Original Article

Variants of Interleukin-7/Interleukin-7 Receptor Alpha are Associated with Both Neuromyelitis Optica and Multiple Sclerosis Among Chinese Han Population in Southeastern China

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Abstract

Background: Neuromyelitis optica (NMO) and multiple sclerosis (MS) are autoimmune demyelinating diseases of the central nerve system. Interleukin-7 (IL-7) and interleukin-7 receptor alpha (IL-7Rα) were proved to be important in the pathogenesis of both diseases because of the roles they played in the differentiations of autoimmune lymphocytes. The variants of both genes had been identified to be associated with MS susceptibility in Caucasian, Japanese and Korean populations. However, the association of these variants with NMO and MS has not been well studied in Chinese Southeastern Han population. Here, we aimed to evaluate the association of six *IL-7* variants (rs1520333, rs1545298, rs4739140, rs6993386, rs7816065, and rs2887502) and one variant of *IL-7RA* (rs6897932) with NMO and MS among Chinese Han population in southeastern China.

Methods: Matrix-assisted laser desorption/ionization time of flight mass spectrometry (MassARRAY system) and Sanger sequencing were used to determine the variants of *IL-7* and *IL-7RA* in 167 NMO patients, 159 MS patients and 479 healthy controls among Chinese Han population in southeastern China. Samples were excluded if the genotyping success rate <90%.

Results: Statistical differences were observed in the genotypes of *IL-7* rs1520333 in MS patients and *IL-7RA* rs6897932 in NMO patients, compared with healthy controls (P = 0.035 and 0.034, respectively). There was a statistically significant difference in the genotypes of *IL-7* rs2887502 between MS and NMO patients (P = 0.014). And there were statistically significant differences in the rs6897932 genotypes (P = 0.004) and alleles (P = 0.042) between NMO-IgG positive patients and healthy controls.

Conclusions: The study suggested that among Chinese Han population in southeastern China, the variant of *IL-7RA* (rs6897932) was associated with NMO especially NMO-IgG positive patients while the variant of *IL-7* (rs1520333) with MS patients. And the genotypic differences of *IL-7* rs2887502 between MS and NMO indicated the different genetic backgrounds of these two diseases.

Key words: Association; Interleukin-7/Interleukin-7 Receptor Alpha; Multiple Sclerosis; Neuromyelitis Optica; Chinese Han Population

Introduction

Neuromyelitis optica (NMO) and multiple sclerosis (MS) are autoimmune inflammatory demyelinating disorders of the central nervous system with unknown etiology, causing nontraumatic neurological disability in young adults.[1-3] NMO is thought to be a subtype of MS but not an independent disease until the discovery of the anti-aquaporin 4 (AQP4) antibody or NMO-IgG.[4-6] Although the exact etiologies of both diseases are still unclear, it is sure that the T-helper cells (Th), directly or indirectly, participate in the pathogenesis and progress of MS and NMO by secreting various cytokines.[2,7-9]

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.169093

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Received: 20-07-2015 **Edited by:** Xin Chen
How to cite this article: Zhuang JC, Wu L, Qian MZ, Cai PP, Liu QB, Zhao GX, Li ZX, Wu ZY. Variants of Interleukin-7/Interleukin-7 Receptor Alpha are Associated with Both Neuromyelitis Optica and Multiple Sclerosis Among Chinese Han Population in Southeastern China. Chin Med J 2015;128:3062-8.

Over recent years, interleukin-7 (IL-7) had been widely considered to be a key cytokine controlling the differentiations and immune responses of several T-cells subsets.[10-14] It is suggested that the function of IL-7 was not only stimulating IL-7 receptor alpha (IL-7Rα) to promote the differentiation of Th1, but also involving in the survival and proliferation of pathogenic Th17 cells in experimental autoimmune encephalomyelitis (EAE) and MS patients.[15-18] The serum IL-7 can be seen as a potential marker monitoring the response to interferon-β in MS patients.[17]

The genetic variants of *IL-7* and *IL-7RA* had been identified to be associated with the susceptibility of MS and NMO in Caucasian, Japanese and some other populations in several studies.[19-24] However, the results had not been replicated in Chinese Han population except our previous study on rs1520333 in *IL-7* and rs6897932 in *IL-7RA*, in which no positive associations were observed.[25]

As the IL-7/IL-7R pathway might be a very attractive therapeutic target for inflammatory disorders, the genetic variants in this pathway were proposed to implicate in the pathogenesis of various autoimmune diseases.[14,18,26-28] Here, we enlarged the sample size to replicate the association of these 2 single nucleotide polymorphisms (SNPs) (rs1520333 in *IL-7* and rs6897932 in *IL-7RA*) with MS and NMO. Meanwhile, we assayed 5 more SNPs of *IL-7* (rs1545298, rs4739140, rs6993386, rs7816065, and 2887502) in the enlarged samples of MS, NMO, and healthy controls.

Methods

Subjects

As described in our previous study,[25] 110 unrelated NMO patients and 304 healthy controls were included. In this study, we recruited 57 more NMO patients and 178 more healthy controls. In total, 167 NMO patients (26 males and 141 females) and 479 healthy controls (255 males and 224 females) among Chinese Han population in Southeastern China were included in this study. All the NMO patients were diagnosed according to the revised 2006 Wingerchuk criteria.[29] In addition, we recruited 159 MS patients (66 males and 93 females), and the diagnosis of which met the 2005 McDonald criteria for MS.[30] All participants signed an informed consent form. The study was approved by the Ethics Committee of Huashan Hospital.

Neuromyelitis optica-IgG antibody detection

NMO-IgG antibodies were detected with an indirect immunofluorescence assay using human embryonic kidney 293 cells transfected with recombinant human *AQP4* gene (Euroimmun, Lubeck, Germany).[6] Each sample was measured at least twice, with the examiners unknowing the origin of the specimens. Samples with twice positive results were reported to be NMO-IgG positive.

Genotyping

Genomic DNA was extracted from peripheral blood samples using a QIAamp DNA Blood Minikit (QIAGEN, Hilden,

Table 1: Primer sequences for analysis of *IL7* and *IL7RA* variants

Variants	PCR primers	MassEXTEND primers	PCR primers for sanger sequencing
rs6993386	Forward: ACGTTGGATGTCAAAAGATGGCCATCTAAG	GATGGCCATCTAAGTTTCTTT	Forward: 5'-TGCCTAGCTGTGATTTGTTTC-3'
	Reverse: ACGTTGGATGCCCTATCAGAAGAATGGCTC		Reverse: 5'-CAGTTATTAATTCATCGACCT-3'
rs4739140	Forward: ACGTTGGATGCAGTTCTCTTCCTCAGTACC	TCCTCAGTACCTCTTTAGT	Forward: 5'-GAAGCAGGGACCTTTGTGGAA-3'
	Reverse: ACGTTGGATGACCACAGAAAAAGTCTGAATG		Reverse: 5'-ATTCTTCTCGATTTTCAGT-3'
rs2887502	Forward: ACGTTGGATGTCTGACCATTGTTGCTCAGG	AGGGTAGTTCAGTACTTC	Forward: 5'-GTGTTGAGCATGAGGAGGGA-3'
	Reverse: ACGTTGGATGAGGAGAGAGACTAAGAGCAG		Reverse: 5'-AGAGACAGAGGTTCTGGCTGA-3'
rs1545298	Forward: ACGTTGGATGGGTAAAACTAGGCCATGAGG	TTCCTGTGTGGCTTAA	Forward: 5'-TCAAGTGGGAGGAAAGGGAAA-3'
	Reverse: ACGTTGGATGGATCAGGAATACTCACCTGC		Reverse: 5'-GTTGAGAAATCCAAGATCAAG-3'
rs7816065	Forward: ACGTTGGATGAGGCATAAAGGCACACTGAC	GTTAGCTGTGTTTTTAGCAAA	Forward: 5'-GGTAGCTGAAACGTAGGCCTG-3'
	Reverse: ACGTTGGATGAAGTGTAGAGCAAGTCTGCC		Reverse: 5'-CTAATGAAATCTGTCCAAAGG-3'
rs1520333	Forward: ACGTTGGATGAGAGGTGGTATGGGTGTATC	CAGCCCACTGGAACCAAAG	Forward: 5'-TCAAAAAAGAAGTGCGTG-3'
	Reverse: ACGTTGGATGTGGGCAAGCAGGTAAGAAAG		Reverse: 5'-GTGGTTGCTAAAAATGAAGTC-3'
rs6897932	Forward: ACGTTGGATGCAGAGCGACACAGAGAAAAAAC	CAAAAAACTCAAAATGCTGATG	Forward: 5'-CAAAGCACCCTGAGACCCTACC-3'
	Reverse: ACGTTGGATGACTGAATGCTCACCACAATC		Reverse: 5'-CAGCGTTTGCCTAATGTCCAGT-3'

PCR: Polymerase chain reaction.

Germany). Six variants in *IL-7* (rs1520333, rs1545298, rs4739140, rs6993386, rs7816065, and 2887502) and one variant in *IL-7RA* (rs6897932) were genotyped using Sequenom MassARRAY system (Sequenom, San Diego, CA, USA) in previous 106 NMO patients and 304 healthy controls, according to the manufacturer's instructions at Fudan-Van Andel Research Institute Center, as we previously described.[31] For quality control, sample duplicates whose genotypes had been identified by sequencing were included in each 96-well plate. Genotyping was performed by technicians blinded to sample status. The average concordance rate between duplicate samples was >99%. Then, the additional samples including 57 NMO patients, 159 MS patients, and 178 healthy controls were genotyped by Sanger sequencing using an ABI 3730 Automated DNA Sequencer (Applied Biosystems, USA). Primers for all these variants are shown in Table 1.

Statistical analysis

Hardy–Weinberg equilibrium (HWE) was tested using the Chi-square test. The genotypes and allele frequencies were compared between cases and controls using the Chi-square test or Fisher's exact test. Continuous variables were shown as mean ± standard deviation (SD). A $P < 0.05$ was considered as statistically significant. All data were analyzed using SPSS 16.0 Software for Windows (SPSS Inc., Chicago, IL, USA).

Results

After genotyping by Sequenom MassARRAY system, 4 NMO patients and 14 healthy controls were excluded for genotyping success rate <90%. Hence, there were 163 NMO patients, 159 MS patients, and 468 healthy controls analyzed. NMO-IgG antibody was tested in the 57 newly recruited NMO patients, and 13 (29.5%) were positive, added with previous 44 antibody positive NMO patients,[25] there were 57 NMO-IgG antibody positive patients in total. No antibody positive MS patient was found in this study.

The general data of participants are shown in Table 2. The sequencing chromatograms of the additional samples are shown in Figure 1. HWE test was performed as Table 3. Most of the SNPs in each group were under the HWE except *IL-7* rs2887502 in MS ($P = 0.033$) and *IL-7RA* rs6897932 in healthy controls ($P = 0.031$). For the C/C genotype of IL-7 rs2887502 did not exist in MS patients and the frequency of

Table 2: Characteristics of all Chinese Han participants in this study

Characteristics	MS ($n = 159$)	NMO ($n = 163$)	Healthy controls ($n = 468$)
Male/female, *n*	66/93	24/139	248/220
Age (years), mean ± SD (range)	39.30 ± 13.69 (9–73)	43.42 ± 13.30 (13–77)	32.90 ± 13.64 (16–85)
Onset age (years), mean ± SD	31.82 ± 13.02	36.26 ± 13.72	NA
Duration of disease (years), mean ± SD	6.96 ± 5.90	6.89 ± 7.29	NA
AQP4-Ab positive, *n* (%)	0 (0)	57 (34.97)	NA

MS: Multiple sclerosis; NMO: Neuromyelitis optica; AQP4-Ab: Anti-aquaporin-4 antibodies; NA: Not applicable; SD: Standard deviation.

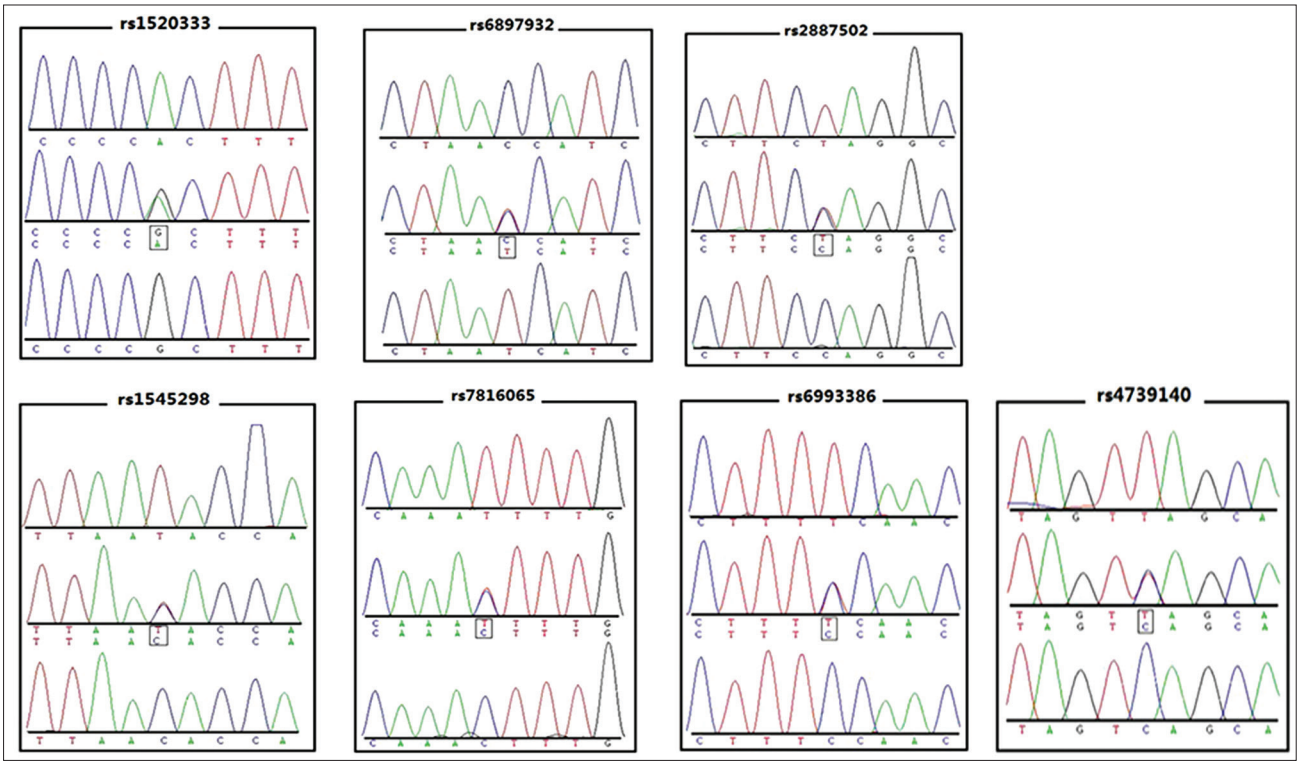

Figure 1: The DNA sequence chromatograms of these seven variants. The upper and the bottom panels indicate the homozygous genotypes, whereas the heterozygous genotype is shown in the middle one.

Table 3: Hardy–Weinberg equilibrium tests for all Chinese Han participants in this study

Variants	MS (n = 159)			NMO (n = 163)			Healthy controls (n = 468)		
	n (expected numbers)	χ^2	P	n (expected numbers)	χ^2	P	n (expected numbers)	χ^2	P
IL7									
rs1520333		2.547	0.110		0.071	0.790		1.892	0.169
GG	46 (50.94)			44 (44.85)			130 (122.56)		
GA	88 (78.11)			83 (81.30)			219 (233.87)		
AA	25 (29.94)			36 (36.85)			119 (111.56)		
rs1545298		0.006	0.937		0.122	0.727		0.784	0.376
CC	10 (9.81)			11 (11.88)			32 (35.83)		
CT	59 (59.37)			66 (64.25)			195 (187.33)		
TT	90 (89.81)			86 (86.88)			241 (244.83)		
rs4739140		2.929	0.087		2.367	0.124		0.066	0.797
AA	0 (2.27)			6 (3.53)			6 (6.58)		
AG	38 (33.46)			36 (40.93)			99 (97.84)		
GG	121 (123.27)			121 (118.53)			363 (363.58)		
rs6993386		3.089	0.079		0.077	0.782		0.143	0.705
CC	15 (20.08)			22 (22.83)			70 (71.95)		
CT	83 (72.85)			78 (76.34)			227 (223.10)		
TT	61 (66.08)			63 (66.83)			171 (172.95)		
rs7816065		0.005	0.943		0.298	0.585		0.041	0.840
CC	14 (14.19)			17 (18.56)			55 (54.02)		
CT	67 (66.62)			76 (72,88)			208 (209.96)		
TT	78 (78.19)			70 (71.56)			205 (204.02)		
rs2887502		4.548	0.033		3.522	0.061		0.174	0.677
CC	0 (3.33)			8 (4.46)			11 (9.88)		
CT	46 (39.35)			39 (45.72)			114 (116.24)		
TT	113 (116.33)			116 (112.64)			343 (341.88)		
IL7RA									
rs6897932		0.412	0.521		0.770	0.380		4.656	0.031
CC	111 (112.09)			111 (109.34)			329 (335.08)		
CT	45 (42.82)			45 (48.32)			134 (121.85)		
TT	3 (4.09)			7 (5.34)			5 (11.08)		

A $P < 0.05$ was considered statistically significant. MS: Multiple sclerosis; NMO: Neuromyelitis optica; *IL7*: Interleukin-7; *IL7RA*: Interleukin-7 receptor alpha.

C/C genotype was much higher in healthy control than that in the NMO-IgG positive NMO patients (70.30% vs. 61.40%), the departure from DHW of both polymorphisms in MS and healthy controls were possibly due to the protective role of C/C genotype according to a previous study.[32]

As listed in Table 4, after enlarging the sample size for both previously studied SNPs, the frequency of the A/A genotype of rs1520333 in *IL-7* gene of MS patients was observed dramatically lower than healthy controls, which reached the statistical difference (P = 0.035). However, the allelic comparisons did not show the statistical significance. Meanwhile, although statistical difference of the genotype was existed between total NMO and healthy controls in *IL-7RA* rs6897932 (P = 0.034), we also found no statistical difference in the allele frequencies ($P > 0.05$). When comparisons were made between NMO-IgG positive patients and MS patients or healthy control, we found that statistical significant differences of genotype and allele distributions were observed in *IL-7RA* rs6897932 (P = 0.004 and P = 0.042) between the NMO-IgG positive patients and healthy controls.

The results of five newly assayed *IL-7* SNPs are listed in Table 5, along with the results of corresponding Chi-square test. The genotypes of *IL-7* rs2887502 were significantly different between NMO and MS patients (P = 0.014). And no statistical difference was found among the other SNPs.

Discussion

Autoimmune diseases are complex trait that develop from intricate and poorly understood interactions between an individual's genetics and the environmental exposures.[1] The genetics of NMO susceptibility largely remain unknown. In this study, we totally investigated the association of 6 variants in *IL-7* and one variant in *IL-7RA* with Chinese NMO and MS patients, especially with the NMO-IgG positive patients. We observed that the genotype of rs6897932 in *IL-7RA* was statistically different between NMO patients and the healthy controls after including more NMO patients and

Table 4: Allele and genotype distributions of *IL7* and *IL7R* variants among MS, NMO and healthy controls, *n* (%)

Variants	Genotype/ allele	Controls (n = 468)	MS (n = 159)	NMO^T (n = 163)	NMO^P (n = 57)	Chi-square or Fisher's exact values				
						MS versus controls	Total NMO		NMO-IgG positive	
							NMO^T versus controls	MS versus NMO^T	NMO^P versus controls	MS versus NMO^P
IL7										
rs1520333	GG	130 (27.78)	46 (28.93)	44 (27.00)	18 (31.58)	χ^2 = 6.695, P = 0.035	χ^2 = 1.006, P = 0.605	χ^2 = 2.125, P = 0.346	χ^2 = 0.370, P = 0.831	χ^2 = 2.973, P = 0.226
	GA	219 (46.79)	88 (55.35)	83 (50.92)	25 (43.86)					
	AA	119 (25.43)	25 (15.72)	36 (22.09)	14 (24.56)					
	G	479 (51.18)	180 (56.60)	171 (52.45)	61 (53.51)	χ^2 = 2.805, P = 0.094	χ^2 = 0.158, P = 0.691	χ^2 = 1.118, P = 0.290	χ^2 = 0.222, P = 0.638	χ^2 = 0.222, P = 0.638
	A	457 (48.82)	138 (43.40)	155 (47.55)	53 (46.49)					
IL7RA										
rs6897932	CC	329 (70.30)	111 (69.81)	111 (68.10)	35 (61.40)	χ^2 = 0.632*, P = 0.729	χ^2 = 6.745, P = 0.034	χ^2 = 1.551*, P = 0.461	χ^2 = 11.223*, P = 0.004	χ^2 = 4.002*, P = 0.135
	CT	134 (28.63)	45 (28.30)	45 (27.61)	18 (31.58)					
	TT	5 (1.07)	3 (1.89)	7 (4.29)	4 (7.02)					
	C	792 (84.62)	267 (83.96)	267 (81.90)	88 (77.19)	χ^2 = 0.077, P = 0.781	χ^2 = 1.319, P = 0.251	χ^2 = 0.483, P = 0.487	χ^2 = 4.126, P = 0.042	χ^2 = 2.625, P = 0.105
	T	144 (15.38)	51 (16.04)	59 (18.10)	26 (22.81)					

*The results of Fisher's exact test. $P < 0.05$ was considered statistically significant. MS: Multiple sclerosis; NMO: Neuromyelitis optica; NMO^T: Total neuromyelitis optica patients; NMO^P: Neuromyelitis optica-IgG positive patients; *IL7*: Interleukin-7; *IL7RA*: Interleukin-7 receptor alpha.

healthy controls. While further comparing the NMO-IgG positive patients with healthy controls, we found that the C/C genotype and C allele significantly decreased in NMO-IgG positive NMO patients. In *IL-7* gene, rs1520333 genotype reached the statistical significant difference between MS patients and healthy controls. The genotypes of *IL-7* rs2887502 were observed statistically different between NMO and MS patients in our present study.

IL-7 belongs to a superfamily of gamma-chain cytokine receptor, and its gene, *IL-7*, is located on chromosome 8q12-13.[33,34] Functionally, IL-7 binds to IL-7Rα (also termed as CD127), which is encoded by the gene *IL-7RA*, plays an essential role in the T cell survival and proliferation in human and animal model.[11,14,35] A recent study revealed that the serum IL-7 reflected the MS patients' responsiveness to interferon-β in Th1-dirven MS, because of the important role of IL-7 played in enhancing the Th1 proliferation. In turn, treatment of IL-7/IL-7Rα blockade seemed benefit to EAE, a murine model of MS.[17]

Numbers of previous studies pointed out the *IL-7/IL-7RA* variants were associated with the morbidity of NMO and MS in different populations and regions of the world.[19-24] The rs6997932 was proved to be a causative variant that affected the expression of *IL-7RA*.[19] Studies on different populations reached a consensus that this SNP was strongly associated with MS, moreover, it was also associated with NMO in the studies performed in Japanese and Korean populations.[22-24,36] Some studies revealed that rs6993386, rs1520333, and rs7816065 of *IL-7* were associated with MS in Caucasian populations, while rs1545298, rs4739140, and rs2887502 did not relate to this disease.[20,22,36]

Previously, we performed a partial replication of the referred studies by assayed rs1520333 of *IL-7* and rs6897932 of *IL-7RA*, however, we did not find any positive association of both SNPs with NMO.[25] In consideration of the different genetic background among populations, we enlarged the sample size and investigated the associations of more SNPs with not only NMO patients, but also MS patients in the current study. Interestingly, statistical significant differences were observed in the genotypes of *IL-7RA* rs6897932 between the cohorts of total NMO patients and healthy controls. While further comparing the NMO-IgG positive patients with healthy controls, significant differences existed in both distributions of genotypes and alleles in *IL-7RA* rs6897932. This result was coherent with the results of studies in Japanese and Korean populations,[23,24] confirming that *IL-7RA* rs6897932 might be a risky factor of NMO in Asians. However, we did not observe the association of *IL-7RA* rs6897932 with the pathogenesis of MS, which indicated the different genetic background among the East Asians. In the comparisons between the MS patients and healthy controls, the genotypes of *IL-7* rs1520333 reached the statistical significant difference, which was first reported in Asian. The significant difference of *IL-7* rs2887502 genotypes between NMO and MS patients was also firstly reported, which indicated the different genetic backgrounds of both diseases.

Although our study reported a potential association between *IL-7/IL-7RA* polymorphisms and MS/NMO, some limitations were present and should be addressed in the future. First, the sample size should be further enlarged in further study. Second, there was a disparity in the gender ratio, since the

Table 5: Allele and genotype distributions of 5 newly studied *IL7* variants among MS, NMO and healthy controls, *n* (%)

Variants	Genotype/ allele	Controls (n = 468)	MS (n = 159)	NMO^T (n = 163)	NMO^P (n = 57)	Chi-square or Fisher's exact values				
						MS versus controls	Total NMO		NMO-IgG (+) NMO	
							NMO^T versus controls	MS versus NMO^T	NMO^P versus controls	MS versus NMO^P
rs1545298	CC	32 (6.84)	10 (6.29)	11 (7.51)	2 (3.51)	χ^2 = 1.249, P = 0.536	χ^2 = 0.079, P = 0.961	χ^2 = 0.481, P = 0.786	χ^2 = 1.061*, P = 0.588	χ^2 = 1.605*, P = 0.448
	CT	195 (41.67)	59 (37.11)	66 (39.31)	26 (45.61)					
	TT	241 (51.50)	90 (56.60)	86 (53.18)	29 (50.88)					
	C	259 (27.67)	79 (24.84)	88 (26.99)	30 (26.32)	χ^2 = 0.964, P = 0.326	χ^2 = 0.056, P = 0.814	χ^2 = 0.388, P = 0.533	χ^2 = 0.095, P = 0.757	χ^2 = 0.081, P = 0.775
	T	677 (72.33)	239 (75.16)	238 (73.00)	84 (73.68)					
rs4739140	CC	6 (1.28)	0 (0)	6 (3.68)	2 (3.51)	χ^2 = 2.481*, P = 0.289	χ^2 = 3.882, P = 0.144	χ^2 = 6.005*, P = 0.050	χ^2 = 2.137*, P = 0.344	χ^2 = 5.684*, P = 0.058
	CT	99 (21.15)	38 (23.90)	36 (22.09)	14 (24.56)					
	TT	363 (77.56)	121 (76.10)	121 (74.23)	41 (71.93)					
	C	111 (11.86)	38 (11.95)	48 (14.72)	18 (15.79)	χ^2 = 0.002, P = 0.966	χ^2 = 1.802, P = 0.179	χ^2 = 1.071, P = 0.301	χ^2 = 1.457, P = 0.227	χ^2 = 1.097, P = 0.295
	T	825 (88.14)	280 (88.05)	278 (85.28)	96 (84.21)					
rs6993386	CC	70 (14.96)	15 (9.43)	22 (13.50)	5 (8.77)	χ^2 = 3.106, P = 0.212	χ^2 = 0.333, P = 0.847	χ^2 = 1.462, P = 0.481	χ^2 = 3.169, P = 0.205	χ^2 = 1.439, P = 0.487
	CT	227 (48.50)	83 (52.21)	78 (47.85)	25 (43.86)					
	TT	171 (36.54)	61 (38.36)	63 (38.65)	27 (47.37)					
	C	367 (39.21)	113 (35.53)	122 (37.42)	35 (30.70)	χ^2 = 1.332, P = 0.249	χ^2 = 0.111, P = 0.739	χ^2 = 0.248, P = 0.619	χ^2 = 3.113, P = 0.078	χ^2 = 0.870, P = 0.351
	T	569 (60.79)	205 (64.47)	204 (62.58)	79 (69.30)					
rs7816065	CC	55 (11.75)	14 (8.81)	17 (10.43)	2 (3.51)	χ^2 = 1.806, P = 0.405	χ^2 = 0.334, P = 0.846	χ^2 = 1.240, P = 0.538	χ^2 = 4.840*, P = 0.089	χ^2 = 4.064*, P = 0.131
	CT	208 (44.44)	67 (42.14)	76 (46.63)	32 (56.14)					
	TT	205 (43.80)	78 (49.06)	70 (42.94)	23 (40.35)					
	C	318 (33.97)	95 (29.87)	110 (33.74)	36 (31.58)	χ^2 = 1.807, P = 0.179	χ^2 = 0.006, P = 0.939	χ^2 = 1.110, P = 0.292	χ^2 = 0.261, P = 0.609	χ^2 = 0.115, P = 0.734
	T	618 (66.03)	223 (70.13)	216 (66.26)	78 (68.42)					
rs2887502	CC	11 (2.35)	0 (0)	8 (4.91)	2 (3.51)	χ^2 = 4.790*, P = 0.091	χ^2 = 2.711, P = 0.258	χ^2 = 8.567*, P = 0.014	χ^2 = 0.422*, P = 0.810	χ^2 = 5.685*, P = 0.058
	CT	114 (24.36)	46 (28.93)	39 (23.93)	15 (26.32)					
	TT	343 (73.29)	113 (71.07)	116 (71.17)	40 (70.18)					
	C	136 (14.53)	46 (14.47)	55 (16.87)	19 (16.67)	χ^2 = 0.001, P = 0.977	χ^2 = 1.032, P = 0.310	χ^2 = 0.705, P = 0.401	χ^2 = 0.369, P = 0.544	χ^2 = 0.318, P = 0.573
	T	800 (85.47)	272 (95.53)	271 (83.13)	95 (83.33)					

*The results of Fisher's exact test. $P < 0.05$ was considered statistically significant. MS: Multiple sclerosis; NMO: Neuromyelitis optica; NMO^T: Total neuromyelitis optica patients. NMO^P: Neuromyelitis optica-IgG positive patients; *IL7*: Interleukin-7.

incidences of both diseases are higher in female than male. Lastly, functional studies of the *IL-7* would be required to understand the actual effect of the IL-7/IL-7R complex in MS and NMO pathogenesis.

In conclusion, the current study replicated some positive-associated SNPs, which were observed in other populations, in Chinese NMO and MS patients. Meanwhile, we investigated the associations of 5 more SNPs of *IL-7* with NMO and MS that were not investigated in Asian previously. To our best knowledge, this study may provide a deeper understanding of the role of IL-7/IL-7R pathway playing in the pathogenesis of NMO and MS within different populations, which hints a new insight to the personal therapy for both diseases in the future. And this study suggested that it might be necessary to monitor the serum IL-7 of NMO-IgG positive patients during the treatment.

Acknowledgments

The authors sincerely thank the patients and their parents for the help and willingness to take part in this study.

Financial support and sponsorship

This work was supported by grants from National Key Clinical Specialty Discipline Construction Program and Key Clinical Specialty Discipline Construction Program of Fujian and the National Natural Science Foundation of China (No. 81125009 and No. 3091110488).

Conflicts of interest

There are no conflicts of interest.

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