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ORIGINAL RESEARCH

The Association of *IL7R* rs6897932 with Risk of Multiple Sclerosis in Southern Chinese

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Objective: To investigate the association between *IL7R* rs6897932 and multiple sclerosis (MS) in southern Chinese people.

Methods: In total, 147 MS patients and 530 healthy controls were recruited according to the revised McDonald criteria. The TaqMan method was used for genotyping.

Results: With genetic models, we can observe that the additive model, the dominant model, and the recessive model of *IL7R* rs6897932 were significantly associated with MS [additive model: p=0.032; dominant model (adjusted): p<0.001, OR=3.61 (95% CI 2.25–5.83); recessive model (adjusted): p<0.001, OR=6.80 (95% CI 3.49–13.89)].

Conclusion: Our results suggest that *IL7R* rs6897932 is associated with MS in a southern Chinese population. More and larger MS studies to explore the genetic risk factors of MS are warranted.

Keywords: single-nucleotide polymorphism, multiple sclerosis, *IL7R*, interleukin

Introduction

Multiple sclerosis (MS) is a progressive autoimmune-mediated demyelinating disorder of the central nervous system.[1,2] There are four clinical forms of MS: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS).[3] The signs of MS vary from person to person, but mainly include problems with vision, painful spasms, numbness, fatigue, weakness, and cognitive impairment. The prevalence of MS in Asia is much lower than that in Western countries.[4]

The pathogenesis of MS is still unclear. We can observe a genetic predisposition in patients who have MS.[1] With the development of genetics, genome-wide association studies (GWAS) have investigated the susceptible loci of MS. *IL7R* rs6897932 (polymorphism T244I) was reported to be associated with MS. In exon number 6 of the IL7Rα gene, a single-nucleotide polymorphism (SNP) called rs6897932 induces a non-conservative amino acid transition at location 244, in which isoleucine is shifted to threonine 244 (Ile → Thr) (ATC/ACC). This amino acid shift affects the expression product of IL7Rα, which results in variation in the amounts of the membrane-bound isoform and the soluble form. Such modifications are accompanied by the regulation of the interleukin-7 (IL-7) signaling pathway and a direct association of MS with this SNP.[5] Although there have been several studies focusing on the association between *IL7R* rs6897932 and MS in Asian populations, the association between *IL7R* rs6897932 and MS in southern Chinese people is still unknown.[6] In this research, we performed a case–control study, aiming to determine the association between *IL7R* rs6897932 and MS in southern Chinese people.

Methods

Study Population

Data on age, gender, age at onset of the disease, and disease duration were obtained. The inclusion criteria were based on the revised McDonald criteria for MS, which was diagnosed individually by two experienced neurologists specializing in MS (WZ and HL).[7] Patients with clinically isolated syndrome were not included. Patients were not included if they were

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reluctant to participate. All MS patients were admitted into the ward of the Department of Neurology of the Affiliated Changshu Hospital of Xuzhou Medical University from January 1st, 2015 to December 31st, 2019. Healthy controls were recruited from the local community and other volunteers matched for age and gender. Information on family history was also obtained. All patients and healthy controls were fully informed and signed consent forms. This study was approved by the ethics committee of the Affiliated Changshu Hospital of Xuzhou Medical University.

DNA Preparation and Genotyping

The 2 mL peripheral blood samples for DNA extraction were collected from MS patients and healthy controls by well-trained nurses. DNA was extracted using the phenol–chloroform–isopropyl alcohol method. We genotyped *IL7R* rs6897932 with real-time polymer chain reaction using TaqMan assays (assay ID: C__2025977_10; ThermoFisher Scientific, catalog number: 4351379). The TaqMan method is based on quantitative polymer chain reaction. The genotype of each sample was detected automatically using an ABI Prism 7500 sequence detection system (Applied Biosystems).

Statistical Analysis

Statistical analysis was performed with the SAS software package (version 9.4 TS1M2; SAS Institute, Cary, NC). The chi-squared test was used to assess Hardy–Weinberg equilibrium (HWE), genotype, and allele distribution between MS patients and healthy controls. Student's *t*-test was used to compare differences in age, age at onset of the disease, and disease duration between MS patients and healthy controls. The additive model is CC vs CT vs TT; the dominant model is (CT + TT) vs CC; the recessive model is TT vs (CC + CT); the overdominant model is (CC + TT) vs CT. Risk analysis was performed by logistic regression. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated. The Cochran–Armitage trend test (CATT) was used to calculate allele dosage. Genetic power was calculated using Power and Sample Size Calculations software (version 3.1.2).

Results

In all, 147 MS patients and 530 healthy controls were enrolled in this study. There were no significant differences in age or gender between MS patients and healthy controls. Ten (6.80%) of the MS patients had a family history of the disease. The average age at onset (mean±SD) was 32.46±8.99 years old, and the disease duration was 2.87±1.91 years. *IL7R* rs6897932 was in HWE (p=0.936) (Table 1).

With regard to the genetic models, we can observe that the additive model, the dominant model, and the recessive model of *IL7R* rs6897932 were significantly associated with MS [additive model: p=0.032; dominant model (adjusted): p<0.001, OR=3.61 (95% CI 2.25–5.83); recessive model (adjusted): p<0.001, OR=6.80 (95% CI 3.49–13.89)] (Table 2).

Table 1 Demographic Information of Cases and Controls

	Healthy Controls (N=530)	MS Patients (N=147)	*p* Value
Gender, female, n (%)	322 (60.75)	96 (65.31)	0.364
Age (years), mean±SD	35.00±9.13	35.33±8.68	0.483
Age at onset (years), mean±SD	–	32.46±8.99	–
Disease duration (years), mean±SD	–	2.87±1.91	–
Family history, n (%)	–	10 (6.80)	–
Genotype of *IL7R* rs6897932 (CC/CT/TT), n	228/244/58	39/71/37	–

Abbreviation: MS, multiple sclerosis.

Table 2 Association of Models With MS Risk

Comparison	Models	Power	*p* Value	OR	95% CI
MS vs Control	Additive model	–	0.032	–	–
	Dominant model	0.114	<0.001	2.09	1.41–3.16
	Dominant model*	0.160	<0.001	3.61	2.25–5.83
	Recessive model	0.134	<0.001	2.74	1.72–4.33
	Recessive model*	0.211	<0.001	6.80	3.49–13.89
	Overdominant model	0.076	0.627	1.10	0.76–1.58
	Overdominant model*	0.144	0.406	1.18	0.80–1.72

Note: *Adjusted for age and gender.
Abbreviations: CI, confidence interval; MS, multiple sclerosis; OR, odds ratio.

Discussion

To our knowledge, this is the first study demonstrating the association between *IL7R* rs6897932 and MS in a southern Chinese population. We found that the additive model, the dominant model, and the recessive model of *IL7R* rs6897932 were significantly associated with MS.

As a key factor regulating the development of T lymphocytes and homeostasis, IL-7 plays an important role in the pathogenesis of MS. IL-7R, also named CD127, is a pleiotropic receptor for thymic stromal lymphopoietin and IL-7.[8] The interaction between IL-7 and IL-7R is vital for T cells, including the development, survival, proliferation, and maintenance of memory T cells.[9–11] IL-7 also influences the proliferative capacity and cell metabolism.[12,13]

IL7R rs6897932 is also associated with other immune-related disorders, such as atopic dermatitis, type 1 diabetes mellitus, and inhalation allergy.[14] It has been reported that blocking of IL-7R could ameliorate the disease course of MS.[15] The risk allele of *IL7R* rs6897932, "C" allele, could increase the serum concentrations of sIL7R compared with "T" allele carriers.[16] *IL7R* rs6897932 also plays a vital role in T-cell-associated disorders, such as infection with human immunodeficiency virus.[17,18]

A meta-analysis focusing on the association between *IL7R* rs6897932 and the susceptibility to MS reported this association in Europeans rather than Asians.[19] In this meta-analysis, there were three studies relating to Asian populations (two in Iran, one in Japan).[6,20,21] The populations were different between Iran and Japan. Persian people are considered to be Caucasians. Besides, we cannot simply merge the results from Japan with our results because of different allele frequencies. Further research in Chinese populations is warranted.

There are some limitations in our study. First, the number of MS patients recruited in this study is relatively small. MS is a disorder with a low prevalence in China. Therefore, the power of our study is restricted. Further studies are warranted. Secondly, we detected only this locus owing to a limited budget. More loci related to MS should be detected in southern Chinese patients. Thirdly, we did not test the IL-7 level or the IL-7R level in the serum or the cerebrospinal fluid. As an immunological factor, IL-7 is influenced by the use of steroids and immunosuppressants. Many patients had received treatment before being admitted to our hospital, which may have influenced the levels of IL-7 and IL-7R.

Our results suggest that *IL7R* rs6897932 is associated with MS in southern Chinese people. More and larger studies exploring the genetic risk factors of MS are warranted.

Highlights

- The additive model of *IL7R* rs6897932 was associated with MS.
- The dominant model of *IL7R* rs6897932 was associated with MS.
- The recessive model of *IL7R* rs6897932 was associated with MS.

Authors' Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Abbreviations

CATT, Cochran–Armitage trend test; CI, confidence interval; GWAS, genome-wide association study; HWE, Hardy–Weinberg equilibrium; IL, interleukin; MS, multiple sclerosis; OR, odds ratio; PPMS, primary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SNP, single-nucleotide polymorphism; SPMS, secondary progressive multiple sclerosis.

Consent to Participate

Written informed consent was obtained from the participants.

Consent for Publication

The patients signed informed consent regarding the publication of their data and photographs.

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Disclosure

All authors have seen and approved the manuscript. The authors declare that they have no conflict of interest.

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