Supplementary Information

***HLA* genotype-clinical phenotype correlations in multiple sclerosis and neuromyelitis optica spectrum disorders based on Japan MS/NMOSD Biobank data**

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Supplementary Table S1. Comparison of the clinical characteristics of MS patients between northern and southern Japan.

	MS		
	Northern (n = 125)	**Southern** (n = 403)	*p*
Female	88/125 (70.4)	280/403 (69.5)	0.912
Age at registration, y	40 [35-48]	41 [34-49]	0.481
Course (RR/SP/PP)	102/23/0 (81.6/18.4/0)	336/47/19 (83.6/11.7/4.7)	**0.001**
Age at onset, y	30 [23-38]	30 [23-39]	0.812
Duration of disease, y	7.5 [4.1-14.2]	9.3 [4.8-15.1]	0.297
Number of relapses	1 [1-2]	2 [1-4]	**<.001**
Annualized relapse rate	0.21 [0.08-0.42]	0.29 [0.14-0.60]	**0.001**
Lesion sites			
Optic nerve (optic neuritis)	45/123 (36.6)	146/396 (36.9)	1
Cerebrum	96/125 (76.8)	249/396 (62.9)	**0.005**
Cerebellum	26/121 (21.5)	83/396 (21.0)	0.899
Brainstem	63/122 (51.6)	191/395 (48.4)	0.536
Spinal cord	93/124 (75.0)	303/396 (76.5)	0.719
Patients with family history of MS or NMOSD	0/125 (0)	9/392 (2.3)	0.122
CSF IgG abnormality	76/102 (74.5)	233/338 (68.9)	0.324
Presence of OCBs	60/94 (63.8)	202/317 (63.7)	1
High IgG index (> 0.658)	52/77 (67.5)	160/297 (53.9)	**0.039**
Anti-AQP4 Ab positivity	1/109 (0.9)	3/345 (0.9)	1
EDSS score	2.0 [1.0-4.5]	2.0 [1.0-3.5]	0.345
PI	0.25 [0.10-0.52]	0.21 [0.06-0.48]	0.117
MSSS	3.18 [0.94-6.25]	2.44 [0.67-5.68]	0.133
FS score[*]			
Visual functions	0 [0-0]	0 [0-1]	0.175
Brainstem functions	0 [0-2]	0 [0-2]	0.074
Pyramidal functions	0 [0-3]	1 [0-3]	0.156
Cerebellar functions	0 [0-2]	0 [0-2]	**0.050**
Sensory functions	0 [0-2]	0 [0-3]	0.144
Bowel and bladder functions	0 [0-2]	0 [0-1]	0.881
Cerebral functions	0 [0-1]	0 [0-1]	0.514

Episodes of			
bilateral optic neuritis	7/123 (5.7)	20/393 (5.1)	0.817
transverse myelitis	3/124 (2.4)	38/389 (9.8)	**0.007**
MRI			
Huge brain lesion > 3cm	2/125 (1.6)	6/397 (1.5)	1
LESCL	1/125 (0.8)	9/398 (2.3)	0.464
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	19/52 (36.5)	82/182 (45.1)	0.341
EDSS ≤ 3 and disease duration ≥ 10y	21/52 (40.4)	106/182 (58.2)	**0.027**
AID/autoantibodies	9/125 (7.2)	68/369 (18.4)	**0.003**
AID	8/125 (6.4)	23/366 (6.3)	1
Sjögren syndrome	0/125 (0)	7/366 (1.9)	0.199
Thyroid diseases (Basedow, Hashimoto)	5/125 (4.0)	10/366 (2.7)	0.547
Autoantibodies	6/123 (4.9)	60/361 (16.6)	**0.001**
ANA	0/123 (0)	26/361 (7.2)	**0.001**
Anti-SS-A / SS-B Ab	0/123 (0)	14/361 (3.9)	**0.026**
Anti-Tg / TPO / TSHR Ab	5/123 (4.1)	21/361 (5.8)	0.643
PSL/IS	16/125 (12.8)	53/401 (13.2)	1
PSL	16/124 (12.9)	41/385 (10.6)	0.513
IS	3/124 (2.4)	21/392 (5.4)	0.225
DMD	115/125 (92.0)	344/403 (85.4)	0.067
IFN-β	90/125 (72.0)	271/403 (67.2)	0.379
fingolimod	55/125 (44.0)	162/400 (40.5)	0.533

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

*In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NA, not applicable; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PP, primary progressive; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S2. Comparison of the clinical characteristics between MS patients with and without *HLA-DRB1*04:05* in northern Japan.

	HLA-DRB1*04:05		
	Positive (n = 51)	**Negative (n = 74)**	***p***
Female	36/51 (70.6)	52/74 (70.3)	1
Age at registration, y	40 [33-50]	40 [35-47]	0.777
Course (RR/SP/PP)	39/12/0 (76.5/23.5/0)	63/11/0 (85.1/14.9/0)	0.246
Age at onset, y	30 [23-38]	30 [23-39]	0.895
Duration of disease, y	8.7 [5.6-15.1]	6.6 [3.8-13.7]	0.176
Number of relapses	1 [1-3]	1 [1-2]	0.462
Annualized relapse rate	0.17 [0.08-0.41]	0.24 [0.07-0.43]	0.564
Lesion sites			
Optic nerve (optic neuritis)	21/50 (42.0)	24/73 (32.9)	0.343
Cerebrum	39/51 (76.5)	57/74 (77.0)	1
Cerebellum	11/49 (22.4)	15/72 (20.8)	0.826
Brainstem	24/49 (49.0)	39/73 (53.4)	0.713
Spinal cord	42/51 (82.4)	51/73 (69.9)	0.142
Patients with family history of MS or NMOSD	0/51 (0)	0/74 (0)	NA
CSF IgG abnormality	25/42 (59.5)	51/60 (85.0)	**0.005**
Presence of OCBs	16/39 (41.0)	44/55 (80.0)	**<.001**
High IgG index (> 0.658)	16/33 (48.5)	36/44 (81.8)	**0.003**
Anti-AQP4 Ab positivity	0/44 (0)	1/65 (1.5)	1
EDSS score	3.0 [1.0-5.0]	2.0 [1.0-4.0]	0.183
PI	0.24 [0.12-0.53]	0.27 [0.08-0.50]	0.910
MSSS	4.83 [1.04-6.82]	2.85 [0.73-5.97]	0.246
FS score[*]			
Visual functions	0 [0-1]	0 [0-0]	0.102
Brainstem functions	0 [0-2]	0 [0-1]	0.296
Pyramidal functions	1 [0-3]	0 [0-3]	**0.029**
Cerebellar functions	0 [0-2]	0 [0-2]	0.519
Sensory functions	0 [0-2]	0 [0-2]	0.614
Bowel and bladder functions	0 [0-2]	0 [0-2]	0.537
Cerebral functions	0 [0-1]	0 [0-0]	0.331

Episodes of			
bilateral optic neuritis	4/50 (8.0)	3/73 (4.1)	0.441
transverse myelitis	0/50 (0)	3/74 (4.1)	0.272
MRI			
Huge brain lesion > 3cm	1/51 (2.0)	1/74 (1.4)	1
LESCL	0/51 (0)	1/74 (1.4)	1
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	8/25 (32.0)	11/27 (40.7)	0.574
EDSS ≤ 3 and disease duration ≥ 10y	9/25 (36.0)	12/27 (44.4)	0.582
AID/autoantibodies	4/51 (7.8)	5/74 (6.8)	1
AID	3/51 (5.9)	5/74 (6.8)	1
Sjögren syndrome	0/51 (0)	0/74 (0)	
Thyroid diseases (Basedow, Hashimoto)	3/51 (5.9)	2/74 (2.7)	0.397
Autoantibodies	4/51 (7.8)	2/72 (2.8)	0.231
ANA	0/51 (0)	0/72 (0)	NA
Anti-SS-A / SS-B Ab	0/51 (0)	0/72 (0)	NA
Anti-Tg / TPO / TSHR Ab	4/51 (7.8)	1/72 (1.4)	0.159
PSL/IS	5/51 (9.8)	11/74 (14.9)	0.587
PSL	5/50 (10.0)	11/74 (14.9)	0.587
IS	0/50 (0)	3/74 (4.1)	0.272
DMD	49/51 (96.1)	66/74 (89.2)	0.198
IFN-β	40/51 (78.4)	50/74 (67.6)	0.226
fingolimod	30/51 (58.8)	25/74 (33.8)	**0.006**

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NA, not applicable; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PP, primary progressive; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S3. Comparison of the clinical characteristics between MS patients with and without *HLA-DRB1*04:05* in southern Japan.

	HLA-DRB1*04:05		
	Positive (n = 163)	**Negative (n = 240)**	*p*
Female	110/163 (67.5)	170/240 (70.8)	0.509
Age at registration, y	41 [32-52]	42 [35-48]	0.740
Course (RR/SP/PP)	135/18/10 (82.8/11.0/6.1)	201/29/9 (84.1/12.1/3.8)	0.537
Age at onset, y	28 [22-38]	32 [25-39]	**0.009**
Duration of disease, y	10.3 [5.8-18]	8.7 [4.4-14.1]	**0.012**
Number of relapses	3 [1-5]	2 [1-4]	0.167
Annualized relapse rate	0.29 [0.13-0.57]	0.29 [0.15-0.64]	0.565
Lesion sites			
Optic nerve (optic neuritis)	68/162 (42.0)	78/234 (33.3)	0.090
Cerebrum	103/161 (64.0)	146/235 (62.1)	0.751
Cerebellum	37/161 (23.0)	46/235 (19.6)	0.452
Brainstem	87/161 (54.0)	104/234 (44.4)	0.066
Spinal cord	121/160 (75.6)	182/236 (77.1)	0.809
Patients with family history of MS or NMOSD	5/160 (3.1)	4/232 (1.7)	0.496
CSF IgG abnormality	78/137 (56.9)	155/201 (77.1)	**<.001**
Presence of OCBs	64/127 (50.4)	138/190 (72.6)	**<.001**
High IgG index (> 0.658)	48/118 (40.7)	112/179 (62.6)	**<.001**
Anti-AQP4 Ab positivity	1/138 (0.7)	2/207 (1.0)	1
EDSS score	2.0 [1.0-4.0]	2.0 [1.0-3.5]	0.823
PI	0.18 [0.05-0.39]	0.24 [0.08-0.49]	0.074
MSSS	2.13 [0.53-5.5]	2.82 [0.82-5.75]	0.137
FS score[*]			
Visual functions	0 [0-2]	0 [0-0]	**0.003**
Brainstem functions	0 [0-2]	0 [0-2]	0.649
Pyramidal functions	1 [0-3]	1 [0-3]	0.380
Cerebellar functions	0 [0-3]	0 [0-2]	0.207
Sensory functions	0 [0-3]	0 [0-3]	0.994
Bowel and bladder functions	0 [0-1]	0 [0-1]	0.938
Cerebral functions	0 [0-1]	0 [0-1]	0.786

Episodes of			
bilateral optic neuritis	11/158 (7)	9/235 (3.8)	0.241
transverse myelitis	16/156 (10.3)	22/233 (9.4)	0.862
MRI			
Huge brain lesion > 3cm	4/161 (2.5)	2/236 (0.8)	0.228
LESCL	3/163 (1.8)	6/235 (2.6)	0.743
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	41/86 (47.7)	41/96 (42.7)	0.552
EDSS ≤ 3 and disease duration ≥ 10y	49/86 (57.0)	57/96 (59.4)	0.765
AID/autoantibodies	31/149 (20.8)	37/220 (16.8)	0.341
AID	9/147 (6.1)	14/219 (6.4)	1
Sjögren syndrome	1/147 (0.7)	6/219 (2.7)	0.250
Thyroid diseases (Basedow, Hashimoto)	3/147 (2)	7/219 (3.2)	0.746
Autoantibodies	27/145 (18.6)	33/216 (15.3)	0.471
ANA	15/145 (10.3)	11/216 (5.1)	0.064
Anti-SS-A / SS-B Ab	4/145 (2.8)	10/216 (4.6)	0.419
Anti-Tg / TPO / TSHR Ab	9/145 (6.2)	12/216 (5.6)	0.821
PSL/IS	23/161 (14.3)	30/240 (12.5)	0.653
PSL	17/155 (11.0)	24/230 (10.4)	0.868
IS	11/159 (6.9)	10/233 (4.3)	0.264
DMD	136/163 (83.4)	208/240 (86.7)	0.391
IFN-β	104/163 (63.8)	167/240 (69.6)	0.236
fingolimod	60/161 (37.3)	102/239 (42.7)	0.300

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PP, primary progressive; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S4. Comparison of the clinical characteristics between MS patients with and without *HLA-DRB1*04:05* in southern Japan excluding PPMS patients.

	HLA-DRB1*04:05		
	Positive (n = 153)	**Negative (n = 231)**	***p***
Female	108/153 (70.6)	165/231 (71.4)	0.909
Age at registration, y	41 [32-52]	41 [35-48]	0.647
Course (RR/SP)	135/18 (88.2/11.8)	201/29 (87.4/12.6)	0.874
Age at onset, y	27 [21-38]	32 [25-39]	**0.002**
Duration of disease, y	10.9 [6.0-18.5]	8.5 [4.1-14.1]	**0.003**
Number of relapses	3 [1-5]	2 [1-4]	0.083
Annualized relapse rate	0.29 [0.16-0.59]	0.30 [0.15-0.65]	0.748
Lesion sites			
Optic nerve (optic neuritis)	67/153 (43.8)	77/227 (33.9)	0.053
Cerebrum	99/152 (65.1)	141/228 (61.8)	0.587
Cerebellum	34/152 (22.4)	43/228 (18.9)	0.436
Brainstem	83/152 (54.6)	100/227 (44.1)	**0.047**
Spinal cord	115/151 (76.2)	176/229 (76.9)	0.902
Patients with family history of MS or NMOSD	5/150 (3.3)	4/223 (1.8)	0.494
CSF IgG abnormality	73/127 (57.5)	147/192 (76.6)	**0.001**
Presence of OCBs	59/118 (50.0)	130/181 (71.8)	**<.001**
High IgG index (> 0.658)	44/108 (40.7)	106/172 (61.6)	**0.001**
Anti-AQP4 Ab positivity	1/129 (0.8)	2/198 (1.0)	1
EDSS score	1.5 [1.0-3.5]	2.0 [1.0-3.0]	0.601
PI	0.16 [0.05-0.34]	0.23 [0.07-0.48]	**0.022**
MSSS	1.98 [0.51-4.46]	2.65 [0.76-5.42]	**0.050**
FS score[*]			
Visual functions	0 [0-2]	0 [0-0]	**0.001**
Brainstem functions	0 [0-2]	0 [0-2]	0.867
Pyramidal functions	1 [0-3]	1 [0-3]	0.181
Cerebellar functions	0 [0-3]	0 [0-2]	0.330
Sensory functions	0 [0-3]	0 [0-3]	0.841
Bowel and bladder functions	0 [0-1]	0 [0-1]	0.809
Cerebral functions	0 [0-1]	0 [0-1]	0.920

Episodes of			
bilateral optic neuritis	10/148 (6.8)	9/228 (3.9)	0.237
transverse myelitis	14/147 (9.5)	22/225 (9.8)	1
MRI			
Huge brain lesion > 3cm	3/151 (2.0)	2/228 (0.9)	0.391
LESCL	3/153 (2.0)	6/226 (2.7)	0.745
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	41/84 (48.8)	41/90 (45.6)	0.761
EDSS ≤ 3 and disease duration ≥ 10y	49/84 (58.3)	57/90 (63.3)	0.536
AID/autoantibodies	30/140 (21.4)	36/212 (17.0)	0.330
AID	9/138 (6.5)	14/211 (6.6)	1
Sjögren syndrome	1/138 (0.7)	6/211 (2.8)	0.252
Thyroid diseases (Basedow, Hashimoto)	3/138 (2.2)	7/211 (3.3)	0.746
Autoantibodies	26/136 (19.1)	32/208 (15.4)	0.380
ANA	14/136 (10.3)	11/208 (5.3)	0.092
Anti-SS-A / SS-B Ab	3/136 (2.2)	9/208 (4.3)	0.377
Anti-Tg / TPO / TSHR Ab	9/136 (6.6)	12/208 (5.8)	0.819
PSL/IS	21/151 (13.9)	29/231 (12.6)	0.757
PSL	16/145 (11)	23/221 (10.4)	0.864
IS	10/149 (6.7)	10/224 (4.5)	0.357
DMD	127/153 (83.0)	201/231 (87.0)	0.303
IFN-β	98/153 (64.1)	162/231 (70.1)	0.222
fingolimod	56/151 (37.1)	99/230 (43.0)	0.286

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PPMS, primary progressive multiple sclerosis; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S5. Comparison of the clinical characteristics of MS patients with *HLA-DRB1*04:05* between northern and southern Japan excluding PPMS patients.

	MS with *HLA-DRB1*04:05*		
	Northern (n = 51)	**Southern (n = 153)**	*p*
Female	36/51 (70.6)	108/153 (70.6)	1
Age at registration, y	40 [33-50]	41 [32-52]	0.937
Course (RR/SP)	39/12 (76.5/23.5)	135/18 (88.2/11.8)	0.065
Age at onset, y	30 [23-38]	27 [21-38]	0.320
Duration of disease, y	8.7 [5.6-15.1]	10.9 [6.0-18.5]	0.254
Number of relapses	1 [1-3]	3 [1-5]	**<.001**
Annualized relapse rate	0.17 [0.08-0.41]	0.29 [0.16-0.59]	**0.006**
Lesion sites			
Optic nerve (optic neuritis)	21/50 (42.0)	67/153 (43.8)	0.871
Cerebrum	39/51 (76.5)	99/152 (65.1)	0.166
Cerebellum	11/49 (22.4)	34/152 (22.4)	1
Brainstem	24/49 (49.0)	83/152 (54.6)	0.514
Spinal cord	42/51 (82.4)	115/151 (76.2)	0.438
Patients with family history of MS or NMOSD	0/51 (0)	5/150 (3.3)	0.332
CSF IgG abnormality	25/42 (59.5)	73/127 (57.5)	0.859
Presence of OCBs	16/39 (41.0)	59/118 (50.0)	0.360
High IgG index (> 0.658)	16/33 (48.5)	44/108 (40.7)	0.547
Anti-AQP4 Ab positivity	0/44 (0)	1/129 (0.8)	1
EDSS score	3.0 [1.0-5.0]	1.5 [1.0-3.5]	0.053
PI	0.24 [0.12-0.53]	0.16 [0.05-0.34]	**0.018**
MSSS	4.83 [1.04-6.82]	1.98 [0.51-4.46]	**0.008**
FS score[*]			
Visual functions	0 [0-1]	0 [0-2]	0.335
Brainstem functions	0 [0-2]	0 [0-2]	0.815
Pyramidal functions	1 [0-3]	1 [0-3]	0.172
Cerebellar functions	0 [0-2]	0 [0-3]	0.382
Sensory functions	0 [0-2]	0 [0-3]	0.316
Bowel and bladder functions	0 [0-2]	0 [0-1]	0.528
Cerebral functions	0 [0-1]	0 [0-1]	0.695

Episodes of			
bilateral optic neuritis	4/50 (8.0)	10/148 (6.8)	0.755
transverse myelitis	0/50 (0)	14/147 (9.5)	**0.023**
MRI			
Huge brain lesion > 3cm	1/51 (2.0)	3/151 (2.0)	1
LESCL	0/51 (0)	3/153 (2.0)	0.575
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	8/25 (32.0)	41/84 (48.8)	0.172
EDSS ≤ 3 and disease duration ≥ 10y	9/25 (36.0)	49/84 (58.3)	0.068
AID/autoantibodies	4/51 (7.8)	30/140 (21.4)	**0.033**
AID	3/51 (5.9)	9/138 (6.5)	1
Sjögren syndrome	0/51 (0)	1/138 (0.7)	1
Thyroid diseases (Basedow, Hashimoto)	3/51 (5.9)	3/138 (2.2)	0.346
Autoantibodies	4/51 (7.8)	26/136 (19.1)	0.074
ANA	0/51 (0)	14/136 (10.3)	**0.012**
Anti-SS-A / SS-B Ab	0/51 (0)	3/136 (2.2)	0.563
Anti-Tg / TPO / TSHR Ab	4/51 (7.8)	9/136 (6.6)	0.753
PSL/IS	5/51 (9.8)	21/151 (13.9)	0.629
PSL	5/50 (10.0)	16/145 (11)	1
IS	0/50 (0)	10/149 (6.7)	0.069
DMD	49/51 (96.1)	127/153 (83.0)	**0.018**
IFN-β	40/51 (78.4)	98/153 (64.1)	0.060
fingolimod	30/51 (58.8)	56/151 (37.1)	**0.009**

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PPMS, primary progressive multiple sclerosis; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S6. Comparison of the clinical characteristics between MS patients with and without *HLA-DPB1*03:01*.

	HLA-DPB1*03:01		
	Positive **(n = 72)**	**Negative** **(n = 456)**	***p***
Female	51/72 (70.8)	317/456 (69.5)	0.891
Age at registration, y	41 [35-48]	41 [34-49]	0.579
Course (RR/SP/PP)	59/10/3 (81.9/13.9/4.2)	379/60/16 (83.3/13.2/3.5)	0.948
Age at onset, y	29 [23-37]	30 [23-39]	0.616
Duration of disease, y	10.3 [4.9-15.4]	9.0 [4.6-15]	0.676
Number of relapses	2 [1-5]	2 [1-4]	0.217
Annualized relapse rate	0.27 [0.12-0.78]	0.26 [0.13-0.53]	0.391
Lesion sites			
Optic nerve (optic neuritis)	27/70 (38.6)	164/449 (36.5)	0.790
Cerebrum	45/70 (64.3)	300/451 (66.5)	0.786
Cerebellum	18/70 (25.7)	91/447 (20.4)	0.344
Brainstem	40/69 (58.0)	214/448 (47.8)	0.122
Spinal cord	52/69 (75.4)	344/451 (76.3)	0.880
Patients with family history of MS or NMOSD	0/71 (0)	9/446 (2)	0.618
CSF IgG abnormality	40/63 (63.5)	269/377 (71.4)	0.234
Presence of OCBs	34/59 (57.6)	228/352 (64.8)	0.308
High IgG index (> 0.658)	27/55 (49.1)	185/319 (58.0)	0.240
Anti-AQP4 Ab positivity	0/61 (0)	4/393 (1)	1
EDSS score	2.0 [1.0-4.5]	2.0 [1.0-4.0]	0.694
PI	0.23 [0.09-0.52]	0.22 [0.07-0.48]	0.659
MSSS	2.44 [0.84-5.71]	2.65 [0.67-5.79]	0.864
FS score[*]			
Visual functions	0 [0-1]	0 [0-1]	0.282
Brainstem functions	0 [0-2]	0 [0-2]	**0.035**
Pyramidal functions	1 [0-3]	1 [0-3]	0.615
Cerebellar functions	0 [0-3]	0 [0-2]	**0.004**
Sensory functions	0 [0-2]	0 [0-3]	0.356
Bowel and bladder functions	0 [0-1]	0 [0-1]	0.597
Cerebral functions	0 [0-2]	0 [0-1]	0.098

Episodes of			
bilateral optic neuritis	5/69 (7.2)	22/447 (4.9)	0.388
transverse myelitis	5/68 (7.4)	36/445 (8.1)	1
MRI			
Huge brain lesion > 3cm	1/72 (1.4)	7/450 (1.6)	1
LESCL	1/71 (1.4)	9/452 (2.0)	1
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	14/37 (37.8)	87/197 (44.2)	0.588
EDSS ≤ 3 and disease duration ≥ 10y	18/37 (48.6)	109/197 (55.3)	0.477
AID/autoantibodies	12/66 (18.2)	65/428 (15.2)	0.584
AID	3/65 (4.6)	28/426 (6.6)	0.784
Sjögren syndrome	0/65 (0)	7/426 (1.6)	0.602
Thyroid diseases (Basedow, Hashimoto)	2/65 (3.1)	13/426 (3.1)	1
Autoantibodies	11/65 (16.9)	55/419 (13.1)	0.437
ANA	6/65 (9.2)	20/419 (4.8)	0.142
Anti-SS-A / SS-B Ab	1/65 (1.5)	13/419 (3.1)	0.705
Anti-Tg / TPO / TSHR Ab	4/65 (6.2)	22/419 (5.3)	0.767
PSL/IS	9/71 (12.7)	60/455 (13.2)	1
PSL	8/70 (11.4)	49/439 (11.2)	1
IS	4/70 (5.7)	20/446 (4.5)	0.552
DMD	63/72 (87.5)	396/456 (86.8)	1
IFN-β	51/72 (70.8)	310/456 (68.0)	0.684
fingolimod	23/71 (32.4)	194/454 (42.7)	0.120

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PP, primary progressive; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S7. Comparison of the clinical characteristics between MS patients with and without *HLA-DRB1*01:01*.

	HLA-DRB1*01:01		
	Positive (n = 29)	**Negative (n = 499)**	*p*
Female	13/29 (44.8)	355/499 (71.1)	**0.006**
Age at registration, y	40 [35-50]	41 [34-49]	0.705
Course (RR/SP/PP)	24/3/2 (82.8/10.3/6.9)	414/67/17 (83.1/13.5/3.4)	0.621
Age at onset, y	35 [23-43]	30 [23-38]	0.257
Duration of disease, y	8.6 [3.7-14.9]	9.1 [4.6-15.1]	0.701
Number of relapses	1 [1-6]	2 [1-4]	0.580
Annualized relapse rate	0.33 [0.06-0.56]	0.26 [0.13-0.55]	0.627
Lesion sites			
Optic nerve (optic neuritis)	8/28 (28.6)	183/491 (37.3)	0.424
Cerebrum	17/28 (60.7)	328/493 (66.5)	0.542
Cerebellum	5/28 (17.9)	104/489 (21.3)	0.814
Brainstem	15/28 (53.6)	239/489 (48.9)	0.700
Spinal cord	16/28 (57.1)	380/492 (77.2)	**0.022**
Patients with family history of MS or NMOSD	0/29 (0)	9/488 (1.8)	1
CSF IgG abnormality	13/23 (56.5)	296/417 (71.0)	0.161
Presence of OCBs	13/22 (59.1)	249/389 (64.0)	0.653
High IgG index (> 0.658)	8/19 (42.1)	204/355 (57.5)	0.236
Anti-AQP4 Ab positivity	0/24 (0)	4/430 (0.9)	1
EDSS score	2.0 [1.0-3.5]	2.0 [1.0-4.0]	0.642
PI	0.21 [0.08-0.39]	0.22 [0.07-0.49]	0.718
MSSS	2.70 [0.70-3.67]	2.65 [0.67-5.87]	0.561
FS score[*]			
Visual functions	0 [0-0]	0 [0-1]	0.423
Brainstem functions	0 [0-1]	0 [0-2]	0.153
Pyramidal functions	1 [0-3]	1 [0-3]	0.431
Cerebellar functions	0 [0-2]	0 [0-2]	0.601
Sensory functions	0 [0-2]	0 [0-2]	**0.048**
Bowel and bladder functions	0 [0-2]	0 [0-1]	0.415
Cerebral functions	0 [0-0]	0 [0-1]	0.174

Episodes of			
bilateral optic neuritis	3/28 (10.7)	24/488 (4.9)	0.175
transverse myelitis	0/29 (0)	41/484 (8.5)	0.155
MRI			
Huge brain lesion > 3cm	0/29 (0)	8/493 (1.6)	1
LESCL	0/29 (0)	10/494 (2.0)	1
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	3/11 (27.3)	98/223 (43.9)	0.358
EDSS ≤ 3 and disease duration ≥ 10y	5/11 (45.5)	122/223 (54.7)	0.555
AID/autoantibodies	6/26 (23.1)	71/468 (15.2)	0.270
AID	4/26 (15.4)	27/465 (5.8)	0.073
Sjögren syndrome	0/26 (0)	7/465 (1.5)	1
Thyroid diseases (Basedow, Hashimoto)	1/26 (3.8)	14/465 (3.0)	0.563
Autoantibodies	3/25 (12.0)	63/459 (13.7)	1
ANA	1/25 (4.0)	25/459 (5.4)	1
Anti-SS-A / SS-B Ab	0/25 (0)	14/459 (3.1)	1
Anti-Tg / TPO / TSHR Ab	1/25 (4.0)	25/459 (5.4)	1
PSL/IS	4/29 (13.8)	65/497 (13.1)	0.783
PSL	2/28 (7.1)	55/481 (11.4)	0.757
IS	3/28 (10.7)	21/488 (4.3)	0.135
DMD	22/29 (75.9)	437/499 (87.6)	0.085
IFN-β	17/29 (58.6)	344/499 (68.9)	0.304
fingolimod	11/28 (39.3)	206/497 (41.4)	1

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PP, primary progressive; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S8. Comparison of the clinical characteristics between MS patients with and without *HLA-DRB1*09:01*.

	HLA-DRB1*09:01		
	Positive (n = 76)	**Negative (n = 452)**	*p*
Female	56/76 (73.7)	312/452 (69.0)	0.500
Age at registration, y	43 [33-50]	41 [34-49]	0.664
Course (RR/SP/PP)	67/5/3 (89.3/6.7/4.0)	371/65/16 (82.1/14.4/3.5)	0.145
Age at onset, y	31 [23-39]	30 [23-38]	0.437
Duration of disease, y	9.0 [4.4-15.0]	9.1 [4.7-15.1]	0.983
Number of relapses	2 [1-3]	2 [1-4]	0.062
Annualized relapse rate	0.23 [0.11-0.43]	0.28 [0.14-0.58]	**0.047**
Lesion sites			
Optic nerve (optic neuritis)	26/74 (35.1)	165/445 (37.1)	0.796
Cerebrum	43/74 (58.1)	302/447 (67.6)	0.114
Cerebellum	11/73 (15.1)	98/444 (22.1)	0.216
Brainstem	24/72 (33.3)	230/445 (51.7)	**0.005**
Spinal cord	52/74 (70.3)	344/446 (77.1)	0.238
Patients with family history of MS or NMOSD	1/74 (1.4)	8/443 (1.8)	1
CSF IgG abnormality	43/63 (68.3)	266/377 (70.6)	0.766
Presence of OCBs	34/55 (61.8)	228/356 (64)	0.765
High IgG index (> 0.658)	32/51 (62.7)	180/323 (55.7)	0.366
Anti-AQP4 Ab positivity	0/65 (0)	4/389 (1.0)	1
EDSS score	1.8 [1.0-3.0]	2.0 [1.0-4.0]	0.434
PI	0.21 [0.07-0.49]	0.22 [0.07-0.49]	0.913
MSSS	2.19 [0.66-5.38]	2.72 [0.67-5.87]	0.412
FS score[*]			
Visual functions	0 [0-0]	0 [0-1]	0.414
Brainstem functions	0 [0-1]	0 [0-2]	0.273
Pyramidal functions	1 [0-3]	1 [0-3]	0.062
Cerebellar functions	0 [0-2]	0 [0-2]	0.131
Sensory functions	1 [0-2]	0 [0-3]	0.355
Bowel and bladder functions	0 [0-1]	0 [0-2]	**0.015**
Cerebral functions	0 [0-0]	0 [0-1]	0.242

Episodes of			
bilateral optic neuritis	3/74 (4.1)	24/442 (5.4)	0.783
transverse myelitis	6/73 (8.2)	35/440 (8.0)	1
MRI			
Huge brain lesion > 3cm	3/76 (3.9)	5/446 (1.1)	0.096
LESCL	2/75 (2.7)	8/448 (1.8)	0.642
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	16/34 (47.1)	85/200 (42.5)	0.709
EDSS ≤ 3 and disease duration ≥ 10y	23/34 (67.6)	104/200 (52.0)	0.098
AID/autoantibodies	8/69 (11.6)	69/425 (16.2)	0.375
AID	3/68 (4.4)	28/423 (6.6)	0.602
Sjögren syndrome	1/68 (1.5)	6/423 (1.4)	1
Thyroid diseases (Basedow, Hashimoto)	2/68 (2.9)	13/423 (3.1)	1
Autoantibodies	7/69 (10.1)	59/415 (14.2)	0.450
ANA	3/69 (4.3)	23/415 (5.5)	1
Anti-SS-A / SS-B Ab	1/69 (1.4)	13/415 (3.1)	0.704
Anti-Tg / TPO / TSHR Ab	2/69 (2.9)	24/415 (5.8)	0.561
PSL/IS	6/75 (8.0)	63/451 (14.0)	0.196
PSL	5/73 (6.8)	52/436 (11.9)	0.235
IS	3/75 (4.0)	21/441 (4.8)	1
DMD	64/76 (84.2)	395/452 (87.4)	0.462
IFN-β	46/76 (60.5)	315/452 (69.7)	0.142
fingolimod	31/76 (40.8)	186/449 (41.4)	1

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PP, primary progressive; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S9. Comparison of the clinical characteristics between MS patients with and without *HLA-DRB1*13:02*.

	HLA-DRB1*13:02		
	Positive (n = 15)	**Negative (n = 513)**	**p**
Female	13/15 (86.7)	355/513 (69.2)	0.252
Age at registration, y	49 [38-54]	41 [34-49]	0.041
Course (RR/SP/PP)	425/68/19 (83.0/13.3/3.7)	13/2/0 (86.7/13.3/0)	0.571
Age at onset, y	33 [28-42]	30 [23-38]	0.153
Duration of disease, y	9.6 [6.4-15.7]	9.1 [4.6-15.1]	0.401
Number of relapses	2 [1-3]	2 [1-4]	0.791
Annualized relapse rate	0.19 [0.09-0.42]	0.27 [0.13-0.56]	0.138
Lesion sites			
Optic nerve (optic neuritis)	5/15 (33.3)	186/504 (36.9)	1
Cerebrum	9/14 (64.3)	336/507 (66.3)	1
Cerebellum	2/14 (14.3)	107/503 (21.3)	0.744
Brainstem	3/14 (21.4)	251/503 (49.9)	0.055
Spinal cord	8/15 (53.3)	388/505 (76.8)	0.058
Patients with family history of MS or NMOSD	0/13 (0)	9/504 (1.8)	1
CSF IgG abnormality	4/11 (36.4)	305/429 (71.1)	**0.019**
Presence of OCBs	2/11 (18.2)	260/400 (65.0)	**0.002**
High IgG index (> 0.658)	3/8 (37.5)	209/366 (57.1)	0.300
Anti-AQP4 Ab positivity	0/12 (0)	4/442 (0.9)	1
EDSS score	1.5 [0.0-3.5]	2.0 [1.0-4.0]	0.440
PI	0.16 [0.00-0.44]	0.22 [0.07-0.49]	0.196
MSSS	1.45 [0.24-5.75]	2.70 [0.67-5.79]	0.182
FS score[*]			
Visual functions	0 [0-1]	0 [0-1]	0.550
Brainstem functions	0 [0-1]	0 [0-2]	0.137
Pyramidal functions	0 [0-4]	1 [0-3]	0.592
Cerebellar functions	0 [0-2]	0 [0-2]	0.651
Sensory functions	0 [0-2]	0 [0-3]	0.863
Bowel and bladder functions	0 [0-1]	0 [0-1]	0.329
Cerebral functions	0 [0-0]	0 [0-1]	0.163

Episodes of			
bilateral optic neuritis	0/15 (0)	27/501 (5.4)	1
transverse myelitis	0/14 (0)	41/499 (8.2)	0.616
MRI			
Huge brain lesion > 3cm	1/15 (6.7)	7/507 (1.4)	0.209
LESCL	0/15 (0)	10/508 (2.0)	1
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	3/7 (42.9)	98/227 (43.2)	1
EDSS ≤ 3 and disease duration ≥ 10y	5/7 (71.4)	122/227 (53.7)	0.458
AID/autoantibodies	4/14 (28.6)	73/480 (15.2)	0.250
AID	3/14 (21.4)	28/477 (5.9)	0.052
Sjögren syndrome	0/14 (0)	7/477 (1.5)	1
Thyroid diseases (Basedow, Hashimoto)	1/14 (7.1)	14/477 (2.9)	0.356
Autoantibodies	1/12 (8.3)	65/472 (13.8)	1
ANA	0/12 (0)	26/472 (5.5)	1
Anti-SS-A / SS-B Ab	1/12 (8.3)	13/472 (2.8)	0.300
Anti-Tg / TPO / TSHR Ab	0/12 (0)	26/472 (5.5)	1
PSL/IS	0/15 (0)	69/511 (13.5)	0.238
PSL	0/12 (0)	57/497 (11.5)	0.378
IS	0/15 (0)	24/501 (4.8)	1
DMD	13/15 (86.7)	446/513 (86.9)	1
IFN-β	9/15 (60.0)	352/513 (68.6)	0.574
fingolimod	5/15 (33.3)	212/510 (41.6)	0.603

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PP, primary progressive; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S10. Comparison of the clinical characteristics between MS patients with and without *HLA-DPB1*04:01*.

	HLA-DPB1*04:01		
	Positive (n = 18)	**Negative (n = 510)**	*p*
Female	15/18 (83.3)	353/510 (69.2)	0.297
Age at registration, y	42 [32-51]	41 [35-49]	0.907
Course (RR/SP/PP)	17/1/0 (94.4/5.6/0)	421/69/19 (82.7/13.6/3.7)	0.264
Age at onset, y	26 [24-39]	30 [23-38]	0.611
Duration of disease, y	8.0 [6.0-16.5]	9.1 [4.6-15.1]	0.778
Number of relapses	3 [1-4]	2 [1-4]	0.461
Annualized relapse rate	0.23 [0.15-0.5]	0.27 [0.13-0.55]	0.817
Lesion sites			
Optic nerve (optic neuritis)	5/18 (27.8)	186/501 (37.1)	0.468
Cerebrum	10/18 (55.6)	335/503 (66.6)	0.323
Cerebellum	4/18 (22.2)	105/499 (21.0)	1
Brainstem	6/18 (33.3)	248/499 (49.7)	0.231
Spinal cord	14/18 (77.8)	382/502 (76.1)	1
Patients with family history of MS or NMOSD	0/17 (0)	9/500 (1.8)	1
CSF IgG abnormality	7/15 (46.7)	302/425 (71.1)	0.079
Presence of OCBs	4/15 (26.7)	258/396 (65.2)	**0.004**
High IgG index (> 0.658)	4/13 (30.8)	208/361 (57.6)	0.084
Anti-AQP4 Ab positivity	0/16 (0)	4/438 (0.9)	1
EDSS score	2.0 [1.0-3.8]	2.0 [1.0-4.0]	0.953
PI	0.23 [0.03-0.50]	0.22 [0.07-0.49]	0.809
MSSS	2.63 [0.25-6.64]	2.65 [0.67-5.75]	0.956
FS score[*]			
Visual functions	0 [0-0]	0 [0-1]	0.444
Brainstem functions	0 [0-2]	0 [0-2]	0.548
Pyramidal functions	1 [0-4]	1 [0-3]	0.691
Cerebellar functions	0 [0-2]	0 [0-2]	0.776
Sensory functions	0 [0-3]	0 [0-2]	0.943
Bowel and bladder functions	0 [0-0]	0 [0-1]	0.072
Cerebral functions	0 [0-0]	0 [0-1]	0.125

Episodes of			
bilateral optic neuritis	0/17 (0)	27/499 (5.4)	1
transverse myelitis	0/18 (0)	41/495 (8.3)	0.384
MRI			
Huge brain lesion > 3cm	1/18 (5.6)	7/504 (1.4)	0.246
LESCL	2/18 (11.1)	8/505 (1.6)	**0.043**
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	3/7 (42.9)	98/227 (43.2)	1
EDSS ≤ 3 and disease duration ≥ 10y	4/7 (57.1)	123/227 (54.2)	1
AID/autoantibodies	1/18 (5.6)	76/476 (16.0)	0.332
AID	0/18 (0)	31/473 (6.6)	0.619
Sjögren syndrome	0/18 (0)	7/473 (1.5)	1
Thyroid diseases (Basedow, Hashimoto)	0/18 (0)	15/473 (3.2)	1
Autoantibodies	1/18 (5.6)	65/466 (13.9)	0.490
ANA	1/18 (5.6)	25/466 (5.4)	1
Anti-SS-A / SS-B Ab	0/18 (0)	14/466 (3.0)	1
Anti-Tg / TPO / TSHR Ab	0/18 (0)	26/466 (5.6)	0.614
PSL/IS	2/18 (11.1)	67/508 (13.2)	1
PSL	2/15 (13.3)	55/494 (11.1)	0.680
IS	1/18 (5.6)	23/498 (4.6)	0.582
DMD	16/18 (88.9)	443/510 (86.9)	1
IFN-β	11/18 (61.1)	350/510 (68.6)	0.607
fingolimod	6/18 (33.3)	211/507 (41.6)	0.628

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS, multiple sclerosis; MSSS, multiple sclerosis severity score; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PP, primary progressive; PSL, prednisolone; RR, relapsing-remitting; SP, secondary progressive; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S11. Comparison of the clinical characteristics between NMOSD patients with and without *HLA-DRB1*08:02*.

	HLA-DRB1*08:02		
	Positive **(n = 30)**	**Negative** **(n = 135)**	***p***
Female	24/30 (80.0)	119/135 (88.1)	0.242
Age at registration, y	56 [46-62]	52 [42-63]	0.914
Age at onset, y	48 [39-53]	44 [33-54]	0.410
Duration of disease, y	7.2 [4.3-10.3]	6.9 [3.2-13.7]	0.881
Number of relapses	2 [1-4]	2 [1-5]	0.474
Annualized relapse rate	0.32 [0.21-0.56]	0.43 [0.21-0.8]	0.502
Lesion sites			
Optic nerve (optic neuritis)	15/30 (50.0)	83/134 (61.9)	0.303
Cerebrum	6/30 (20.0)	33/133 (24.8)	0.644
Cerebellum	2/30 (6.7)	12/133 (9.0)	1
Brainstem	8/30 (26.7)	55/133 (41.4)	0.152
Spinal cord	25/30 (83.3)	113/134 (84.3)	1
Patients with family history of MS or NMOSD	1/30 (3.3)	4/131 (3.1)	1
CSF IgG abnormality	6/26 (23.1)	49/111 (44.1)	0.074
Presence of OCBs	0/23 (0)	20/95 (21.1)	**0.012**
High IgG index (> 0.658)	6/23 (26.1)	40/99 (40.4)	0.239
Anti-AQP4 Ab positivity	30/30 (100)	125/133 (94.0)	0.353
EDSS score	3.5 [2.0-6.0]	3.5 [2.0-5.5]	0.965
PI	0.43 [0.29-0.86]	0.42 [0.23-0.94]	0.657
FS score[*]			
Visual functions	0 [0-4]	0 [0-5]	0.123
Brainstem functions	0 [0-1]	0 [0-1]	0.342
Pyramidal functions	2 [0-3]	2 [0-4]	0.307
Cerebellar functions	0 [0-0]	0 [0-1]	0.402
Sensory functions	2 [0-4]	1 [0-4]	0.190
Bowel and bladder functions	0 [0-4]	0 [0-2]	0.990
Cerebral functions	0 [0-0]	0 [0-0]	0.481
Episodes of			
bilateral optic neuritis	4/29 (13.8)	25/131 (19.1)	0.603
transverse myelitis	15/29 (51.7)	49/134 (36.6)	0.146

MRI			
Huge brain lesion > 3cm	2/30 (6.7)	5/135 (3.7)	0.612
LESCL	21/29 (72.4)	72/133 (54.1)	0.097
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	1/7 (14.3)	8/43 (18.6)	1
EDSS ≤ 3 and disease duration ≥ 10y	3/7 (42.9)	10/43 (23.3)	0.357
AID/autoantibodies	17/28 (60.7)	47/127 (37.0)	**0.033**
AID	7/28 (25.0)	16/123 (13.0)	0.143
Sjögren syndrome	4/28 (14.3)	12/123 (9.8)	0.500
Thyroid diseases (Basedow, Hashimoto)	2/28 (7.1)	1/123 (0.8)	0.089
Autoantibodies	16/27 (59.3)	44/121 (36.4)	**0.032**
ANA	9/27 (33.3)	20/121 (16.5)	0.061
Anti-SS-A / SS-B Ab	10/27 (37.0)	21/121 (17.4)	**0.035**
Anti-Tg / TPO / TSHR Ab	3/27 (11.1)	11/121 (9.1)	0.721
PSL/IS	28/30 (93.3)	134/135 (99.3)	0.085
PSL	28/29 (96.6)	129/134 (96.3)	1
IS	17/30 (56.7)	94/134 (70.1)	0.195
DMD	3/30 (10.0)	24/135 (17.8)	0.416
IFN-β	3/30 (10.0)	24/135 (17.8)	0.416
fingolimod	1/30 (3.3)	0/134 (0)	0.183

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS = multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PSL, prednisolone; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S12. Comparison of the clinical characteristics between NMOSD patients with and without *HLA-DPB1*05:01*.

	HLA-DPB1*05:01		
	Positive (n = 135)	Negative (n = 30)	p
Female	118/135 (87.4)	25/30 (83.3)	0.557
Age at registration, y	53 [44-63]	50 [36-65]	0.621
Age at onset, y	45 [34-53]	45 [32-59]	0.642
Duration of disease, y	7.9 [4.1-13.1]	4.3 [1.5-8.6]	**0.016**
Number of relapses	3 [1-6]	1 [0-2]	**0.001**
Annualized relapse rate	0.43 [0.23-0.75]	0.24 [0-0.77]	0.155
Lesion sites			
Optic nerve (optic neuritis)	80/135 (59.3)	18/29 (62.1)	0.837
Cerebrum	36/134 (26.9)	3/29 (10.3)	0.090
Cerebellum	14/134 (10.4)	0/29 (0)	0.077
Brainstem	53/134 (39.6)	10/29 (34.5)	0.678
Spinal cord	115/135 (85.2)	23/29 (79.3)	0.412
Patients with family history of MS or NMOSD	5/132 (3.8)	0/29 (0)	0.586
CSF IgG abnormality	47/112 (42)	8/25 (32)	0.499
Presence of OCBs	19/99 (19.2)	1/19 (5.3)	0.191
High IgG index (> 0.658)	38/98 (38.8)	8/24 (33.3)	0.815
Anti-AQP4 Ab positivity	128/134 (95.5)	27/29 (93.1)	0.633
EDSS score	3.5 [2.0-5.0]	3.5 [1.5-6.0]	0.894
PI	0.40 [0.23-0.79]	0.83 [0.27-1.85]	**0.034**
FS score[*]			
Visual functions	0 [0-5]	0 [0-6]	0.896
Brainstem functions	0 [0-1]	0 [0-2]	0.860
Pyramidal functions	2 [0-3]	0 [0-4]	0.130
Cerebellar functions	0 [0-1]	0 [0-0]	0.454
Sensory functions	2 [0-4]	1 [0-4]	0.751
Bowel and bladder functions	0 [0-2]	0 [0-3]	0.544
Cerebral functions	0 [0-0]	0 [0-0]	0.915
Episodes of			
bilateral optic neuritis	23/131 (17.6)	6/29 (20.7)	0.790
transverse myelitis	56/133 (42.1)	8/30 (26.7)	0.149

MRI			
Huge brain lesion > 3cm	6/135 (4.4)	1/30 (3.3)	1
LESCL	79/132 (59.8)	14/30 (46.7)	0.222
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	8/44 (18.2)	1/6 (16.7)	1
EDSS ≤ 3 and disease duration ≥ 10y	11/44 (25)	2/6 (33.3)	0.643
AID/autoantibodies	55/127 (43.3)	9/28 (32.1)	0.299
AID	23/123 (18.7)	0/28 (0)	**0.008**
Sjögren syndrome	16/123 (13.0)	0/28 (0)	**0.044**
Thyroid diseases (Basedow, Hashimoto)	3/123 (2.4)	0/28 (0)	1
Autoantibodies	51/121 (42.1)	9/27 (33.3)	0.517
ANA	24/121 (19.8)	5/27 (18.5)	1
Anti-SS-A / SS-B Ab	30/121 (24.8)	1/27 (3.7)	**0.016**
Anti-Tg / TPO / TSHR Ab	11/121 (9.1)	3/27 (11.1)	0.721
PSL/IS	133/135 (98.5)	29/30 (96.7)	0.455
PSL	128/133 (96.2)	29/30 (96.7)	1
IS	90/134 (67.2)	21/30 (70)	0.832
DMD	25/135 (18.5)	2/30 (6.7)	0.171
IFN-β	25/135 (18.5)	2/30 (6.7)	0.171
fingolimod	1/134 (0.7)	0/30 (0)	1

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

[*]In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS = multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PSL, prednisolone; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S13. Comparison of the clinical characteristics between NMOSD patients with and without *HLA-DRB1*09:01*.

	HLA-DRB1*09:01		
	Positive (n = 15)	**Negative (n = 150)**	*p*
Female	14/15 (93.3)	129/150 (86.0)	0.695
Age at registration, y	59 [49-65]	52 [43-62]	0.249
Age at onset, y	45 [31-56]	45 [33-53]	0.721
Duration of disease, y	7.3 [2.4-20.7]	7.0 [3.6-12.2]	0.723
Number of relapses	2 [1-13]	2 [1-5]	0.567
Annualized relapse rate	0.42 [0.14-1.18]	0.41 [0.21-0.74]	0.765
Lesion sites			
Optic nerve (optic neuritis)	9/15 (60.0)	89/149 (59.7)	1
Cerebrum	4/15 (26.7)	35/148 (23.6)	0.757
Cerebellum	0/15 (0)	14/148 (9.5)	0.367
Brainstem	8/15 (53.3)	55/148 (37.2)	0.269
Spinal cord	11/15 (73.3)	127/149 (85.2)	0.262
Patients with family history of MS or NMOSD	0/15 (0)	5/146 (3.4)	1
CSF IgG abnormality	7/13 (53.8)	48/124 (38.7)	0.375
Presence of OCBs	4/10 (40.0)	16/108 (14.8)	0.065
High IgG index (> 0.658)	5/9 (55.6)	41/113 (36.3)	0.295
Anti-AQP4 Ab positivity	13/14 (92.9)	142/149 (95.3)	0.521
EDSS score	3.5 [1.5-7.0]	3.5 [2.0-5.5]	0.914
PI	0.42 [0.24-0.55]	0.42 [0.23-0.95]	0.553
FS score[*]			
Visual functions	0 [0-5]	0 [0-5]	0.943
Brainstem functions	0 [0-1]	0 [0-1]	0.275
Pyramidal functions	1 [0-5]	2 [0-3]	0.917
Cerebellar functions	0 [0-1]	0 [0-1]	0.603
Sensory functions	2 [0-4]	1 [0-3]	0.323
Bowel and bladder functions	0 [0-4]	0 [0-2]	0.374
Cerebral functions	0 [0-2]	0 [0-0]	0.875
Episodes of			
bilateral optic neuritis	2/15 (13.3)	27/145 (18.6)	1
transverse myelitis	4/15 (26.7)	60/148 (40.5)	0.408

MRI			
Huge brain lesion > 3cm	2/15 (13.3)	5/150 (3.3)	0.124
LESCL	10/15 (66.7)	83/147 (56.5)	0.586
Benign course			
EDSS ≤ 2 and disease duration ≥ 10y	1/5 (20.0)	8/45 (17.8)	1
EDSS ≤ 3 and disease duration ≥ 10y	1/5 (20.0)	12/45 (26.7)	1
AID/autoantibodies	5/13 (38.5)	59/142 (41.5)	1
AID	5/13 (38.5)	18/138 (13.0)	**0.030**
Sjögren syndrome	4/13 (30.8)	12/138 (8.7)	**0.034**
Thyroid diseases (Basedow, Hashimoto)	0/13 (0)	3/138 (2.2)	1
Autoantibodies	3/12 (25.0)	57/136 (41.9)	0.361
ANA	2/12 (16.7)	27/136 (19.9)	1
Anti-SS-A / SS-B Ab	3/12 (25.0)	28/136 (20.6)	0.716
Anti-Tg / TPO / TSHR Ab	0/12 (0)	14/136 (10.3)	0.605
PSL/IS	15/15 (100)	147/150 (98.0)	1
PSL	15/15 (100)	142/148 (95.9)	1
IS	11/14 (78.6)	100/150 (66.7)	0.552
DMD	4/15 (26.7)	23/150 (15.3)	0.274
IFN-β	4/15 (26.7)	23/150 (15.3)	0.274
fingolimod	0/15 (0)	1/149 (0.7)	1

Values are median [interquartile ranges] or count (%). Bold values indicate significant differences.

*In the section of functional system scores, values are median [10-90th percentile].

Ab, antibody; AID, autoimmune disease; ANA, anti-nuclear antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FS, functional system; IFN, interferon; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; MS = multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; PI, progression index; PSL, prednisolone; Tg, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyroid stimulating hormone receptor; y, years.

Supplementary Table S14. Clinical and genetic factors associated with EDSS scores in NMOSD.

EDSS score (ordinal scale)	Univariable		Multivariable	
	Std β	*p*	Std β	*p*
Sex [female/male]	0.063	0.418	0.006	0.944
Age at onset (y)	0.074	0.346	0.255	**0.004**
Disease Duration (y)	0.342	**<.001**	0.260	**0.008**
Number of relapses	0.380	**<.001**	0.284	**0.004**
Episode(s) of bilateral optic neuritis [+/−]	0.143	0.071	0.084	0.281
LESCL [+/−]	0.189	**0.016**	0.052	0.512
AID/autoantibody [+/−]	−0.051	0.529	−0.027	0.724
PSL/IS [treated/non-treated]	−0.060	0.443	−0.065	0.407
*HLA-DPB1*05:01* [+/−]	−0.011	0.893	−0.102	0.187

Significant correlations are in bold.

AID, autoimmune disease; EDSS, expanded disability status scale; IS, immunosuppressants; LESCL, longitudinally extensive spinal cord lesion; NMOSD, neuromyelitis optica spectrum disorders; PSL, prednisolone; Std, standardized; y, years.