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 nervous 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.

Keywords: 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]

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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.\textsuperscript{10-14} It is suggested that the function of IL-7 was not only stimulating IL-7 receptor alpha (IL-7R\textsubscript{\alpha}) 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.\textsuperscript{15-18} The serum IL-7 can be seen as a potential marker monitoring the response to interferon-\beta in MS patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 Mini kit (QIAGEN, Hilden, Table 1: Primer sequences for analysis of IL7 and IL7RA variants

| Variants       | PCR primers | MassEXTEND primers | PCR primers for sanger sequencing |
|----------------|-------------|--------------------|----------------------------------|
| rs69931386     | Forward: ACGTTGGATGTCAAAAGATGGCCATCTAAG | AGTCCTAGCTGTGATTTGTTTC | Forward: 5'-TGCCTAGCTGTGATTTGTTTC-3' |
| rs4739140      | Forward: ACGTTGGATGCAGTTCTCTTCCTCAGTACC | GTCTCTCTCTCTCTCTCTCT | Reverse: 5'-AGAGCAGGGACCTTTGTGGAA-3' |
| rs2887502      | Forward: ACGTTGGATGTCTGACCATTGTTGCTCAGG | AGGGTAGTTCAGTACTTC | Forward: 5'-TCAAGTGGGAGGAAAGGGAAA-3' |
| rs1545298      | Forward: ACGTTGGATGGGTAAAACTAGGCCATGAGG | TCTCCTGCCTAAGTGGTCTGA | Reverse: 5'-GTTGAGAAATCCAAGATCAAG-3' |
| rs7816065      | Forward: ACGTTGGATGAGGCATAAAGGCACACTGAC | GTCTGCCTGCCTGCCTGCCT | Reverse: 5'-CAAAGCACCCTGAGACCCTACC-3' |
| rs1520333      | Forward: ACGTTGGATGAGAGGTGGTATGGGTGTATC | AGCCCACTGGAACCAAAG | Reverse: 5'-AGAGACAGAGGTTCTGGCTGA-3' |
| rs6897932      | Forward: ACGTTGGATGCAGAGCGACAGAGAAAAAAC | AGAAAAACTCAAAATGCTGATG | Reverse: 5'-CAGCGTTTGCCTAATGTCCAGT-3' |
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                        |

**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.
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.\cite{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 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.

### Discussion

Autoimmune diseases are complex trait that develop from intricate and poorly understood interactions between an individual’s genetics and the environmental exposures.\cite{11} 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 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 (n = 163) | NMO+ (n = 57) | Chi-square or Fisher’s exact values
|-----------|-----------------|-------------------|--------------|---------------|---------------|---------------------------------|
|           |                 |                   | MS           | NMO           | NMO+          | MS versus controls | NMO versus controls | NMO+ versus controls | NMO versus controls |
| IL7       |                 |                   |              |               |               |                   |                   |                   |                   |
| rs152033  | GG              | 130 (27.78)       | 46 (28.93)   | 44 (27.00)    | 18 (31.58)    | $\chi^2 = 6.695$, $P = 0.035$ | $\chi^2 = 1.006$, $P = 0.605$ | $\chi^2 = 2.125$, $P = 0.346$ | $\chi^2 = 0.370$, $P = 0.831$ | $\chi^2 = 2.973$, $P = 0.226$ |
|           | GA              | 219 (46.79)       | 88 (55.35)   | 83 (50.92)    | 25 (43.86)    | $\chi^2 = 0.515$, $P = 0.791$ | $\chi^2 = 0.158$, $P = 0.691$ | $\chi^2 = 1.118$, $P = 0.290$ | $\chi^2 = 0.222$, $P = 0.638$ | $\chi^2 = 0.222$, $P = 0.638$ |
|           | AA              | 119 (25.43)       | 25 (15.72)   | 36 (22.09)    | 14 (24.56)    | $\chi^2 = 0.515$, $P = 0.791$ | $\chi^2 = 0.158$, $P = 0.691$ | $\chi^2 = 1.118$, $P = 0.290$ | $\chi^2 = 0.222$, $P = 0.638$ | $\chi^2 = 0.222$, $P = 0.638$ |
|           | G               | 479 (51.18)       | 180 (56.60)  | 171 (52.45)   | 61 (53.51)    | $\chi^2 = 0.515$, $P = 0.791$ | $\chi^2 = 0.158$, $P = 0.691$ | $\chi^2 = 1.118$, $P = 0.290$ | $\chi^2 = 0.222$, $P = 0.638$ | $\chi^2 = 0.222$, $P = 0.638$ |
| C         | A               | 457 (48.82)       | 138 (43.40)  | 155 (47.55)   | 53 (46.49)    | $\chi^2 = 0.515$, $P = 0.791$ | $\chi^2 = 0.158$, $P = 0.691$ | $\chi^2 = 1.118$, $P = 0.290$ | $\chi^2 = 0.222$, $P = 0.638$ | $\chi^2 = 0.222$, $P = 0.638$ |
| IL7RA     |                 |                   |              |               |               |                   |                   |                   |                   |
| rs6897932 | CC              | 329 (70.30)       | 111 (69.81)  | 111 (68.10)   | 35 (61.40)    | $\chi^2 = 0.632^*$, $P = 0.729$ | $\chi^2 = 6.745$, $P = 0.034$ | $\chi^2 = 1.551^*$, $P = 0.461$ | $\chi^2 = 11.223^*$, $P = 0.004$ | $\chi^2 = 4.002^*$, $P = 0.135$ |
|           | CT              | 134 (28.63)       | 45 (28.30)   | 45 (27.61)    | 18 (31.58)    | $\chi^2 = 0.077$, $P = 0.781$ | $\chi^2 = 1.319$, $P = 0.251$ | $\chi^2 = 0.483$, $P = 0.487$ | $\chi^2 = 4.126$, $P = 0.042$ | $\chi^2 = 2.625$, $P = 0.105$ |
|           | TT              | 5 (1.07)          | 3 (1.89)     | 7 (4.29)      | 4 (7.02)      | $\chi^2 = 0.077$, $P = 0.781$ | $\chi^2 = 1.319$, $P = 0.251$ | $\chi^2 = 0.483$, $P = 0.487$ | $\chi^2 = 4.126$, $P = 0.042$ | $\chi^2 = 2.625$, $P = 0.105$ |
|           | C               | 792 (84.62)       | 267 (83.96)  | 267 (81.90)   | 88 (77.19)    | $\chi^2 = 0.077$, $P = 0.781$ | $\chi^2 = 1.319$, $P = 0.251$ | $\chi^2 = 0.483$, $P = 0.487$ | $\chi^2 = 4.126$, $P = 0.042$ | $\chi^2 = 2.625$, $P = 0.105$ |
|           | T               | 144 (15.38)       | 51 (16.04)   | 59 (18.10)    | 26 (22.81)    | $\chi^2 = 0.077$, $P = 0.781$ | $\chi^2 = 1.319$, $P = 0.251$ | $\chi^2 = 0.483$, $P = 0.487$ | $\chi^2 = 4.126$, $P = 0.042$ | $\chi^2 = 2.625$, $P = 0.105$ |

*The results of Fisher’s exact test. $P < 0.05$ was considered statistically significant. MS: Multiple sclerosis; NMO: Neuromyelitis optica; NMO+: Total neuromyelitis optica patients; NMO+IgG: 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 IL7 gene, rs152033 genotype reached the statistical significant difference between MS patients and healthy controls. The genotypes of IL7 rs2887502 were observed statistically different between NMO and MS patients in our present study.

IL7 belongs to a superfamily of gamma-chain cytokine receptor, and its gene, IL-7, is located on chromosome 8q12-13. 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. A recent study revealed that the serum IL-7 reflected the MS patients’ responsiveness to interferon-β in Th1-dervied MS, because of the important role of IL-7 played in enhancing the Th1 proliferation. In turn, treatment of IL-7/IL-7RA blockade seemed benefit to EAE, a murine model of MS.

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. The rs6997932 was proved to be a causative variant that affected the expression of IL-7RA. 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. 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.

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. 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, 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
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.

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Conflicts of interest
There are no conflicts of interest.

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

| Variants | Genotype/allele | Controls (n = 488) | MS (n = 159) | NMO (n = 163) | NMO* (n = 57) | Chi-square or Fisher’s exact values |
|----------|----------------|-------------------|-------------|--------------|--------------|-----------------------------------|
| rs1545298 | CC             | 32 (6.84)         | 10 (6.29)   | 11 (7.51)    | 2 (3.51)     | \( \chi^2 = 1.249, \ P = 0.536 \)  \( \chi^2 = 0.079, \ P = 0.961 \)  \( \chi^2 = 0.481, \ P = 0.786 \)  \( \chi^2 = 1.061*, \ P = 0.588 \)  \( \chi^2 = 1.605*, \ P = 0.448 \) |
| 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)   |              |                                   |
| 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)     | \( \chi^2 = 2.481*, \ P = 0.289 \)  \( \chi^2 = 3.882, \ P = 0.144 \)  \( \chi^2 = 6.005*, \ P = 0.050 \)  \( \chi^2 = 2.137*, \ P = 0.344 \)  \( \chi^2 = 5.684*, \ P = 0.058 \) |
| 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 (23.51)    | 38 (11.95)        | 48 (14.72)  | 18 (15.79)   |              |                                   |
| 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)     | \( \chi^2 = 3.106, \ P = 0.212 \)  \( \chi^2 = 0.333, \ P = 0.847 \)  \( \chi^2 = 1.462, \ P = 0.481 \)  \( \chi^2 = 3.169, \ P = 0.205 \)  \( \chi^2 = 1.439, \ P = 0.487 \) |
| 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)   |              |                                   |
| 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)     | \( \chi^2 = 1.806, \ P = 0.405 \)  \( \chi^2 = 0.334, \ P = 0.846 \)  \( \chi^2 = 1.240, \ P = 0.538 \)  \( \chi^2 = 4.840*, \ P = 0.089 \)  \( \chi^2 = 4.064*, \ P = 0.131 \) |
| 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)   |              |                                   |
| 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)     | \( \chi^2 = 4.790*, \ P = 0.091 \)  \( \chi^2 = 2.711, \ P = 0.258 \)  \( \chi^2 = 8.567*, \ P = 0.014 \)  \( \chi^2 = 0.422*, \ P = 0.810 \)  \( \chi^2 = 5.685*, \ P = 0.058 \) |
| CT        | 114 (24.36)    | 46 (28.93)        | 39 (23.93)  | 15 (26.32)   |              |                                   |
| TT        | 114 (24.36)    | 46 (28.93)        | 39 (23.93)  | 15 (26.32)   |              |                                   |
| C         | 136 (14.53)    | 46 (14.47)        | 55 (16.87)  | 19 (16.67)   |              |                                   |
| 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*: Total neuromyelitis optica patients. IL7: Interleukin-7.
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