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The *GTF2I* rs117026326 polymorphism is associated with neuromyelitis optica spectrum disorder but not with multiple sclerosis in a Northern Han Chinese population

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ABSTRACT

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are common demyelinating disorders of the central nervous system. The etiology and pathogenesis of MS and NMOSD remain unclear. The pathogenesis of these two diseases involves a genetic predisposition as well as environmental factors. NMOSD sometimes co-exists with Sjögren's syndrome, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA), and these diseases are frequently associated with central nervous system disorder involvement, as manifest in MS- and NMOSD-like clinical features. Genetic variant rs117026326 upstream of the general transcription factor II-I (*GTF2I*) has been associated with primary Sjögren's syndrome, SLE and RA in East Asian populations. In this study, we genotyped single nucleotide rs117026326 polymorphisms of the *GTF2I* gene in 168 patients with MS, 144 patients with NMOSD, and 1403 healthy controls. We observed a significant genetic association between the variant rs117026326 and NMOSD ($P = 1.09 \times 10^{-11}$, OR = 2.535), however, the association with MS was not significant ($P = .4289$, OR = 1.129). Gene expression analyses showed that there was no significant association between the messenger RNA expression of *GTF2I* and genotypes at the variant. We conclude that the risk T allele of rs117026326 increases the risk of NMOSD, suggesting that NMOSD and MS may have different genetic risk factors.

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system (CNS) and a common cause of neurological disability in young adults (Compston and Coles, 2008). The prevalence of MS in Asia is lower than that in the Western countries. Although the precise etiology of the disease remains unknown, a genetic predisposition as well as environmental factors are generally considered to be involved in the pathogenesis of MS (Ascherio, 2013; Xie et al., 2015). In the past few years, genome-wide association studies (GWASs) of MS have demonstrated that the human leukocyte antigen (HLA) is the major locus of MS susceptibility; these studies have also provided unequivocal evidence for the association between 110 additional non-HLA candidate genetic variants and susceptibility to the disease (International Multiple Sclerosis Genetics et al., 2013; International Multiple Sclerosis Genetics et al., 2007; Patsopoulos et al., 2011).

Neuromyelitis optica spectrum disorder (NMOSD) is an idiopathic inflammatory disease of the CNS primarily affecting the optic nerves

Abbreviations: MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; *GTF2I*, general transcription factor II-I; pSS, primary Sjögren's syndrome; mRNA, messenger RNA; CNS, central nervous system; GWASs, genome-wide association studies; HLA, human leukocyte antigen; AQP4-IgG, autoantibody that targets aquaporin 4; TFII-I, transcription factor II-I; VEGFR2, vascular endothelial growth factor receptor-2; 7dupASD, 7q microduplication syndrome; ASD, autism spectrum disorder; PBMCs, peripheral blood mononuclear cells; EDSS, Expanded Disability Status Scale; ARR, Annual Recurrence Rate; ANOVA, one-way analysis of variance

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and the spinal cord (Han et al., 2017; Jarius et al., 2014; Wingerchuk et al., 2007). NMOSD has been distinguished from MS following the discovery of an autoantibody that targets aquaporin 4 (AQP4-IgG) (Lennon et al., 2004). The prevalence of NMOSD in the general population ranges from 0.0003% to 0.0044% (Cabrera-Gomez et al., 2009), with some regional and racial differences compared to the occurrence of MS (Wingerchuk et al., 2007). NMOSD is relatively common in non-white populations, particularly in East Asia (Kira, 2008; Wingerchuk et al., 2015). As in MS, genetic and environmental risk factors contribute to the occurrence and development of NMOSD. In previous genetic studies, the frequency of HLA genes such as *HLA-DPB1*0501* (Wang et al., 2011), *HLA-DRB1*10* (Blanco et al., 2011), and *HLA-DRB1*03* (Brum et al., 2010; Deschamps et al., 2011) correlated with the risk of NMOSD. In non-HLA genetic study series, risk polymorphisms such as *CD6 TNFRSFIA* (Park et al., 2013), *CD58* (Kim et al., 2014), *AQP4* (Ogasawara et al., 2016; Park et al., 2014), *CYP7A1* (Kim et al., 2010; Zhao et al., 2013; Zhuang et al., 2015), *IL17* (Wang et al., 2012), *IL2RA* (Ainiding et al., 2014; Dai et al., 2013), *ATG5* (Cai et al., 2014), and *FCRL3* (Wang et al., 2016) were found to confer susceptibility to NMOSD. However, compared to MS, there have been fewer studies on only the genetics of NMOSD.

GTF2I encodes the transcription factor II-I (TFII-I), and is located closely on chromosome 7 of humans. TFII-I exhibits the α, β, γ, and δ alternatively spliced isoforms in humans. As a signal induced transcription factor, TFII-I plays a crucial role in the transcriptional regulation of the vascular endothelial growth factor receptor-2 (VEGFR2), and participates in the regulation of triggering of the B cell receptor and T cell receptor (Roy, 2017). Previous studies have suggested that the gene copy number variations are implicated in Williams-Beuren syndrome (Enkhmandakh et al., 2009; Sanders et al., 2011) and 7q microduplication syndrome (7dupASD, ASD, autism spectrum disorder) (Sanders et al., 2011). Several recent GWASs have revealed that *GTF2I* rs117026326 is involved in three autoimmune diseases: primary Sjögren's syndrome (pSS) (Li et al., 2013), systemic lupus erythematosus (SLE) (Sun et al., 2016) in a Chinese Han population, and rheumatoid arthritis(RA) (Kim et al., 2016) in a Korean population.

Several studies have shown that there is a strong association between NMOSD and other autoimmune diseases, especially pSS and SLE (Adawi et al., 2014). pSS is often associated with the CNS disorders with clinical features of MS or NMOSD (Adawi et al., 2014; Furukawa et al., 2017; Gu et al., 2016; Jayarangaiah et al., 2014), possibly due to common genetic factors predisposing the patient to autoimmunity. The discovery of AQP4-IgG supports the notion that humoral immunity is involved in the pathogenesis of NMOSD. Previous studies have concluded that TFII-I directly or indirectly controls B cell proliferation via regulation of NF-κB (Ashworth and Roy, 2007), however, the association between NMOSD/MS and *GTF2I* variants needs to be further investigated. In this study, we evaluated the frequencies of rs117026326 alleles and genotypes in patients with NMOSD and MS in a Chinese Han population, and analyzed the associated risk of susceptibility to these diseases.

2. Materials and methods

2.1. Subjects

This study included three subject groups: 168 patients with MS, 144 patients with NMOSD, and 1403 control subjects. All subjects were of northern Han Chinese descent. Information about the subjects, including their age, sex, age at disease onset, and duration of the disease is listed in Table 1. All subjects were patients admitted to the Department of Neurology and the Neuroscience Center at The First Hospital of Jilin University between 2015 and 2017. Patients with MS were diagnosed by neurologists according to the revised McDonald criteria (Polman, 2011). Patients with NMOSD met the revised diagnostic criteria for NMOSD (Wingerchuk et al., 2015). A total of 1403 healthy controls were recruited from the staff of the same hospital to be genotyped and compared with the patients as part of a case-control study. All patients and healthy control subjects provided written informed consent, and the study was approved by the ethics committee of The First Hospital of Jilin University, Changchun, China (reference No.2015-249).

Table 1
Clinical profiles of the study subjects.

	NMOSD	MS	Controls
Number of subjects (n)	144	168	1403
Age at medical examination [year, mean (range)]	41.75 (16–71)	38.98 (17–63)	42.13 (15–84)
Sex (male/female)	1/9	22/49	1/9
Age at onset [year, mean (range)]	40.14 (16–68)	35.41 (17–54)	–
Duration [year, mean (range)]	3.2 (0–8)	5.1 (0–14)	–
Anti-AQP4 antibody Positive	84	0	0
Anti- MOG antibody Positive	3	0	0

NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis.

2.2. DNA extraction and genotyping

Genomic DNA samples were extracted using a blood/tissue DNA magnetic bead extraction kit (GeneOn BioTech, Changchun, China), following the manufacturer's instructions. For the selected single nucleotide rs117026326 polymorphisms, designed TaqMan single nucleotide rs117026326 polymorphism genotyping assays were used. The sequences of primers and probes synthesized by Invitrogen Trading Co., Ltd. (Shanghai, China) were as follows: rs117026326, forward primer: CTG TTT TCT GTT TTA GGT TAG TTT GCA; reverse primer: CAA CGC TGT GGA TGA ATT TCA; risk probe: FAM-ACT ATT TTC ATG GGC TGG- MGB; non-risk probe: HEX-ACT ATT TTC ATG GGC CGG-MGB. Genomic DNA from each sample was amplified, and the genotype at rs117026326 for each sample was determined using a TaqMan single nucleotide rs117026326 polymorphism genotyping assay (Thermo Fisher Scientific Inc. Beijing, China) on an Applied Biosystems™ OpenArray™ real-time PCR instrument. In addition to the TaqMan single nucleotide rs117026326 polymorphism genotyping assays, several PCR products were randomly selected and subjected to Sanger sequencing to confirm the results.

2.3. Messenger RNA (mRNA) expression of the GTF2I gene in peripheral blood mononuclear cells (PBMCs)

PBMCs were isolated from peripheral blood of patients with MS (n = 16) and NMOSD (n = 17). Total RNA was extracted with TRIzol (Invitrogen Inc., Carlsbad, CA, USA) according to the manufacturer's instructions. The concentrations of total RNA were determined using NanoDrop (Thermo Fisher Scientific Inc., Wilmington, DE, USA), and cDNA from each sample was synthesized using iScript cDNA Synthesis Kits (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The mRNA expression of *GTF2I* and *GTF2IRD1* in each sample was determined using real-time quantitative reverse transcription PCR and was normalized to the *GAPDH* control.

2.4. Statistical analysis

The Hardy-Weinberg equilibrium was initially determined. Statistical analysis was then performed using Plink, version 1.90 and GraphPad Prism 7.0 software. Multiple models were used to compare the genotype and allele frequencies between patients with NMOSD or MS and controls. The relative risk (estimated as the odds ratios [OR]) and 95% confidence intervals (CI) were calculated. A P-value of less than 0.05 was considered statistically significant.

Table 2
Association of the *GTF2I* rs117026326 polymorphism with NMOSD and anti-AQP4 antibody phenotype.

	N	Genotype			Allele frequency		NMOSD cases vs Controls	Anti-AQP4 + NMOSD vs Controls	Anti-AQP4 - NMOSD vs Controls	Anti-AQP4 + NMOSD vs Anti-AQP4 – NMOSD
							OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
		CC	CT	TT	C	T	*P*-value	*P*-value	*P*-value	*P*-value
Cases	144	57	69	18	0.64	0.36	2.535	2.31	2.288	1
Controls	1403	957	398	48	0.82	0.18	1.09E-11	1.26E-06	1.68E-05	1

The rs117026326 polymorphism was genotyped by direct sequencing of the PCR product amplified with forward primer: CTG TTT TCT GTT TTA GGT TAG TTT GCA; reverse primer: CAA CGC TGT GGA TGA ATT TCA. OR and *P*-value were calculated using a logistic test for the comparison of T allele vs C allele. NMOSD, neuromyelitis optica spectrum disorder.

3. Results

3.1. Single nucleotide rs117026326 polymorphism is associated with NMOSD

The characteristics of the 144 patients and 1403 independent controls included in this study are shown in Table 1. All patients and control subjects in the analysis are self-reported Han Chinese. As shown in Tables 2 and 3, the T allele frequency of rs117026326 in patients with NMOSD (T = 36%) was significantly higher than in patients with MS (T = 18%) and controls (T = 18%). A single-marker association was performed using logistic regression. We observed a significant association between variant rs117026326 and NMOSD ($P = 1.09 \times 10^{-11}$, OR = 2.535) in our cohort. The results demonstrate a significant association between the genetic variant at the *GTF2I* locus and NMOSD in Chinese Han patients and suggest an important role of the *GTF2I* locus in the pathogenesis of NMOSD. The T allele of rs117026326 increases risk for NMOSD. In order to find the associations between the T allele of rs117026326 and clinical characteristics of NMOSD, we further explored the relationship of the T allele of rs117026326 with Expanded Disability Status Scale (EDSS) scores and Annual Recurrence Rate (ARR) in NMOSD using one-way analysis of variance (ANOVA). Our results ($P_{EDSS} = 0.4203$, $P_{ARR} = 0.6314$) showed that the T allele of rs117026326 had no significant correlation with the EDSS scores and ARR (see Figs. 2 and 3). Further functional studies are needed for a better understanding of the underlying molecular mechanisms.

3.2. The rs117026326 variant does not affect the risk for MS

To assess whether the rs117026326 variant carries a risk for MS, we genotyped the variant in 168 patients with MS and matched population controls. Further assessments of allele frequencies of the variants in patients with MS and control subjects revealed that the minor allele frequency of the variant was 18% in patients with MS and 18% in controls (Table 3). A genetic association test, adjusted for age and gender, was performed using logistic regression with multiple models. We did not detect a significant association between the variant and MS ($P = .4289$, OR = 1.129).

Table 3
Association of the *GTF2I* rs117026326 polymorphism with MS.

	N	Genotype			Allele frequency		OR (95% CI)	*P*-value
		CC	CT	TT	C	T		
Cases	168	110	55	3	0.82	0.18	1.129	0.4289
Controls	1403	957	398	48	0.82	0.18		

The rs117026326 polymorphism was genotyped by direct sequencing of the PCR product amplified with forward primer: CTG TTT TCT GTT TTA GGT TAG TTT GCA; reverse primer: CAA CGC TGT GGA TGA ATT TCA. OR and *P*-value were calculated using the logistic test for the comparison of T allele vs C allele. MS, multiple sclerosis.

3.3. Genetic variant rs117026326 does not influence mRNA expression of GTF2I and neighboring genes GTF2IRD1 in PBMCs from patients

Previous studies showed no significant associations between the genotypes of the variant rs117026326 and *GTF2I* expression in Sjögren's syndrome, SLE, and RA. To evaluate the expression level of *GTF2I* and the neighboring genes, *GTF2IRD1,* we determined the expression of *GTF2I* and *GTF2IRD1* in circulating leucocytes of 16 patients with MS and 17 patients with NMOSD. In line with published gene expression data, we did not detect correlations between the genotypes of the variant and mRNA expression of the *GTF2I* and *GTF2IRD1* genes (see Fig. 1).

4. Discussion

The first GWAS for pSS in Han Chinese recently reported that the *GTF2I* rs117026326 C/T polymorphism is the locus indicating the strongest susceptibility to the disease, with the T allele being the risk allele ($P = 1.31 \times 10^{-53}$, OR 2.20) for pSS (Li et al., 2013). Since SLE and pSS have a close clinical relationship and a shared pathophysiology, further studies have been carried out. Celi Sun and his colleagues confirmed that *GTF2I* rs733666469 polymorphism increases the risk of SLE in a study in six East Asian cohorts with 4478 SLE cases and 12,656 controls (Sun et al., 2016). A later study confirmed that the *GTF2I* polymorphism is associated with the pathogenesis of RA in Asian cohorts (Kim et al., 2016). Another replication study in Chinese patients with pSS showed that this polymorphism is associated only with anti-SSA-positive but not anti-SSA-negative pSS (Zheng et al., 2015). In the current study, we found that the frequency of the risk T allele of *GTF2I* rs117026326 was significantly increased in patients with NMOSD, but not in those with MS.

TFII-I encoded by *GTF2I* is an essential gene in mice, and it has been reported to be involved in the regulation of T and B cell activation by deregulation of *VEGFR2* gene in previous studies (Makeyev and Bayarsaihan, 2009; Ren et al., 2011; Roy, 2017). TFII-I controls B cell proliferation via regulating NF-κB, although the precise mechanism underlying these processes is not clear (Ashworth and Roy, 2007). Dysregulation of B cells may affect NMOSD disease activity via antigen presentation, proinflammatory and anti-inflammatory cytokine production, and immunoglobulin production. Potential mechanisms include the expansion of AQP4-specific plasmablast clones, failure to eliminate autoreactive B cell subsets, insufficient antigen-specific regulatory B cells, and/or the loss of anergic maintenance (Bennett et al., 2015; Fan et al., 2016). In this study, we found that the rs117026326 polymorphism is associated with NMOSD; however, the mechanism remains unclear and needs to be elucidated in future studies. EDSS scores represent the severity of NMOSD, and ARR can be used as a disease feature to evaluate disease status. Our results showed that the T allele of rs117026326 had no significant correlation with EDSS scores

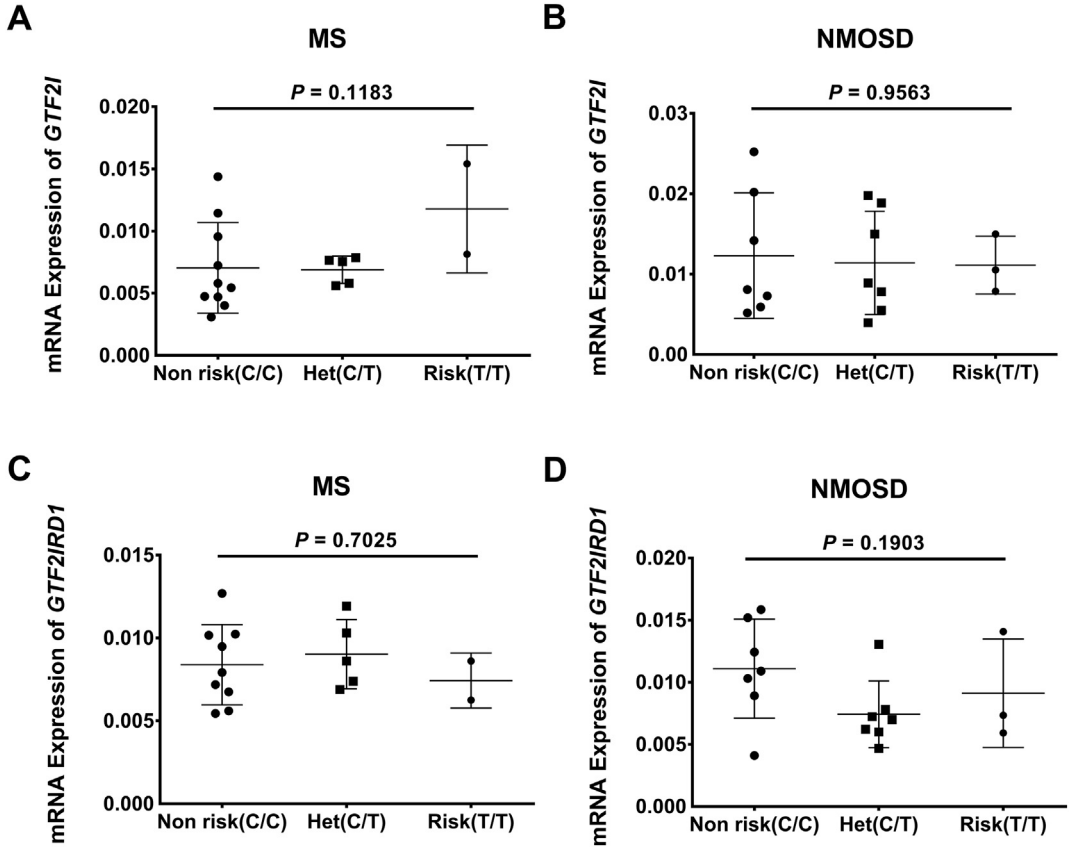

Fig. 1. Effect of rs117026326 polymorphism on mRNA expression of the *GTF2I* gene in PBMCs from patients with MS and NMOSD. Total RNA was isolated from the PBMCs from patients with MS and NMOSD. The mRNA expression of *GTF2I* and *GTF2IRD1* in each sample was determined using real-time quantitative reverse transcription PCR and was normalized to the GAPDH control. On the X-axis, the three different genotypes for SNP rs117026326 are displayed corresponding to homozygote non-risk, heterozygote risk, and homozygote risk of the variant. The Y-axis depicts the level of mRNA expression for the *GTF2I* gene. Each dot represents the expression level of *GTF2I* for one individual. All samples were stratified according to their genotype at the rs117026326 variant. *P*-values were calculated using one-way analysis of variance (ANOVA).
NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis.

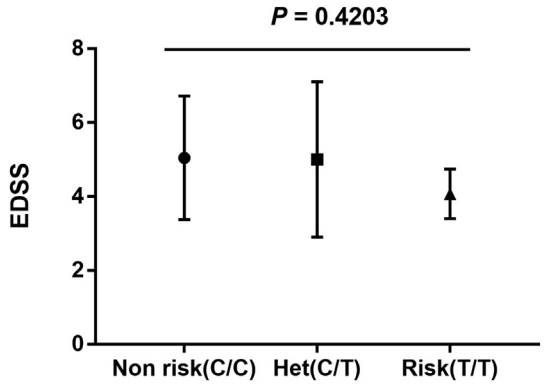

Fig. 2. The relationship between rs117026326 and disease severity in patients with NMOSD. EDSS scores were given to the enrolled patients. The X-axis represents different genotypes, the Y-axis represents EDSS scores, and the dot, square and triangle represent EDSS scores of patients with three genotypes, respectively. *P* value is calculated by one-way analysis of variance (ANOVA).

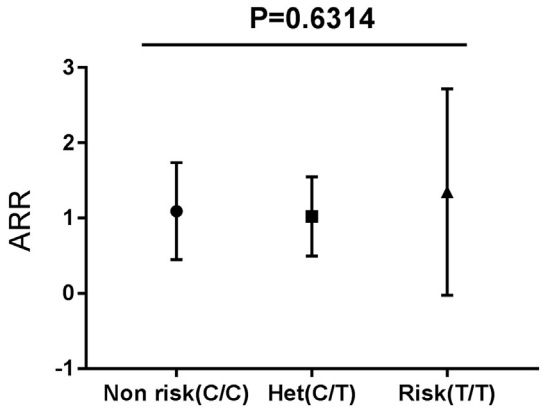

Fig. 3. The relationship between rs117026326 and Annual Recurrence Rate in patients with NMOSD. The Annual Recurrence Rate (ARR) of enrolled patients was calculated and one-way analysis of variance (ANOVA) was used for analysis. The X-axis represents different genotypes, the Y-axis represents ARR, and the dot, square and triangle represent EDSS scores of patients with three genotypes, respectively.

or ARR. It could be related with a small number of case samples. And more clinical characteristics of patients like total disease duration and spinal cord lesion segments should be considered.

While the small number of case samples is one limitation of our study, we intentionally only recruited patients whose diagnoses were clear, to avoid case ascertainment errors.

In conclusion, our results show that the *GTF2I* rs117026326 polymorphism is associated with NMOSD in Han Chinese, but not with MS. Our findings shed new light on the pathogenesis of NMOSD independent of MS, and suggest that the two diseases may have different genetic risk factors.

Disclosures

The authors declare that there are no conflicts of interest related to the work described in this manuscript.

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