C-C chemokine receptor 2 genes, and platelet-activating factor receptor gene. In contrast, linkage studies could not identify any MS-associated non-HLA genes, even in an ambitious genome-wide microsatellite screen employing the largest multinational collection of MS families (n = 730) [39]. However, with the arrival of GWAS, the first such study in MS patients identified the non-HLA genes encoding the interleukin-7 receptor a (IL7RA) and IL2RA in 2007 [13]. Simultaneously, the IL7RA gene was confirmed to be associated with the disease in other MS cohorts [40,41]. In the years that followed, a new series of GWAS and meta-analyses were performed in large cohorts, cumulatively identifying close to 110 MS-associated variants by the end of 2013 [14-16].

Among non-HLA genes identified by MS GWAS in Caucasians, we evaluated the IL-7RA SNP rs6897932, located within the alternatively spliced exon 6; this SNP modifies the ratio of membrane-bound-to-soluble IL-7Ra [40,41], and was genotyped by real-time PCR using TaqMan SNP genotyping assays, in Japanese patients with MS and NMO (78 NMO, 187 MS and 158 controls) [42]. The IL-7RA SNP rs6897932 C alleles and CC genotype were also associated with MS/CMS in Japanese, as seen in Caucasian patients with MS. By contrast, this SNP was not associated with NMO/OSMS in Japanese.

We then examined the association of two SNPs, rs2104286,

and rs12722489, in an intron of the IL2RA gene, and one SNP, rs7090512, in an intergenic region near the IL2RA gene in Japanese patients with MS and NMO (75 NMO patients, 115 MS patients and 238 controls) [43]. All three IL2RA SNPs showed no association with the risk of either MS or NMO in our Japanese population. However, IL2RA gene polymorphisms were able to modify disease activity in female MS patients, but had no influence on either susceptibility or disease phenotype in NMO patients.

Based on the results of an MHC-wide SNP study on idiopathic demyelinating disease showing that the G allele of rs422951 in the NOTCH4 gene, which is located on the short arm of chromosome 6 (approximately 0.4 Mb telomeric of HLA-DRB1), is protective against idiopathic demyelinating disease in Japanese population [27], we evaluated the relation of the NOTCH4 SNP rs422951 to Japanese MS and NMO using DNA sequencing (106 NMO patients, 118 MS patients and 152 controls) [44]. The minor G allele of NOTCH4 rs422951 was negatively associated with MS, but not with NMO. After adjusting for the significant HLA-DRB1 alleles (HLA-DRB1*0405 was positively associated with MS while DRB1*0901 was negatively associated) and gender in a logistic regression analysis, rs422951 was still significantly associated with MS, suggesting that the G allele of NOTCH4 rs422951 is an independent resistance allele for MS in Japanese. The G allele was not associated with any clinic parameters.

Genetic studies focusing on CSF IgG abnormalities in Japanese MS patients

Abnormal intrathecal synthesis of IgG, reflected by CSF OBs and an increased IgG index, is much less frequently observed in Japanese MS cohorts compared with Western cohorts. There are some reports focusing on the differences in immunogenetic backgrounds between OB-positive and OB-negative Japanese MS patients.

First, Fukazawa et al. [45] compared the HLA profiles of patients with MS between groups with and without OBs in the CSF in Hokkaido, Japan. The OB positivity rate was 56.1% (32/57) in CMS patients. DR2 is associated with OB-positive MS while DR4 is associated with OB-negative MS. Additionally, the demographic features, clinical course, disability, and MRI findings were similar in OB-positive and OB-negative patient groups.

Later, Kikuchi et al. [46] verified the interaction between immunogenetic backgrounds and OB positivity in an expanded data set from 99 CMS patients in Hokkaido in Japan. A relatively low OB positivity rate (53.3%) and associations of HLA-DR15 with OB-positive MS and of DR4 with OB-negative MS were confirmed. DR15 was not associated with OB-negative MS. Demographic features, disease course, and disability were similar in the OB-negative and OB-positive groups, whereas there was a preponderance of women in the OB-positive group. An independent negative association of DRB1*0405 with OB positivity was found.

Recently, we analyzed the relationship of CSF IgG abnormalities, defined as the presence of CSF OBs and/or increased IgG index (>0.658), with MS, when NMO and NMOSD patients were excluded (94 MS patients and 367 controls) (submitted for publication). CSF IgG abnormalities were found in 59 of 94 (62.8%) MS patients. CSF IgG abnormality-positive MS is associated with DRB1*1501, whereas CSF IgG abnormality-negative MS is associated with DRB1*0405. The only significant difference between CSF IgG abnormality-positive MS patients and CSF IgG abnormality-negative MS patients was the more frequent presence of brain MRI lesions meeting the Barkhof criteria in the former group.

Taken together, these findings reveal that MS is heterogeneous in its association with HLA alleles and based on immunogenetic differences, MS patients in Japanese populations include at least two HLA-related subpopulations with and without CSF IgG abnormalities.

Genetic studies focusing on the neuroimaging characteristics in Japanese MS patients

In Westerners, brain magnetic resonance imaging (MRI) lesions fulfilling the Barkhof criteria [47] (Barkhof brain lesions) are commonly observed in MS, and Barkhof brain lesions are regarded as a hallmark of MS. However, according to the fourth nationwide survey of MS in Japanese people, the most common type of MS was that with neither Barkhof brain lesions nor LESCLs, comprising 44% of patients [48]. In contrast, longitudinally extensive spinal cord lesions (LESCLs) extending over three or more vertebral segments are regarded as characteristic of NMO [30]. However, more than half of Asian OSMS patients do not have LESCLs [48], while LESCLs are present in about one-fourth of patients with CMS [49, 50]. Thus, there remains considerable overlap between CMS and OSMS/NMO in Japanese. Therefore, we checked the existence of HLA associations with subgroups of patients with idiopathic demyelinating disease, including MS and NMO, defined by characteristic MRI findings such as LESCLs and brain lesions fulfilling the Barkhof criteria (121 total MS patients, 27 Barkhof-positive with LESCLs, 33 Barkhof-positive without LESCLs, 29 Barkhof-negative with LESCLs and 32 Barkhof-negative without LESCLs) [51]. The DRB1*0901 allele was negatively associated with the absence of Barkhof brain lesions, whereas the DRB1*1501 allele tended to be associated with the presence of Barkhof brain lesions. The DRB1*0405 allele showed a positive association with MS with neither Barkhof brain lesions nor LESCLs, whereas disability and CSF OBs showed a negative association.

We then searched for common and distinct genes that confer susceptibility to or resistance against MS with or without Barkhof brain lesions in Japanese MS patients, excluding patients with NMO/NMOSD (123 total MS patients, 74 Barkhof brain lesion-positive MS patients, 35 Barkhof brain lesion-negative MS patients and 367 controls), recruited from the SJMSSC [52]. In this study, DRB1*0405, DPB1*0301 and the IL-7RA rs6897932 CC genotype were found to be susceptibility alleles for MS, whereas DRB1*0901, DPB1*0401 and the NOTCH4 rs422951 G allele were found to be resistance alleles for MS. When the patients were classified into two subgroups, DPB1*0301 and the IL-7RA SNP rs6897932 CC genotype were positively associated only with Barkhof brain lesion-positive MS, whereas DRB1*0405 was positively associated only with Barkhof brain lesion-negative MS. DRB1*0901 and DPB1*0401 alleles are negatively associated only with Barkhof brain lesion-positive MS, while the NOTCH4
rs422951 G allele appears to confer resistance to both Barkhof brain lesion-positive and -negative MS in Japanese.

Thus, MS-associated genes contribute differentially to characteristic MRI features in Japanese MS patients.

DISCUSSION

The recent genetic study by the South Japan Multiple Sclerosis Genetics Consortium revealed the genetic profiles of Japanese MS and NMO patients. We found a unique subgroup of MS patients harboring DRB1*0405, a genetic risk factor for MS in Japanese. Additionally, the genetic profiles differed between anti-AQP4 antibody-positive and -negative patients. Therefore, idiopathic CNS demyelinating disease in Japanese could be subclassified according to the presence or absence of HLA*0405 alleles and anti-AQP4 antibody status, as summarized in Figure 1.

HLA-DRB1*0405-positive MS

A recent genetic study determined that the DRB1*0405 allele was a significant risk determinant in Japanese MS patients [29]. DRB1*0405-positive MS patients showed distinct features: a younger age at onset, a lower EDSS scores, a lower progression index, and a lower frequency of MS-like brain lesions compared with DRB1*0405-negative patients. Therefore, DRB1*0405-positive MS patients could be a unique subgroup with having a relatively benign disease course from an earlier age. According to the fourth nationwide survey of MS in Japanese people, the patients with the most common type of MS had neither Barkhof brain lesions nor LESCLs [48]. Hence, it is remarkable that such a subtype of MS with DRB1*0405 as a susceptibility risk is the most common type in Japanese MS patients; while it is present in a relatively minor population of Caucasian MS patients [53]. It is interesting to note that the proportion and absolute numbers of MS patients with DRB1*0405 have increased successively with advancing year of birth and that this group of MS patients has a significantly younger age at disease onset. Therefore, the recent increase in the numbers of patients in this subgroup of MS patients may explain the recently observed decrease in age at onset in Japanese MS patients, and could be partly responsible for the recent increase in MS prevalence in Japan [17]. Additionally, DRB1*0405-positive MS patients demonstrated a tendency to show a lower frequency of CSF IgG abnormalities compared with DRB1*0405-negative MS patients. Meanwhile CSF IgG abnormality-negative MS was associated with DRB1*0405 in Japanese patients. This is consistent with results from other groups showing that DRB1*04 is associated with OB-negative MS in Swedish patients [53] and the Japanese population of Hokkaido [46]. A low prevalence of OBs (54%) was also reported in Japanese MS patients as a unique feature compared with Western MS [2, 54]. The relatively high frequency of Japanese MS patients carrying the DRB1*0405 allele may be partly responsible for the low prevalence of OBs in Japanese MS patients. Therefore, DRB1*0405-positive MS patients represent a unique subgroup of Japanese MS patients in terms of CSF characteristics.

HLA-DRB1*0405-negative MS

DRB1*0405-negative MS patients have features similar to Western-type MS in terms of the association with DRB1*1501, greater brain MRI lesion loads and increased CSF IgG abnormalities. The presence of the DRB1*1501 allele promotes the development of more T2 lesions [55] and abnormal intrathecal IgG synthesis [56] in MS patients. Similar biological mechanisms may occur in Asian patients.

Anti-AQP4 antibody-positive NMO

We demonstrated that the DBP1*0501 allele, a well-known risk allele for OSMS and NMO in Japanese [21,25] and Southern Han Chinese [56], increased susceptibility to only anti-AQP4 antibody-positive NMO, but not to anti-AQP4 antibody-negative NMO. The same was true for the DBP1*1602 allele, which was
also reported to be a risk factor for NMO in Southern Han Chinese [57]. We found that anti-AQP4 antibody-positive NMO patients tended to have higher relapse rates [28]. These observations are partially consistent with the previous finding that the anti-AQP4 antibody is associated with frequent relapses [9]. Therefore, it is conceivable that the pathogenic mechanisms underlying anti-AQP4 antibody-positive NMO may differ from those underlying the anti-AQP4 antibody-negative type, and that development of AQP4 autoimmunity is in part based on genetic background; in Asians this is conferred by DPB1*0501 and DRB1*1602 and in Caucasians it is conferred by other HLA class II genes, such as DRB1*03 [58,59].

**Anti-AQP4 antibody-negative NMO**

To date, we have not observed any significant association of the genetic factors examined with AQP4 antibody-negative NMO, except for DRB1*0901 as a protective factor. Thus, AQP4 antibody-negative NMO may represent a heterogeneous mixture of several disease phenotypes. Further elucidation of the pathogenic factors underlying this type of NMO is warranted.

**Distinct genetic background between MS and NMO in Japanese patients**

As mentioned above, disease-associated HLA class II genes were distinct between NMO and MS patients except for DRB1*0901 as a protective factor. Even among non-HLA genes, the IL-7RA SNP rs6897932 and the NOTCH4 SNP rs422951 were associated with only MS, but not NMO in Japanese. Thus, it is plausible that even non-HLA genes are differentially associated with MS or NMO. However, we could not demonstrate any association of the three SNPs of IL-2RA with the risk of MS or NMO, although we did find that rs2104286 and rs12722489, located in the intron of the IL2RA gene and within the same LD block, influenced the annualized relapse rates in female MS patients. The failure to detect any associations of IL2RA SNPs with MS may be partly explained by the fact that we only evaluated 115 MS patients and 238 healthy controls. However, Akkad et al. [60] also failed to confirm any associations of rs2104286 and rs12722489 with the risk of MS, even though they evaluated 1295 MS patients and 887 controls. However, Akkad et al. [60] also failed to confirm any associations of rs2104286 and rs12722489 with the risk of MS, even though they evaluated 1295 MS patients and 887 controls.

Moreover, the IL-7RA rs6897932 C allele was negatively associated with the risk of either MS or NMO, but not with the risk of either disease in Japanese patients, although we did find that rs2104286 and rs12722489, located in the intron of the IL2RA gene and within the same LD block, influenced the annualized relapse rates in female MS patients. The failure to detect any associations of IL2RA SNPs with MS may be partly explained by the fact that we only evaluated 115 MS patients and 238 healthy controls. However, Akkad et al. [60] also failed to confirm any associations of rs2104286 and rs12722489 with the risk of MS, even though they evaluated 1295 MS patients and 887 controls. However, Akkad et al. [60] also failed to confirm any associations of rs2104286 and rs12722489 with the risk of MS, even though they evaluated 1295 MS patients and 887 controls.

**Common genetic background between MS and NMO in Japanese patients**

We found that DRB1*0901, one of the most prevalent DRB1 alleles in the Japanese population, had a strong protective effect against both MS and NMO, regardless of anti-AQP4 antibody status. A recent meta-analysis in Chinese patients disclosed that the DRB1*0901 allele was protective against MS [62]. The observation that MS and NMO have at least one common protective factor may suggest the existence of a common mechanism by which the two conditions. The DRB1*0901 allele is more frequently observed in Asians than in other ethnic groups (Japanese 30% vs. Caucasians 1%) [63]. Thus, one explanation for the lower MS prevalence in Japan and other Asian countries may be that the frequency of the DRB1*0901 allele is very high in those regions.

**CONCLUSION**

We have reviewed the distinct and common genetic profiles of MS and NMO patients in Japanese. Susceptibility genes appear to vary according to disease phenotype and the presence or absence of anti-aquaporin-4 antibody, while DRB1*0901 is a common protective allele. DRB1*0405-negative Japanese MS patients show similar trends to Caucasians in terms of an association with DRB1*1501, greater brain MRI lesion loads and increased CSF IgG abnormalities. In contrast, DRB1*0405-positive MS seems to be a unique subtype that may be, in part, responsible for the recent increase in the prevalence of multiple sclerosis in young Japanese people.

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