Neuromyelitis optica (NMO) appears to be a severe inflammatory demyelinating disease occurring in the central nervous system. Furthermore, the Fc receptor-like 3 (FCRL3) gene was previously found to be susceptible for a certain inflammatory demyelinating diseases (such as multiple sclerosis). The present study, therefore, was aimed to explore the possible association of FCRL3 gene polymorphisms with susceptibility to NMO in a Chinese Han population.

Seven single nucleotide polymorphisms (SNPs) of FCRL3 were, respectively, genotyped in 132 NMO patients and 264 healthy controls via PCR assay. Moreover, the r-test and the chi-square test were used to estimate the association between genetic mutations of FCRL3 and the risk of NMO with Statistical Analysis System (SAS) software (Version 9.0).

It was demonstrated that FCRL3_3, 5, 6 and 8, SNPs were remarkably associated with susceptibility to NMO in both alleles [OR = 1.50 (95% CI: 1.11–2.03, \( P = 0.008 \)], OR = 1.44 (1.07–1.94, \( P = 0.015 \)], OR = 1.45 (1.08–1.95, \( P = 0.014 \)], and OR = 2.01 (1.13–3.60, \( P = 0.016 \)] and homozygous models [OR = 2.19 (95% CI: 1.19–3.99, \( P = 0.010 \)], OR = 2.09 (1.15–3.80, \( P = 0.014 \)], OR = 2.04 (1.13–3.67, \( P = 0.016 \)], and OR = 5.33 (1.02–27.9, \( P = 0.027 \)]. However, the other 4 SNPs, FCRL3_4, FCRL3_7, FCRL3_9, did not show the significant associations with NMO.

Conclusions in the present study could be drawn that 4 SNPs in FCRL3 (FCRL3_3>C, 5>C, 6>A, 8>G) might account for increased risk of NMO in a Chinese-Han population. Nevertheless, further cohort studies are in demand to validate the association in the future.
might also impose secondary effects on the *FCRL3* gene,\(^{17}\) cumulatively influencing the development of Graves’ disease. Considering the above complicated effects of polymorphisms in *FCRL3* on the occurrence of certain diseases of great significance, a specific study was required to estimate the relationship between genetic mutations in *FCRL3* and the risk of NMO. The aim of the present study, therefore, was to investigate the association between SNPs in *FCRL3* and susceptibility to NMO in a Chinese Han population.

**MATERIALS AND METHODS**

**Ethic Statement**

All patients have signed written informed-consent forms before participating in this study, and the present study was approved by the First Hospital of Jilin University.

**Participants**

A retrospective case-control study was performed to investigate the association between SNPs of *FCRL3* and the risk of NMO. The participants were made up of 132 NMO patients (male/female = 62/70) and 264 healthy controls (male/ female = 128/136). The NMO patients were recruited between April 2012 and March 2014 and they satisfied the 2006 criteria for diagnosis of NMO.\(^{32}\) All of the involved patients were ascertained by clinical neurologists and were then confirmed with clinical laboratory NMO-IgG seropositive tests. The control subjects were approved by the First Hospital of Jilin University. Before participating in this study, and the present study was performed on an automated ABI PRISM 3100 DNA sequence detection system (Applied Biosystems, Foster City, CA) to identify the target SNPs. To be specific, DNA (10 ng), TaqMan Master Mix (2.5 µl), assay mixture (0.065 µl), and distilled, DNase-free water (2.435 µl) were mixed together for each PCR assay. After that, the SNPs were amplified following different protocols (Table 1). Finally, the PCR products were sequenced directly with a DNA sequencing kit and the Big Dye Terminator on an automated ABI PRISM 3100 DNA sequence detection system (Applied Biosystem, Forster City, CA). Furthermore, the genotyping accuracy of the above results was confirmed with random samples detected by TaqMan.

**SNP Selection**

The International HapMap Project database (HapMap Data Rel 24/phaseII Nov08, on NCBI B36 assembly, dbSNP b126) contains the genotyped data from Chinese Han individuals without genetic associations. Based on the above database, the target SNPs were selected with usage of HaploView software (version 4.2) if the following criteria were all satisfied: (1) minor allele frequency (MAF) was >0.05, (2) \(P\) value of Hardy–Weinberg equilibrium (HWE) was >0.1, (3) \(r^2\) was greater than 0.8. Besides, several previously reported SNPs were also under consideration.

**SNP Genotyping**

First, 10 ml venous blood was collected from each patient with the ethylene diamine tetraacetic acid tube. Then, the Blood DNA Extraction kits II (Beijing Biotake Co. Ltd) was used to extract the genomic DNA from venous blood. The polymerase chain reaction (PCR) assay was subsequently executed with TaqMan Mior Groove Binder (MGB) chemistry (Applied Biosystems, Foster City, CA) to identify the target SNPs. To be specific, DNA (10 ng), TaqMan Master Mix (2.5 µl), assay mixture (0.065 µl), and distilled, DNase-free water (2.435 µl) were mixed together for each PCR assay. After that, the SNPs were amplified following different protocols (Table 1). Finally, the PCR products were sequenced directly with a DNA sequencing kit and the Big Dye Terminator on an automated ABI PRISM 3100 DNA sequence detection system (Applied Biosystem, Forster City, CA). Furthermore, the genotyping accuracy of the above results was confirmed with random samples detected by TaqMan.

**Statistical Analysis**

\(P\) value of HWE was calculated with HaploView software (Version 4.2) to measure the genotyping distributions for the cases and healthy controls. The Haplotype frequencies and linkage disequilibrium were also calculated with the same software. Moreover, the chi-square test, coupled with the odds ratio (OR) and its 95% confidence interval (95%CI), was used to examine the association between selected SNPs and the risk of NMO in allelic, dominant, recessive, and homozygous models. Additionally, the differences between case and control groups in certain variables, such as age and sex, were identified using the \(t\)-test and Pearson’s chi-square test. All of the above statistical tests were performed with Statistical Analysis System (SAS) software (Version 9.0).

**TABLE 1. Primers of FCRL3 Gene Polymorphisms for PCR Amplification**

| SNP      | dbSNP rs# | Primers Sequence | PCR Conditions | Enzyme |
|----------|-----------|------------------|----------------|--------|
| FCRL3_3  | rs7528684 | F: 5’- ATAATACAAATGTACAGATC-3’ | 94°C, 20s; 53°C, 44s; 72°C, 20s | Alul   |
| FCRL3_4  | rs11264799| F: 5’- TGAAGGCGATTAGCTGG-5’ | 93.5°C, 20s; 55°C, 45s; 72°C, 25s | Dral   |
| FCRL3_5  | rs945635 | F: 5’- CACAGAAGACATGGGACC-3’ | 94°C, 20s; 55°C, 45s; 72°C, 20s | Ecorl  |
| FCRL3_6  | rs3761959 | F: 5’- GGTTTCTACTGCTA-3’ | 93.5°C, 20s; 48°C,45s; 72°C, 20s | Hinfl  |
| FCRL3_7  | rs2210913 | F: 5’- TTCTGACACTGTTAC-3’ | 93.7°C, 20s; 48°C, 45s; 72°C, 25s | Hinfl  |
| FCRL3_8  | rs2282284 | F: 5’- TCTGGTGAGGAGGCTAGT-3’ | 94°C, 20s;55°C, 45s; 72°C,20s | Pstl   |
| FCRL3_9  | rs2282283 | F: 5’- CAGATCAGACAGGAGGAGA-3’ | 93.7°C, 20s;48°C,45s; 72°C, 25s | Hinfl  |

\(F\) = forward, \(R\) = reverse, SNP = single-nucleotide polymorphism.
RESULTS

Characteristics of SNPs

A total of 7 SNPs (rs7528684, rs11264799, rs945635, rs3761959, rs2210913, rs2282284, rs2282283) of FCRL3 gene were selected for this study in accordance with HWE. The detailed information about each polymorphism, such as primer sequence, PCR assay condition and enzyme, were displayed in Table 1. Moreover, Figure 1 shows the relative positions of the 7 selected SNPs in the FCRL3 gene. Specifically, rs7528684 and rs11264799 are approximately near the promoter region (5′), whereas rs945635 is exactly in the promoter region. Besides, rs2282283 is situated in the terminator region and rs2282284 is located in the exon 13 region. The remaining 2 SNPs lie in the intron 2 region.

Characteristics of Participants

The demographic and clinical characteristics of NMO patients and healthy groups are shown in Table 2. The sex distribution (male/female) was 62/70 in NMO patients group and 128/136 in the healthy group. No significant difference between cases and control subjects was observed in mean age (P = 0.196) and sex ratio (P = 0.776). The average onset age (± SD) and duration of NMO (± SD) were 40.1 (± 11.9) and 6.5 (± 5.3), respectively. In addition, more data about clinical variables were collected for NMO patients’ group, such as annual relapse rate, positive AQP4-Ab, visual activity, abnormal brain MRI at last test, and so on.

Distribution of Genotype Frequency and the Risk of NMO

The case-control analysis demonstrated that rs7528684 (FCRL3_3), rs945635 (FCRL3_5), rs3761959 (FCRL3_6), and rs2282284 (FCRL3_8) showed significant associations with risk of NMO, whereas other 3 SNPs were not. To be specific, the FCRL3_3+C, FCRL3_5+C, FCRL3_6+A, FCRL3_8+G allelic frequencies were significantly higher in the case group than those in the control group (OR = 1.50, 95% CI: 1.11–2.03, P = 0.008; OR = 1.44, 95% CI: 1.07–1.94, P = 0.015; OR = 1.45, 95% CI: 1.08–1.95, P = 0.014; OR = 2.01, 95% CI: 1.13–3.60, P = 0.016). Moreover, their recessive models (except rs3761959) and homozygous models also revealed the remarkable associations between the genetic variants and the risk of NMO. However, the dominant models or the allelic models failed to show any significant correlations between the rest 3 SNPs and the risk of NMO (Table 3). In addition, haplotype analysis showed that FCRL3_3+C, FCRL3_6+A, and FCRL3_8+G were in a strong linkage disequilibrium (LD), except FCRL3_5 (Figure 2).

DISCUSSION

The present study revealed an association between genetic mutations in FCRL3 (rs7528684, rs945635, rs3761959, and rs2282284) and elevated risk of NMO in a Chinese Han population. The notable associations were confirmed with homozygous and allelic models as well.

As is demonstrated, FCRL3 encoded a member of the immunoglobulin receptor superfamily, which could directly act against myelin-derived antigens. Furthermore, although the precise function of FCRL3 remains to be unknown, the contained immunoreceptor-tyrosine inhibitory motifs (ITIMs) and immunoreceptor-tyrosine activation motifs (ITAMs) are deemed to be involved in the regulation of the immune system. More specifically, both ITIMs and ITAMs are in the cytoplasmic domain, indicating that this membranous receptor participates in transduction of the signal into the cell through its cytoplasmic tail. Based on the above basic features of FCRL3, plenty of studies have revealed the association of polymorphisms of FCRL3 with susceptibility to several autoimmune disorders. Nevertheless, there has been no study reporting the association between polymorphisms of FCRL3 and the risk of NMO in the Chinese population. Therefore, the present study, up to date, was the first investigation focused on the association.

This study demonstrated that the 4 polymorphisms (rs7528684, rs945635, rs3761959, and rs2282284) of FCRL3 could account for an elevated risk of NMO. The FCRL3_3 (rs7528684) is common in previous studies, which have reported that plenty of autoimmune disorders were associated with this polymorphism. More specifically, the association of FCRL3_3C allele with rheumatoid arthritis has been investigated in both Japanese and Canadian populations. Although this association failed to be replicated in independent studies for certain Europeans, who reside in North America, UK, and Spain, a meta-analysis further confirmed the susceptibility of rheumatoid arthritis in Asians, rather than Europeans. In fact, the frequency of putative disease causal
### TABLE 2. Demographic and Clinical Characteristics and Treatment in NMO Patients

|               | NMO                  | Controls             | P Value |
|---------------|----------------------|----------------------|---------|
| No.           | 132                  | 264                  | NA      |
| Age, mean (SD)| 45.4 (12.3)          | 43.6 (13.4)          | 0.196   |
| Sex (M/F)     | 62/70                | 128/136              | 0.776   |
| BMI, kg/m²    | 25.8 (2.4)           | 25.6 (4.8)           | 0.622   |
| Disease duration, mean (SD) | 6.5 (5.3) | NA                  | NA      |
| Age at onset, mean (SD) | 40.1 (11.9) | NA                  | NA      |
| EDSS score at last follow-up, mean (SD) | 3.3 ± 2.1 | NA                  | NA      |
| Annual relapse rate, mean (range) | 1.1 (0.3–1.9) | NA                  | NA      |
| Positive AQP4-Ab, n (%) | 88 (66.7) | NA                  | NA      |
| Normal brain, n (%) | 63 (47.7) | NA                  | NA      |
| More than one ON episode, n (%) | 18 (13.6) | NA                  | NA      |
| Visual acuity, mean (SD) | 0.75 (0.36) | NA                  | NA      |
| Patients with LESCLS, n (%) | 113 (85.6) | NA                  | NA      |
| Abnormal brain MRI at last test, n (%) | NA | NA                  | NA      |
| Spinal cord   | 121 (91.7)           | NA                  | NA      |
| Brainstem     | 40 (17.2)            | NA                  | NA      |
| Cerebrum      | 98 (74.2)            | NA                  | NA      |
| Cerebellum    | 27 (20.5)            | NA                  | NA      |
| Treatments    | NA                  | NA                  | NA      |
| Prednisolone  | 42 (31.8)            | NA                  | NA      |
| Interferon-β-1a | 11 (8.3) | NA                  | NA      |
| Interferon-β-1a | 7 (5.3)  | NA                  | NA      |
| Fingolimod    | 2 (1.5)              | NA                  | NA      |

AQP4-Ab = aquaporin-4-antibody, BMI = body mass index, EDSS = expanded disability status scale, LESCLS = longitudinally extensive spinal cord lesions, NA = not applicable, NMO = neuromyelitis optica, ON = optic neuritis.

### TABLE 3. Allele and Genotype Distributions of FCRL3 SNPs in NMO Patients and Controls

| Variants            | Genotype | Case, N (%) | Control, N (%) | P_RWE | Analyzing Model       | OR (95% CI) | P OR |
|---------------------|----------|-------------|----------------|-------|-----------------------|-------------|------|
| FCRL3_3 (promoter)  | rs7528684| T allele    | 123 (46.6)     | 194 (36.7) | 0.532 | Allelic | 1.50 (1.11–2.03) | 0.008 |
|                     |          | TT          | 39 (29.5)      | 108 (40.9) |       | Dominant | 1.65 (1.06–2.58) | 0.027 |
|                     |          | CT          | 63 (47.7)      | 118 (44.7) |       | Recessive | 1.75 (1.03–2.98) | 0.038 |
|                     |          | CC          | 30 (22.7)      | 38 (14.4)  |       | Homozygous | 2.19 (1.19–3.99) | 0.010 |
| FCRL3_4 (promoter)  | rs11264799| A allele    | 72 (27.3)      | 148 (50.9) | 0.937 | Allelic | 0.96 (0.69–1.34) | 0.822 |
|                     |          | GG          | 71 (53.8)      | 103 (35.1) |       | Dominant | 0.93 (0.61–1.41) | 0.722 |
|                     |          | GA          | 50 (37.9)      | 106 (40.1) |       | Recessive | 1.05 (0.49–2.25) | 0.896 |
|                     |          | AA          | 11 (8.3)       | 21 (8.0)   |       | Homozygous | 1.01 (0.46–2.21) | 0.979 |
| FCRL3_5 (5’UTR)    | rs945635 | C allele    | 140 (53.0)     | 231 (43.9) | 0.666 | Allelic | 1.44 (1.07–1.94) | 0.015 |
|                     |          | GG          | 30 (22.7)      | 81 (30.8)  |       | Dominant | 1.51 (0.93–2.45) | 0.092 |
|                     |          | GC          | 64 (48.5)      | 133 (50.6) |       | Recessive | 1.77 (1.08–2.88) | 0.022 |
|                     |          | CC          | 38 (28.8)      | 49 (18.6)  |       | Homozygous | 2.09 (1.15–3.80) | 0.014 |
| FCRL3_6 (Intron 2) | rs3761959| A allele    | 142 (53.8)     | 235 (44.5) | 0.356 | Allelic | 1.45 (1.08–1.95) | 0.014 |
|                     |          | GG          | 29 (22.0)      | 85 (32.2)  |       | Dominant | 1.69 (1.04–2.74) | 0.034 |
|                     |          | GA          | 64 (48.5)      | 123 (46.6) |       | Recessive | 1.56 (0.97–2.51) | 0.067 |
|                     |          | AA          | 39 (29.5)      | 56 (21.2)  |       | Homozygous | 2.04 (1.13–3.67) | 0.016 |
| FCRL3_7 rs2210913  | G allele  | 109 (41.3)  | 224 (42.4)     | 0.526 | Allelic | 0.95 (0.71–1.29) | 0.760 |
|                     | AA        | 45 (34.1)   | 85 (32.2)      |       | Dominant | 0.92 (0.59–1.43) | 0.705 |
|                     | GA        | 65 (49.2)   | 134 (50.8)     |       | Recessive | 0.97 (0.56–1.70) | 0.924 |
|                     | GG        | 22 (16.7)   | 45 (17.0)      |       | Homozygous | 0.92 (0.49–1.72) | 0.803 |
| FCRL3_8 (Exon 14)  | rs2282284 | G allele    | 24 (9.1)       | 25 (4.7)  | 0.055 | Allelic | 2.01 (1.13–3.60) | 0.016 |
|                     | AA        | 45 (34.1)   | 85 (32.2)      |       | Dominant | 1.76 (0.92–3.37) | 0.083 |
|                     | GA        | 65 (49.2)   | 134 (50.8)     |       | Recessive | 5.16 (0.99–26.95) | 0.031 |
|                     | GG        | 5 (3.8)     | 2 (0.8)        |       | Homozygous | 5.33 (1.02–27.9) | 0.027 |
| FCRL3_9 (3’UTR)    | rs2282283 | C allele    | 63 (23.9)      | 135 (25.6) | 0.465 | Allelic | 0.91 (0.65–1.29) | 0.602 |
|                     | AA        | 75 (28.6)   | 144 (28.4)     |       | Dominant | 0.91 (0.59–1.39) | 0.668 |
|                     | AC        | 51 (38.6)   | 105 (39.8)     |       | Recessive | 0.79 (0.30–2.08) | 0.634 |
|                     | CC        | 6 (4.5)     | 15 (5.7)       |       | Homozygous | 0.77 (0.29–2.06) | 0.399 |

CI = confidence interval, NMO = neuromyelitis optica, OR = odds ratio, SNP = single nucleotide polymorphism.
allele of the FCRL3_3 is similar in Caucasians (40%) and Asians (35%). Therefore, the dissimilar associations of Caucasians and Asians with this autoimmune disorder could not be explained by the ethnic distinctions alone. Instead, the unique environmental or the geographical conditions could trigger genetic variations that are relevant to the susceptibility to rheumatoid arthritis. Apart from rheumatoid arthritis, Graves’ disease and Behçet’s disease were also observed to be significantly associated with this polymorphism in the FCRL3 gene.

Furthermore, a Japanese study and a couple of independent Spanish studies have identified the association of FCRL3_3 polymorphisms with susceptibility to multiple sclerosis among Asians and Caucasians, respectively. However, opposite conclusions regarding the association were suggested. In the present study, the SNPs that have been considered to be associated with the multiple sclerosis were assumed to be significantly correlated with risk of NMO as well. Moreover, there exist no notable associations of FCRL3_4 with susceptibility to both multiple sclerosis in the Spanish study and NMO in the present study. The above phenomena could be explained by the fact that the etiology of multiple sclerosis and that of NMO still possess some similar points despite some dissimilarities to some extent, for example, the presence of multiple sclerosis and NMO are both partly due to the invasion of the immune system through the central nervous system under misdirection. Nonetheless, rs945635 (FCRL3_5), rs3761959 (FCRL3_6), and rs2282284 (FCRL3_8) that were previously not indicated to be associated with risk of multiple sclerosis or NMO displayed a remarkable association with susceptibility to NMO in the present study. Among the 3 SNPs, the polymorphisms of FCRL3_6 and FCRL3_8, which are situated in the coding region, could easily cause changes in amino acids, indicating their positive effects on the risk of NMO in the Chinese populations. Whereas the genetic mutations of FCRL3 had been rarely studied in the association with risk of NMO, there were several studies suggesting the significant associations of FCRL3 polymorphisms with multiple sclerosis. After comprehensively comparing this study results with previous studies, conclusions could be drawn that the polymorphisms in FCRL3 might have similar associations with both multiple sclerosis and NMO, even though the sample size and ethnicities in diverse studies regarding multiple sclerosis and NMO were different.

Although FCRL3 polymorphisms are considered to be potentially associated with risk of NMO in the present study, some limitations still exist and they need to be addressed in the future. First, the limited number of patients and controls enrolled in the study could have interfered with the statistical power, for example, the P value of HWE for the selected polymorphisms was reduced. Second, the study subjects were not fully representative since the study was hospital-based and that the gender ratio in the case group was not consistent with the standard ratio, which was concluded from a review study. To make up for this disparity, subgroup analysis on the basis of gender could help us to understand whether the disease distribution differs between males and females. Last, the study in terms of additional relevant polymorphisms would be in urgent demand to explore the actual effects of FCRL3 genetic mutations on NMO.

In conclusion, the association analyses between FCRL3 polymorphisms and susceptibility to NMO have been conducted in the present study. The results demonstrated that 4 SNPs (rs7528684, rs945635, rs3761959, and rs2282284) could significantly elevate the risk of NMO. Even though the functional background of the above 4 SNPs has been partly concluded based on previously published studies, certain specific mechanisms still remain vague. The present study would play a valuable part in investigating the etiology of NMO among Asians through identifying the significant association between FCRL3 polymorphisms and the risk of NMO in a Chinese Han population. Nevertheless, further investigations are required to confirm the functional role of FCRL3 polymorphisms on NMO and more guidance for treatments of NMO would thus be provided.

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