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Original article

IRAK1 polymorphisms are associated with susceptibility to neuromyelitis optica spectrum disorder

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ABSTRACT

Background: X chromosome-linked interleukin-1 receptor-associated kinase (*IRAK1*) polymorphisms have been demonstrated to be associated with the risks of several autoimmune diseases, such as systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, and autoimmune thyroid diseases. However, no studies have investigated the association of *IRAK1* polymorphisms with neuromyelitis optica spectrum disorder (NMOSD). This case-control study was performed to determine the correlation between *IRAK1* polymorphisms and the risk of NMOSD.

Methods: Two single nucleotide polymorphisms (SNPs) rs1059703G > A and rs3027898C > A of *IRAK1* were selected and genotyped using SNPscan in a Chinese cohort, including 332 patients with NMOSD and 520 healthy controls. Chi-square tests and logistic regression analyses were used to determine the associations between *IRAK1* polymorphisms and the risk of NMOSD.

Results: Patients with NMOSD showed a lower frequency of the minor allele A of rs1059703 than did controls (Odds ratio [OR] = 0.68; 95% confidence intervals [CI], 0.52–0.88; P^{corr} = 0.007). Compared with wild genotype GG of rs1059703, homozygous mutation AA and heterozygous mutation GA were significantly associated with the decreased risk of NMOSD after adjusting for sex and age (adjusted OR = 0.64; 95%CI, 0.49–0.84; P^{corr} = 0.002). Similar associations were also observed for *IRAK1* rs3027898C > A. Stratification analysis according to sex revealed that the significantly different allele distributions of the two SNPs were mainly found in females. However, *IRAK1* polymorphisms were not correlated with aquaporin-4-IgG, onset symptoms, or age at onset.

Conclusions: This study is first to demonstrate that X-chromosome-linked *IRAK1* polymorphisms are associated with the risk of NMOSD and provide novel insights into the underlying mechanisms of this disease. Further studies are needed to elucidate the function of *IRAK1* variants in the pathogenesis of NMOSD and the underlying molecular mechanisms.

NMOSD: neuromyelitis optica spectrum disorder;
IRAK1: interleukin-1 receptor-associated kinase;
SNP: single nucleotide polymorphism;
SLE: systemic lupus erythematosus;
SSc: systemic sclerosis (SSc);
RA: rheumatoid arthritis;
AITD: autoimmune thyroid diseases;
AQP4: aquaporin-4;
FCRL3: Fc receptor-like protein 3;
STAT4: signal transducer and activator of transcription 4;
TNFSF4: tumor necrosis factor ligand superfamily member 4;
HWE: Hardy-Weinberg equilibrium (HWE);
LD: linkage disequilibrium;
TLR: toll-like receptor.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory demyelinating central nervous system (CNS) disease that usually results in severe visual impairment and lower limb disability (Wingerchuk et al., 2015). Serum antibodies specifically against aquaporin-4 (AQP4) are found in most patients with NMOSD and are involved in the pathogenesis of NMOSD (Lennon et al., 2004), and AQP4-IgG and complement-dependent cytotoxicity orchestrate astrocyte

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death and demyelination in patients with NMOSD. Dysregulation of immunomodulatory genes, including *FCRL3, CD40, CD58, STAT4,* and *TNFSF4,* could induce the onset of NMOSD, as well as other types of autoimmune diseases (Wang et al., 2016; Shi et al., 2017a,b; Liu et al., 2017; Lian et al., 2017), and 10–40% of NMOSD patients are found to suffer from systemic lupus erythematosus (SLE), Sjögren syndrome (SS), and autoimmune thyroid diseases (AITDs) (Wingerchuk et al., 2007). These findings suggest that multigene dysregulation is implicated in autoimmune diseases.

Most of the autoimmune diseases are more common in women, probably because of hormonal and genetic factors. Similar to other autoimmune diseases, NMOSD is predominantly observed in females, with 5–9 times higher incidence in females than in males (Drori and Chapman, 2014; Flanagan et al., 2016; Houzen et al., 2017). The interleukin-1 receptor-associated kinase (*IRAK1*) gene is located on the X chromosome and encodes a serine/threonine protein kinase, which plays a pivotal role in the Toll/IL-1 receptor (TIR) signalling pathway via the upregulation of transcription factor NF-κB and induction of inflammation (Rao et al., 2005). Single nucleotide polymorphisms (SNPs) rs3027898C > A and rs1059703G > A of *IRAK1* have been demonstrated to be associated with increased risks of many autoimmune diseases, including SLE, systemic sclerosis (SSc), rheumatoid arthritis (RA), and AITDs (Kaufman et al., 2013; Netea et al., 2012; Song et al., 2015; Chatzikyriakidou et al., 2010). According to the distributions of *IRAK1* alleles in different populations, the frequencies of rs3027898 ($C = 0.80$) and rs1059703 ($G = 0.79$) were are significantly higher in the East Asian population than in the Europe population ($C = 0.18$ and $G = 0.16$, respectively) (data from the 1000Genomes, https://www.ncbi.nlm.nih.gov/snp /rs3027898#frequency_tab). Notably, there is a higher prevalence of NMOSD in the Asian populations than in the Caucasian population (Mori et al., 2018). The findings suggest the association of IRAK1 polymorphisms with NMOSD. In this case-control study, we determined whether the variants of *IRAK1* (rs3027898 and rs1059703) are associated with susceptibility to NMOSD in a Chinese cohort.

2. Participants and methods

2.1. Participants

A total of 332 Chinese patients with established NMOSD (296 females and 36 males) and 520 Chinese healthy controls (HCs) (400 females and 120 males) were consecutively recruited between September 2014 and June 2017 at the Neurology Department of West China Hospital. All participants were Han Chinese from the Southwest China. All patients met the latest diagnosis criteria of NMOSD (2015) (Mori et al., 2018), and all HCs had no autoimmune diseases, tumors, nervous system diseases, or any other common systemic diseases. Demographics and clinical characteristics, including sex, age, age at onset, onset symptoms, and serum AQP4-IgG status (cell-based assay) (Jarius et al., 2010), were recorded for each case. This study was approved by the Medical Ethics Committee of West China Hospital, Sichuan University and was performed in accordance with the ethical standards of the Declaration of Helsinki. All participants provided informed consent prior to their inclusion in this study.

2.2. SNP selection and genotyping

The blood sample was collected from each participant, and genomic DNA was extracted and purified using the AxyPrep Blood Genomic DNA Midi-prep Kit 25-prep (AxyGen, Shanghai, China) and was stored at −20 °C until genotyping (Shi et al., 2017b). Two common functional polymorphisms in *IRAK1*, including rs1059703 G/A located in exon 12 (a nonsynonymous mutation, p. Ser532Leu) and rs3027898 C/A located in the 3′ flanking region, were selected for genotyping based on previously reported associations with SLE, SSc, and AITD. Genotyping was conducted using SNPscan kit (Genesky Biotechnologies Inc. Shanghai, China), as described in previous study (Chen et al., 2012). Several random samples accounting for ~5% ($n = 68$) of the total DNA samples were directly sequenced to confirm the genotyping results using the Big Dye-terminator version 3.1 cycle sequencing kit and an ABI3730XL automated sequencer (Applied Biosystems, Carlsbad, CA, USA). The genotypes of the repeated sequencing samples were completely identical to those of the first sequencing results. Quality control analysis was performed so that only SNPs and samples that passed the 95% quality control threshold were subjected to further statistical analysis. All genotype call rates were manually recorded, and conflicting results were liberally re-genotyped by sequencing.

2.3. Statistical analysis

Demographic and clinical data are showed as mean ± standard deviation (SD), and frequencies are presented as number and percentages. Differences in sex and age between patients with NMOSD and controls were analysed using Pearson's chi-square test and Student's *t*-test, respectively. Given that *IRAK1* is located on the X chromosome, Hardy-Weinberg equilibrium (HWE) was determined in only female participants for the two SNPs by chi-square tests, with *P* values higher than 0.05 indicating no significant deviation in allele or genotype distribution among participants (Song et al., 2015). Chi-square tests and logistic regression analyses were conducted for comparing alleles and genotypes of the two SNPs, respectively. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess the risk of NMOSD. Sex and age were adjusted by logistic regression analysis. Stratification analysis of sex and association analysis of clinical characteristics with *IRAK1* variants were further conducted using chi-square test. Student *t*-test and one-way ANOVA were used for comparing continuous variable between groups. PLINK v1.07 was used for association analysis of SNPs with NMOSD. *IRAK1* linkage disequilibrium (LD) patterns ($r^2 > 0.8$ means strong linkage) were analyzed with SHEsis software (http://analysis.bio-x.cn/myAnalysis.php) (Shi and He., 2005). Other statistical analyses were performed using SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). The multiple comparison correction was conducted using Bonferroni correction. A *P* value of < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics

Demographics and clinical characteristics of all participants are summarised in Table 1. A total of 332 patients with NMOSD (296 females, 89%) and 520 HCs (400 females, 80%) were investigated (sex, $P < 0.001$). The average age of NMOSD patients was 44.36 ± 12.78 years, and that of HCs was 41.97 ± 11.71 years ($P = 0.005$). The mean onset age of NMOSD was 38.64 ± 13.32 years, and 287 (89%) patients with NMOSD had serum AQP4-IgG.

Table 1
Demographics and clinical characteristics of participants.

	NMOSD $n = 332$	Controls $n = 520$	*P* values
Sex, no. (%) of females	296/332 (89)	400/520 (77)	< 0.001
Age, y (mean ± SD)	44.36 ± 12.78	41.97 ± 11.71	0.005
Age at onset, y (mean ± SD)	38.64 ± 13.32	NA	NA
AQP4-IgG, no. (%) of patients[a]	287/324(89)	NA	NA
Onset symptoms, no. (%) of patients[b]			
Optic neuritis	103/316(33)	NA	NA
Acute myelitis	137/316(43)	NA	NA
Brain attacks	32/316(10)	NA	NA
Mix attacks	44/316(14)	NA	NA

SD, standard deviation; NA, not applicable; [a] Data on AQP4-IgG were available for 324 patients; [b] Data on onset symptoms were available for 316 patients. Brain attacks include brainstem and brain attacks.

Table 2
Logistic regression analysis of associations between *IRAK1* rs1059703 or rs3027898 and the risk of NMOSD.

		Controls (n = 520)	NMOSD (n = 332)	OR(95%CI)	P values	Adjusted OR (95%CI)	P^{corr} values	
rs1059703								
Alleles	A	208(23)	104(17)	0.68(0.52–0.88)	0.004			0.007
	G	712(77)	524(83)					
Genotypes[a]	AA	47(9)	9(3)	0.67(0.51–0.87)	0.003	0.64(0.49–0.84)		0.002
	GA	141(27)	89(27)					
	GG	332(64)	234(70)					
rs3027898								
Alleles	A	201(22)	100(16)	0.68(0.52–0.88)	0.004			0.008
	G	719(78)	529(84)					
Genotypes[a]	AA	43(8)	10(3)	0.66(0.51–0.87)	0.003	0.63(0.48–0.84)		0.002
	CA	142(27)	83(25)					
	CC	335(64)	239(72)					

HC, healthy controls; NMOSD, neuromyelitis optica spectrum disorders; aadditive model, AA vs GA vs GG; OR: Odds ratios; CI: confidence intervals; Adjusted OR, data was adjusted for gender and age; P^{corr}, corrected P values by Bonferroni correction.

Table 3
Stratification analysis of associations of *IRAK1* rs1059703 or rs3027898 with the risk of NMOSD according to sex.

	Alleles	HC	NMOSD	OR (95%CI)	P values	P^{corr} values
Females						
rs1059703 G > A	A	181 (0.23)	101 (0.17)	0.70 (0.54–0.92)	0.011	0.022
	G	619 (0.77)	491 (0.83)			
rs3027898 C > A	A	174 (0.22)	97 (0.16)	0.71(0.54–0.93)	0.012	0.024
	C	626 (0.78)	495 (0.84)			
Males						
rs1059703 G > A[a]	A	27 (0.23)	3 (0.08)	0.31 (0.09–1.10)	0.058	NA
	G	93 (0.77)	33 (0.92)			

HC, healthy controls; NMOSD, neuromyelitis optica spectrum disorders; OR: Odds ratios; CI: confidence intervals; P^{corr}, corrected P values by Bonferroni correction. [a]Because there was a complete linkage between rs1059703 and rs3027898 in males (r^2 = 1), only allele distributions of rs1059703 were presented. NA, not applicable.

3.2. SNP genotyping and LD

The call rates of rs1059703 and rs3027898 were 99.6% and 99.7%, respectively. Genotype and allele frequency distributions in female controls and patients with NMOSD were in HWE for rs1059703 (P = 0.89 and P = 0.28, respectively) and rs3027898 (P = 0.39 and P = 0.69, respectively). We further calculated LDs for the two SNPs using D' and r^2 values and found that variants rs1059703 and rs3027898 exhibited a strong linkage (female participants: D' = 0.99, r^2 = 0.93; male participants: D' = 1.0, r^2 = 1.0).

3.3. Associations of IRAK1 rs1059703 or rs3027898 with the risk of NMOSD

The distributions of alleles and genotypes of *IRAK1* rs1059703 and rs3027898 polymorphisms in patients and controls are shown in Table 2. Patients with NMOSD showed significantly lower frequencies of rs1059703 A allele (17%) than did controls (23%) (OR = 0.68; 95%CI, 0.52–0.88; P = 0.004, P^{corr} = 0.007). Logistic regression analysis revealed that the homozygous AA genotype and heterozygous GA genotype of rs1059703 were associated with a lower risk of NMOSD compared with the wild GG genotype (OR = 0.67; 95%CI, 0.51–0.87; P = 0.003). Importantly, this association remained significant after adjusting for sex and age (adjusted OR = 0.64; 95%CI, 0.49–0.84; P^{corr} = 0.002). Similarly, rs3027898 also showed obviously different distributions of alleles and genotypes between female patients with NMOSD and healthy controls (Table 2).

3.4. Stratification analysis of associations of IRAK1 rs1059703 or rs3027898 with the risk of NMOSD according to sex

Because *IRAK1* is located on the X chromosome, its genetic models might be affected by X-inactivation (dosage compensation effect). Therefore, we further analysed the associations of the allele distributions of *IRAK1* rs1059703 and rs3027898 with the risk of NMOSD in females and males separately. Among females, patients with NMOSD showed significantly lower frequencies of rs1059703 A allele (0.17) than did healthy controls (0.23), suggesting that A allele is associated with a decreased risk of NMOSD (OR = 0.70; 95%CI, 0.54–0.92; P = 0.011, P^{corr} = 0.022). Similar results were observed for rs3027898. In males, the rs1059703 A allele was more common in healthy controls than in patients with NMOSD (0.23 vs 0.08), while the G allele was more frequent in patients with NMOSD (0.92 vs 0.77) than in healthy controls (Table 3). However, the allele distributions of rs1059703 did not differ between patients with NMOSD and healthy controls, possibly because of the relatively small sample size of male patients with NMOSD.

3.5. Stratification analysis of IRAK1 polymorphisms according to clinical characteristics of female patients with NMOSD

To investigate the relationship between *IRAK1* polymorphisms and clinical characteristics of NMOSD, we further analysed serum AQP4-IgG levels, onset symptoms, and age at onset based on genotypes of rs1059703 and rs3027898. Given that the majority of NMOSD patients in this study were female, we further performed the subgroup analysis of clinical characteristics in female patients. Notably, the genotypes of the two SNPs were not associated with AQP4-IgG, onset symptoms, or age at onset in female patients (Table 4).

4. Discussion

NMOSD is an autoimmune disease of the CNS with complex pathogenesis, and the exact aetiology remains unknown. Genetic factors have been demonstrated to be involved in the development of NMOSD. Although there is a remarkably sex-biased difference in the risk of NMOSD, no sex-linked genes related to the development of this disease

Table 4
Association *of* ***IRAK1*** *rs1059703 and rs3027898 with* clinical characteristics of female patients with NMOSD.

Clinical characteristics	rs1059703				rs3027898			
	AA	GA	GG	*P* values	AA	CA	CC	*P* values
AQP4-IgG, n								
positive	4(2)	78(30)	177(68)	0.289	5(2)	72(28)	182(70)	0.376
negative	2(7)	8(28)	19(65)		2(7)	8(28)	19(65)	
Onset symptoms, n								
Optic neuritis	1(1)	31(33)	63(66)	0.562	1(1)	29(31)	65(68)	0.387
Acute myelitis	4(3)	36(30)	81(67)		5(4)	33(27)	83(69)	
Brain attacks	0(0)	7(25)	21(75)		0(0)	7(23)	23(77)	
Mix attacks	0(0)	10(27)	27(73)		0(0)	9(24)	28(76)	
Age at onset,								
Mean ± SD, years	42.31 ± 15.98	39.48 ± 12.50	37.06 ± 13.09	0.271	39.61 ± 15.76	40.15 ± 12.17	36.92 ± 13.31	0.168

have been identified. This study investigated the association of *IRAK1* polymorphisms located on the X chromosome with the risk of NMOSD, and significant differences in distributions of genotypes and alleles were found between patients with NMOSD and controls. The chi-square test and logistic regression analysis showed that the minor allele A of rs1059703 conferred protective effects against NMOSD, while the major allele G of rs1059703 was associated with an increased risk of NMOSD. The stratification analysis according to sex showed that this significant difference was mainly found in females. A similar association was also observed for *IRAK1* rs3027898 C > A. However, there was no significant association between *IRAK1* SNPs and clinical characteristics of NMOSD. To the best of our knowledge, this study is the first to demonstrate that *IRAK1* polymorphisms are associated with the risk of NMOSD, and the findings provide some insights into the underlying molecular mechanisms of NMOSD and help identify potential therapeutic targets.

IRAK1 plays pivotal roles in numerous inflammatory diseases via the toll-like receptor (TLR) signalling pathway and activation of the transcription factor NF-κB. IRAK1is phosphorylated by TLR ligand stimulation and then promotes NF-κB activation, which subsequently enhances the expression of IL-6, tumour necrosis factor (TNF)-α, and IL-8 (Akira and Takeda, 2004; Dunne and O'Neill, 2003; Shaker et al., 2018). In contrast, overexpression of IRAK1 suppresses NF-κB activation and blocks IL-1β-induced IL-6 and TNF-α production in multiple cellular systems (Rao et al., 2005). A previous study indicated that interleukin-2 increased AQP4-IgG production through Toll-like receptor (TLR) signaling pathways (by plus TLR stimulation) (Wilson et al., 2018). In addition, AQP4-IgG-mediated cellular damage, released mitochondrial DNA and elicited innate immune cascades via TLR9 (Yamashita et al., 2018). A recent study reported that astrocyte-derived IL-15 could protect against NMO pathology via NF-κB signaling (Li et al., 2018). In addition, IRAK1 accelerates polarisation of naïve $CD4^+$ *T* cells toward Th17 cells, and IRAK1 inhibition significantly decreases Th17 differentiation and IL-17A production, which is closely associated with the immune response of NMOSD (Sagan et al., 2016; Dos et al., 2016; Zhou et al., 2018). Notably, miR-146a negatively regulates the TLR2/IRAK1 signalling pathway, thus enhancing demyelination in the model of experimental autoimmune encephalomyelitis (EAE) (Zhang et al., 2019). These findings suggest that IRAK1 may be implicated in the pathogenic mechanisms of NMOSD through the TLR signalling and NF-κB signalling pathways.

A large number of studies have demonstrated that *IRAK1* polymorphisms (including rs3027898 and rs1059703) are associated with susceptibility to multiple autoimmune diseases, such as RA, SLE, and AITD (Chatzikyriakidou et al., 2010; Zhai et al., 2013; Kaufman et al., 2013; Zhang et al., 2015; Song et al., 2015), and the major allele C of *IRAK1* rs3027898 is related to an increased risk of RA in Asian, European, and African populations (Shaker et al., 2018; Yang et al., 2017; Khalifa et al., 2017). In this study, we found that the functional SNP rs1059703 (Ser532Leu) of *IRAK1*, which leads to an amino acid change from leucine to serine at position 532, was associated with protection against NMOSD. In other words, the minor allele A of rs1059703 (mutated type) was related to a reduced susceptibility to NMOSD, while the major allele G (wild type) increased the risk of this disease. Similar consequences were also observed for SNP rs3027898 located in the 3′ flanking region of *IRAK1,* which has a strong linkage with rs1059703. The findings indicate an association of IRAK1 polymorphisms with susceptibility to NMOSD. Notably, most of the autoimmune diseases related to *IRAK1* polymorphisms, including NMOSD, RA, and SLE, are significantly more common in females. In this study, we also found significantly different distributions of rs3027898 and rs1059703 genotypes and alleles in female populations, and the findings are supported by those in previous studies (Shaker et al., 2018; Khalifa et al., 2017). The present findings might partly explain the prevalence of NMOSD in females.

Although the exact clinical significance of *IRAK1* SNPs remains unclear, increasing studies have attempted to explore functions of these variants in IRAK1 expression. Previous studies found that the variant of rs1059703 in *IRAK1* was associated with NF-κB activation and inflammatory responses (Liu et al., 2007), and the AA genotype of rs3027898 was associated with significant down-regulation of *IRAK1* mRNA levels (Vreca et al., 2018); in addition, *IRAK1* rs1059703 and rs3027898 variants were related to expression levels of serum TNF-α and IL-6 (Degirmenci et al., 2019). These findings suggest that IRAK1 variants may affect the expression levels of related inflammatory cytokines through altering gene expression, thereby affecting the risk of autoimmune diseases. Therefore, further studies are needed to investigate the roles of IRAK1 gene variants in altered protein expressions and increased risks of NMOSD.

There are some limitations in our study. First, the small sample size of male patients may reduce the statistical power; thus, further studies including more male participants are needed to identify the role of *IRAK1* variants in male patients with NMOSD. Second, this single-centre study included only Chinese patients with NMOSD; thus, the correlation between *IRAK1* variants and the risk of NMOSD should be further evaluated in other populations. Third, we genotyped two SNPs of *IRAK1* but did not sequence IRAK1, probably leading to the overlooking of other potential functional variants. Fourth, the functional roles of the two SNPs in the pathogenesis of NMOSD were not evaluated in this study but should be determined in future studies.

5. Conclusions

Our study is the first to demonstrate that *IRAK1* is associated with the risk of NMOSD, and the findings provide some insights into the underlying mechanisms of this disease. Further studies are needed to elucidate the function of the *IRAK1* variants in the pathogenesis of NMOSD and the underlying molecular mechanisms.

Data statement

Prof. Hongyu Zhou and Dr. Ziyan Shi had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Individual participant data that underlie

the results reported in this article (text, tables, and figures) will be available and in particular shared following publication.

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Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.101438.

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