Inflammation, Vol. 36, No. 2, April 2013 (© 2012)
DOI: 10.1007/s10753-012-9564-0

Association Study of *IFIH1* rs1990760 Polymorphism with Systemic Lupus Erythematosus in a Chinese Population

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Abstract—Systemic lupus erythematosus (SLE) is a complex autoimmune disease arising from the action of multiple genetic and environmental risk factors. The aim of this study was to examine the association of a single-nucleotide polymorphism, rs1990760, of the *interferon induced with helicase C domain 1* (*IFIH1*) gene with SLE in a Chinese population. A total of 877 SLE patients and 978 healthy control subjects were enrolled in the present study. The genotype of the *IFIH1* rs1990760 polymorphism was determined by Sequenom MassARRAY technology. The *IFIH1* rs1990760 T allele was significantly increased in patient group compared with control subjects (T *versus* C, Odds ratio=1.20, 95 % confidence interval=1.02–1.40). However, no significant difference in genotype distribution was found between cases and controls (P=0.07). No significant evidence was detected for the association of the *IFIH1* rs1990760 polymorphism with SLE under neither dominant nor recessive model (TT + TC *versus* CC, P=0.06; TT *versus* TC + CC, P=0.08). We also analyzed the association of the *IFIH1* rs1990760 T allele with clinical features, whereas no significant signal was found. In conclusion, our study represents the first report demonstrating an association of the *IFIH1* rs1990760 polymorphism with SLE susceptibility in a Chinese population.

KEY WORDS: *IFIH1*; polymorphism; systemic lupus erythematosus; chinese population.

INTRODUCTION

Systemic lupus erythematosus (SLE), a complex autoimmune disease arising from the action of multiple genetic and environmental risk factors, is characterized by the production of a wide range of autoantibodies and multiple organ involvement. Viral infection has been speculated to be potential trigger of autoimmune diseases including SLE, and several possible mechanisms have been proposed to explain this connection, including molecular mimicry and by-stander activation [1]. Immune responses to viral infection initiate after the recognition of so-called pathogen-associated molecular patterns by germ line-encoded pattern recognition receptors (PRRs) [2]. These PRRs including Toll-like receptors, C-type lectin receptors, as well as NOD-like receptors and Retinoic acid-inducible gene-I-like receptors (RLRs). The signaling cascades triggered by these receptors eventually result in transcription of type I interferon (IFN-I) and other proinflammatory mediators. However, an inappropriate response of these sensor proteins to self-derived, intracellular nucleic acids might contribute to autoimmunity [3]. During past few years, a common nonsynonymous single-nucleotide polymorphism (SNP) of *interferon induced with helicase C domain 1* (*IFIH1*) has been reported to be significantly associated with susceptibility to multiple autoimmune diseases, indicating virus-induced autoimmunity might be genetically determined [4].

The IFIH1 gene, which is better known as melanoma differentiation-associated gene 5 (*MDA5*) or

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helicard, is located at 2q24.3 and encodes a cytoplasmic dsRNA helicase belonging to the RLR family [5]. Initially, a genome-wide association study (GWAS) of nonsynonymous coding polymorphisms revealed that an alanine to threonine amino acid change at codon 946 of *IFIH1* gene (SNP ID rs1990760) was associated with type 1 diabetes with genome-wide level of significance [6]. This finding was intriguing, providing possible molecular link between the development of this autoimmune disease with viral infection. Accumulating evidence indicates that viral infection is associated with multiple autoimmune diseases [1], and it has become increasingly clear that there might be common genes underlying multiple autoimmune disorders [7]. Thus, subsequently, association of the *IFIH1* rs1990760 polymorphism with SLE has also been investigated [8–11]. It has been demonstrated that the *IFIH1* rs1990760 polymorphism is significantly associated with SLE in populations of European ancestry [8–10]. However, an investigation conducted in Japanese population did not detect significant evidence for the association of the *IFIH1* rs1990760 polymorphism with genetic predisposition to SLE [11]. So far, the role of the *IFIH1* rs1990760 polymorphism in genetic background of SLE has not been evaluated in Chinese population. Thus, the aim of the present study was to examine the association between the *IFIH1* rs1990760 polymorphism and SLE in a Chinese population.

MATERIALS AND METHODS

Patients and Control Subjects

A total of 877 patients with SLE (91 males and 786 females, mean ± SD age 35.80±12.68 years) were recruited from the First Affiliated Hospital of Anhui Medical University and Anhui Provincial Hospital. The diagnosis of SLE was based on the presence of at least four of the 1997 American College of Rheumatology revised criteria [12]. The control group consisted of 978 geographically and ethnicity-matched healthy individuals (307 males and 671 females, mean ± SD age 32.36± 11.57 years). All participants were of self-reported Chinese Han origin. Clinical data including malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, and neurological disorder were obtained through reviewing medical records or by questionnaire. This study was reviewed and approved by the ethics committee of Anhui Medical University. Informed consent was provided by all participants.

DNA Extraction and Genotyping

EDTA anti-coagulated venous blood sample was collected from each subject enrolled in the current investigation. Genomic DNA was extracted from peripheral blood lymphocytes according to the standard procedures. The genotypes of *IFIH1* rs1990760 were determined by Sequenom MassARRAY technology (Sequenom iPLEX assay, San Diego, USA), according to the manufacturer's instructions.

Statistical Analysis

The differences of genotypic and allelic frequencies between patient and control groups were determined by chi-square test. Estimated odds ratios (ORs) and 95 % confidence intervals (95 % CIs) were calculated. Hardy–Weinberg equilibrium was evaluated in control group. Statistical power was calculated by the free-download software—Power and Sample Size Calculation Software (http://biostat.mc.vanderbilt.edu/PowerSampleSize). Statistical analysis was performed by SPSS11.0 software. A two-tailed P value less than 0.05 was considered significant.

RESULTS

The genotype and allele frequencies of the *IFIH1* rs1990760 polymorphism in patients and controls are shown in Table 1. No deviation from HWE was observed in control subjects (P=0.97). The statistical power of the current study to detect a 1.5-fold increased risk at the significance level of 0.05 was >0.99 for the *IFIH1* rs1990760 T allele.

Association of *IFIH1* rs1990760 Polymorphism with Risk of SLE

As shown in Table 1, no significant difference in genotype distribution was found between cases and controls (P=0.07). The *IFIH1* rs1990760 T allele was significantly increased in patient group compared with control subjects (T *versus* C, OR=1.20, 95 % CI=1.02–1.40). We also determined the association of rs1990760 polymorphism with SLE under dominant and recessive model. However, no significant evidence was detected (TT + TC *versus* CC, P=0.06; TT *versus* TC + CC, P=0.08).

Table 1. The distribution of genotype and allele frequencies of the *IFIH1* rs1990760 polymorphism in patients with systemic lupus erythematosus and control subjects

IFIH1 (rs1990760)	Patients *N* (%)	Controls *N* (%)	*P* value	OR (95 % CI)
Genotype				
T/T	46 (5.2)	35 (3.6)	0.07[a]	
T/C	297 (33.9)	306 (31.3)		
C/C	534 (60.9)	637 (65.1)		
Allele				
T	389 (22.2)	376 (19.2)	0.03[b]	1.20 (1.02–1.40)
C	1,365 (77.8)	1,580 (80.8)		reference
Dominant Model				
T/T + T/C	343 (39.1)	341 (34.9)	0.06[b]	1.20 (0.99–1.45)
C/C	534 (60.9)	637 (65.1)		reference
Recessive Model				
T/T	46 (5.2)	35 (3.6)	0.08[b]	1.49 (0.95–2.34)
T/C + C/C	831 (94.8)	943 (96.4)		reference

N number, *OR* odds ratio, *95% CI* 95 % confidence interval
[a] Patients *versus* controls using 3×2 contingency table
[b] Patients *versus* controls using 2×2 contingency table

Association of *IFIH1* rs1990760 Polymorphism with Clinical Features in Patients with SLE

Given that SLE is an extremely heterogeneous disease with highly variable manifestations, a case-only analysis was conducted to examine potential genetic association between the *IFIH1* rs1990760 T allele with specific clinical feature, and the results are summarized in Table 2. When we compared the allele frequency between patients positive and negative for the presence of specific clinical feature, nonsignificant association signal was found.

DISCUSSION

In the present study, we investigated the association between the *IFIH1* rs1990760 polymorphism and SLE in a Chinese population. Our results indicated that the *IFHI1* rs1990760 T allele was significantly associated with the susceptibility to SLE, and the effect size was found to be modest and was similar to the results in European populations (OR=1.20). However, when we performed the association analysis under dominant model and recessive model for the *IFIH1* rs1990760 T allele, no significant association was detected, and this might be due to the relatively small true effect size accounting for the lack of power. The statistical power of the present study to detect a 1.2-fold increased risk at the significance level of 0.05 was only 0.47 and 0.12 for the *IFIH1* rs1990760 T allele under dominant and recessive model, respectively. We also failed to detect any significant association signal for the association between the *IFIH1* rs1990760 T allele and specific clinical feature. Previous studies conducted in populations of European ancestry also showed that the *IFIH1* rs1990760 T allele was significantly associated with SLE susceptibility [8–10]. Notably, the T allele of the *IFIH1* rs1990760 SNP was major allele in European population, which was in contrast to the fact of T allele being minor allele in Chinese population, indicating genetic heterogeneity between European population and Chinese population. Nonetheless, a study performed in Japanese population did not find significant association of the *IFIH1* rs1990760 polymorphism with SLE [11], and this might be due to the small sample size accounting for the lack of statistical power to detect the true association.

The IFIH1 protein is an ubiquitously expressed cytoplasmic sensor of dsRNA, which is comprised of N-terminal caspase recruitment domain (CARD) and C-terminal helicase domain [13]. The transcripts of the IFIH1 gene are relatively higher expressed in immune cells, making it a strong candidate gene for autoimmune diseases. IFIH1 detects cytoplasmatic viral dsRNA,

Table 2. Association analysis of *IFIH1* rs1990760 polymorphism in patients with SLE stratified by clinical features

Clinical features	Positive (Freq)	Negative (Freq)	*P* value[a]	OR (95 % CI)
Malar rash	353 (44.3)	443 (55.7)	0.33	1.13 (0.89–1.43)
Discoid rash	84 (10.6)	712 (89.4)	0.66	0.92 (0.62–1.36)
Photosensitivity	269 (33.8)	527 (66.2)	0.89	1.02 (0.79–1.31)
Oral ulcers	158 (19.8)	638 (80.2)	0.35	0.86 (0.64–1.18)
Arthritis	468 (58.8)	328 (41.2)	0.74	0.96 (0.75–1.22)
Serositis	44 (5.5)	752 (94.5)	0.59	1.15 (0.69–1.91)
Renal disorder	296 (37.2)	500 (62.8)	0.35	1.13 (0.88–1.44)
Neurological disorder	116 (14.6)	680 (85.4)	0.49	1.12 (0.81–1.57)

Freq frequency, *OR* odds ratio, *95% CI* 95 % confidence interval
[a] Comparisons between positive and negative groups by chi-square test of allelic distribution

resulting in production of IFN-I via activation of interferon regulatory factor-3 and nuclear factor kappa-B [5, 14, 15], and this inappropriate activation of these virus-sensitive proteins might have an effect in autoimmunity [3]. A growing body of evidence suggests that dysregulated production of IFN-I, which is reflected in the overexpression of IFN-I–stimulated genes in peripheral blood mononuclear cells (PBMCs), is associated with SLE [16, 17]. In addition, several mouse models have documented a possible role of IFN-I in lupus [18–20]. Recently, Crampton *et al*. [21] generated a transgenic mouse containing multiple copies of *Ifih1*, and their results revealed that MDA5 overexpression could lead to a chronic IFN-I state. When combined with the lupus-susceptible background of the FcγR2B deficiency, MDA5 overexpression accelerated the production of switched autoantibodies, the incidence of glomerulonephritis, and early lethality, suggesting an important role of chronic IFN-I state caused by IFIH1 overexpression in exacerbating an ongoing autoimmune pathology. The *IFIH1* rs1990760 SNP does not reside in either the CARD or the helicase domain of the protein, but it is conserved between mammals and might influence the active domains though effects on tertiary structure [6]. Liu *et al*. found that the *IFIH1* gene expression in PBMCs is significantly associated with the *IFIH1* genotypes [22], whereas other studies did not replicate this result [23, 24]. Recently, Robinson *et al*. [25] found that the *IFIH1* rs1990760 risk allele T was associated with dsDNA Abs, and this risk allele increased sensitivity to IFN-α signaling in patients with anti-dsDNA Abs. Thus, the *IFIH1* rs1990760 T allele might cause the overactivity of the IFN-α pathway, which has been strongly implicated in the pathogenesis of SLE [26].

In conclusion, our study represents the first report demonstrating an association of the *IFIH1* rs1990760 polymorphism with SLE susceptibility in a Chinese population. However, it should be noted that two GWAS in China have not found significant association of this SNP with SLE [27, 28]. Therefore, further studies based on larger sample size and meta-analysis are required to validate this result, and functional studies are also needed to elucidate the mechanism by which the *IFIH1* rs1990760 polymorphism influences genetic susceptibility of SLE.

ACKNOWLEDGMENTS

This work was supported by grants from the key program of National Natural Science Foundation of China (30830089). We wish to thank the patients and healthy control subjects for their cooperation.

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