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BRIEF ARTICLE

RAGE gene three polymorphisms with Crohn's disease susceptibility in Chinese Han population

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Abstract

AIM: To investigate the association of three polymorphisms in the receptor for advanced glycation end product (*RAGE*) gene with Crohn's disease (CD) risk in a Chinese population.

METHODS: A hospital-based case-control association study involving 312 CD patients and 479 healthy controls was conducted. Peripheral blood samples were collected from 791 study subjects, and genomic DNA was extracted. Genotyping was performed using polymerase chain reaction-ligase detection reaction method. The association between polymorphic genotype and CD predisposition was determined using odds ratio and 95% confidence interval (CI). Data were analyzed using Haplo.stats program.

RESULTS: Significant differences were observed between patients and controls in allele/genotype distributions of rs1800624 (P_{allele} = 0.012; $P_{genotype}$ = 0.005) and in allele distributions of rs2070600 (P = 0.02). The risk for CD associated with the rs1800624-A mutant allele decreased by 36% (95%CI: 0.47-0.88, P = 0.005) under the additive model and by 35% (95%CI: 0.46-0.91, P = 0.013) under the dominant model. Carriers of rs2070600-A mutant allele showed a 37% (95%CI: 1.02-1.83, P = 0.036) increased risk of developing CD relative to the GG genotype carriers. In haplotype analysis, haplotype T-A-G (in the order rs1800625, rs1800624, and rs2070600) decreased the odds of CD by 33% (95%CI: 0.49-0.94, P = 0.018).

CONCLUSION: CD is an immune-related disease with genetic predisposition. Genetic defects in the *RAGE* gene are strongly associated with CD in Chinese population.

Key words: Receptor for advanced glycation end product; Polymorphism; Crohn's diseases; Susceptibility; Association study

Core tip: The receptor for advanced glycation end products (RAGE) is a pattern recognition receptor involved in several pathophysiological processes associated with inflammation. Therefore, we considered that *RAGE* gene is a candidate gene susceptible to Crohn's disease (CD). This study is the first to investigate the association of the three most commonly studied polymorphisms in *RAGE* gene with CD risk in a Chinese population. The results suggest that *RAGE* rs1800624 and rs2070600 polymorphisms are associated with CD occurrence. The present findings support the hypothesis that a genetically impaired innate defense immunity system is a predisposing factor in the etiology of CD.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory condition of the gastrointestinal tract that comprises two main subtypes, namely, Cohn's disease (CD) and ulcerative colitis (UC), which have overlapping but distinct clinical and pathological features. Considerable efforts have been devoted to elucidating the etiology and pathogenesis of IBD, but underlying regulatory and molecular mechanisms remain elusive. Epidemiological studies have documented that first-degree relatives of individuals with IBD have approximately 20-fold to 50-fold increased risk of developing the disease compared with the general population for CD and 10-fold to 20-fold increased risk for developing UC[1], suggesting a genetic basis for inheritance of IBD. Genome-wide linkage analyses have identified multiple candidate regions on several chromosomes for IBD. Meanwhile, numerous immunity-related genes have been found to locus on several IBD-susceptibility regions[2-4]. As a result of the importance of immunity in IBD, investigations on IBD-susceptibility genes involved in immunity have increasingly elicited research interest.

The receptor for advanced glycation end products (RAGE) is a member of the immunoglobulin protein family of cell surface molecules[5], and was initially isolated as the receptor of advanced glycation end products (AGEs) that accumulate during diabetes and senescence as a result of nonenzymatic glycation and oxidation of proteins and lipids[6]. RAGE has since been shown to bind a diverse set of ligands in addition to AGEs, including high-mobility group box-1, several members of the S100 protein family and b amyloid peptides, leading to the activation of several proinflammatory signaling pathways[7,8]. Presently, RAGE is a pattern recognition receptor involved in several pathophysiological processes associated with inflammation, such as diabetes complications[9], arthritis[10], systemic lupus erythematosus[11], multiple sclerosis[12], as well as CD[13]. In addition, animal model studies suggest that RAGE has an important function in innate defense mechanisms[14]. Meanwhile, recent studies have discovered nearly 20 naturally occurring RAGE-splicing variants in humans[15-19]. These isoforms are characterized by whole or parts of mRNA transcripts with missing or additional exons/introns or resulting from alternative splicing of the RAGE pre-mRNA and gene expression regulation[19]. Subsequent studies have presented convincing statistical evidence for a novel functional single nucleotide polymorphism, -374T/A, in RAGE being the CD susceptible locus in a German population, but not in an American population[13].

Considering that susceptibility genes in CD vary across different ethnic groups, we performed a hospital-based case-control association study on the three widely evaluated polymorphisms of *RAGE* gene and assessed the association between RAGE haplotypes and CD.

Table 1 Characteristics of Crohn's disease patients and healthy controls in a Chinese Han population

Characteristics	CD patients	Control subjects
Number	312	479
Male/female	205/107	308/171
Age, mean ± SD (yr)	34.0 ± 13.0	36.5 ± 15.1
Age at diagnosis (ys)		
< 17	42	63
17-40	212	324
> 40	58	92
CD behavior		
Inflammatory	179	
Stricturing	90	
Penetrating	43	
CD location		
Ileum	194	
Colon	27	
Ileocolon	91	
Perianal lesions		
Yes	92	
No	220	
Appendectomy		
Yes	18	
No	294	
Abdominal operation		
Yes	72	
No	240	

CD: Crohn's disease.

MATERIALS AND METHODS

Study populations

A hospital-based case-control study was conducted, involving 312 sporadic patients with CD and 479 healthy volunteers. All patients were recruited through the Outpatient Clinic at the Department of Gastroenterology at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine as part of an ongoing project to examine genetic factors that contribute to the etiology of IBD. The demographics in the study population are summarized in Table 1. In this study, 42 patients were diagnosed under 17 years old in the CD group and there were 63 patients in the control group, without statistical difference in the proportion ($P = 0.97$).

Cases and controls were well matched by age and gender. Informed consent was obtained from all participants, and the study was approved by the Institutional Ethics Board of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

Genotyping

Blood samples (1 mL) were collected, and genomic DNA was extracted from white blood cells using TIANamp Blood DNA Kit (Tiangen Biotech Co., Ltd., Beijing, China). Genotyping was conducted by the PCR-ligase detection reactions (LDR) method using ABI 9600 system (Applied Biosystems, United States)[20]. The following cy-

Table 2 Genotype distributions and allele frequencies of the studied polymorphisms in patients and controls, and their risk prediction for Crohn's disease under three genetic models of inheritance

Polymorphism		Patients (n = 312)	Controls (n = 479)	P (χ^2)	Genetic models	OR; 95%CI
rs1800624	TT	248	343		Additive	0.64; 0.47-0.88
	AT	62	123	0.012	Dominant	0.65; 0.46-0.91
	AA	2	13		Recessive	0.23; 0.05-1.03
	A	10.6%	15.6%	0.005		
rs1800625	TT	228	353		Additive	0.98; 0.73-1.33
	CT	82	118	0.460	Dominant	1.03; 0.75-1.42
	CC	2	8		Recessive	0.38; 0.08-1.80
	C	13.8%	14.0%	0.940		
rs2070600	GG	174	303		Additive	1.29; 1.03-1.62
	AG	112	148	0.086	Dominant	1.37; 1.02-1.83
	AA	26	28		Recessive	1.46; 0.84-2.55
	A	26.3%	21.3%	0.022		

OR: Odds ratio.

cling parameters were used: 94 ℃ for 2 min; 35 cycles of 94 ℃ for 20 s; 56 ℃ for 20 s; 72 ℃ for 40 s; and a final extension step at 72 ℃ for 3 min. Two specific probes to discriminate the specific bases and one common probe were synthesized (available upon request). The common probe was labeled at the 3' end with 6-carboxy-fluorescein and phosphorylated at the 5' end. The following reaction conditions of LDR were followed: 94 ℃ for 2 min, 30 cycles of 94 ℃ for 30 s, and 56 ℃ for 3 min. After the reaction, 1 mL of LDR reaction products was mixed with 1 mL of ROX passive reference and 1 mL of loading buffer, denatured at 95 ℃ for 3 min, and chilled rapidly in ice water. The fluorescent products of LDR were differentiated using ABI sequencer 377 (Applied Biosystems, United States).

Statistical analysis

Comparisons between CD patients and controls were conducted using unpaired t test for continuous variables and χ^2 test for categorical variables. To avoid gross genotyping error, all polymorphisms were checked for consistency with Hardy-Weinberg equilibrium on a contingency table of observed-versus-predicted genotype frequencies using Pearson χ^2 test or Fisher's exact test. Genotypes were compared by logistic regression analysis under assumptions of additive, dominant, and recessive models of inheritance. $P < 0.05$ was considered statistically significant. Haplotype frequencies were estimated using the haplo.em program, and odds ratio (ORs) and 95% confidence interval (CI) were estimated using haplo.cc and haplo.glm programs according to a generalized linear model[21]. The haplo.score was used to model an individual's phenotype as a function of each inferred haplotype, which was weighted by their estimated probability to account for haplotype ambiguity. The haplo.em, haplo.glm, and haplo.score were evaluated using haplo.stats software (version 1.4.0) developed using R (http://www.r-project.org/). Study power was estimated using PS Power and Sample Size Calculations software (version 3.0).

RESULTS

Single-locus analysis

No deviations from Hardy-Weinberg equilibrium were found for all studied polymorphisms in the controls ($P > 0.05$). The genotype/allele distributions of the three selected polymorphisms in RAGE are shown in Table 2. Significant differences between CD patients and controls were observed in allele and genotype distributions of rs1800624 ($P_{allele} = 0.012$ and $P_{genotype} = 0.005$) and in allele distributions of rs2070600 ($P = 0.022$).

Notably, for rs1800624, the risk associated with mutant allele or genotype decreased by 36% (95%CI: 0.47-0.88) under the additive model and by 35% (95%CI: 0.46-0.91) under the dominant model. For rs2070600, a significant difference in association with CD under the additive (OR = 1.29; 95%CI: 1.03-1.62) and dominant (OR = 1.37; 95%CI: 1.02-1.83) models was observed. No significant association was detected for rs1800625 under the three genetic models.

Haplotype analysis

Haplotype frequencies of the three polymorphisms examined were estimated and compared between cases and controls (Table 3). The frequency of haplotype T-A-G (in the order rs1800625, rs1800624, and rs2070600) was significantly lower ($P = 0.005$) in patients, whereas the frequency of haplotype T-T-A was significantly higher ($P = 0.027$) in patients compared with the controls. After assigning the most common haplotype T-T-G as the reference, haplotype T-A-G decreased the odds of CD by 33% (95%CI: 0.49-0.94, $P = 0.018$).

Power calculation

Power calculation was performed to estimate the risk of obtaining false-negative results because of small sample size. Based on the two-sided test at the 0.05 significance level, this study exhibited 69% and 53% power in successfully detecting a significant association between rs1800624 and rs2070600 polymorphisms and risk of

Table 3 Haplotype frequencies of the studied polymorphisms in patients and controls, and their risk prediction for Crohn's disease

haplotype	Case	Control	Hapscore	*P* value	*P*sim	OR	95%CI	*P* value
T-T-G	49.40%	49.10%	0.075	0.94	0.92	Reference		
T-T-A	26.30%	21.30%	2.21	0.027	0.032	1.2	0.94-1.53	0.14
T-A-G	10.60%	15.60%	-2.82	0.005	0.002	0.67	0.49-0.94	0.018
C-T-G	13.80%	14.00%	-0.12	0.91	0.88	0.97	0.70-1.33	0.83

Alleles in haplotype were presented in order of polymorphisms *rs1800625*, *rs1800624* and *rs2070600*. OR: Odds ratio; P_{sim}: Simulated *P*.

CD under a dominant genetic model, respectively.

DISCUSSION

In this study, we investigated the role of three potential polymorphisms of *RAGE* gene in the risk of CD susceptibility in a Han Chinese population. The results reveal that the *RAGE* gene polymorphisms and the haplotype were associated with CD. Although the haplotype T-A-G (rs1800625- rs1800624- rs2070600), had low penetrance, it was negatively correlated with CD and could have a protective function in the latter. To the authors' knowledge, the present study is the first to explore the genetic susceptibility of *RAGE* gene to CD in Chinese population.

The rs1800624 polymorphism located at position -374 of the promoter region could be a functional polymorphism that results in reduced binding of a nuclear factor to a regulatory element of the *RAGE* gene promoter. *In vitro* experiments by Hudson *et al*[22] demonstrated that -374A resulted in a threefold increase in transcriptional activity compared with the T allele. Däbritz *et al*[13] found that *-374T/A RAGE* polymorphism is negatively associated with CD in a German population, supporting the hypothesis that the *-374T/A RAGE* polymorphism increases the levels of circulating soluble RAGE to neutralize proinflammatory mediators. However, this claim warrants further investigation.

Another variant (rs2070600, also known as *G82S* polymorphism) that causes a glycine-to-serine substitution at position 82 within the V-domain exhibits significantly different distribution between CD and control individuals (*P* allele = 0.022). The rs2070600 polymorphism is located in an exon in a region that has a crucial function in ligand binding. The 82S variant increases the ligand-binding affinity of the receptor[23,24], and consequently increases nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and inflammatory gene expression. In addition, the *G82S* polymorphism is associated with reduced levels of soluble RAGE that magnifies the contribution from RAGE toward inflammation in a number of diseases[25]. The *G82S RAGE* polymorphism is associated with arthritis[23]. However, Däbritz *et al*[13] did not detect any association between G82S polymorphism and CD in either German or American population. They found that the minor A allele frequency of this polymorphism was below 5% in all study samples. In contrast, in the present study, the minor A allele frequencies were 26.3% and 21.3% in the cases and in the controls, respectively. The discrepancy in the results may be mainly explained by the heterogeneous genetic predispositions of individuals of different ethnicities. Genetic markers representing predisposition to IBD vary across geographical and racial groups. As proven by our previous meta-analyses, *CD14* gene *C-260T* polymorphism exhibited remarkable heterogeneity with UC across ethnic groups, with statistical significance in Asians but not in Caucasians[26]. However, considering the relatively smaller sample size in the present study, more studies are required to validate the effects for RAGE G82S.

In this study, haplotype analysis of the rs1800625-rs1800624-rs2070600 combination revealed four main and rare haplotypes. The common haplotype T-T-G showed a similar frequency between CD and control individuals (49.4% *vs* 49.1%). Compared with the common haplotype, haplotype T-A-G showed a highly significant negative correlation between CD and control individuals (10.6% *vs* 15.6%, *P* = 0.0049; OR = 0.67), suggesting that it is a protective haplotype. Haplotype analysis further confirmed the results that rs1800624 and rs2070600 are the susceptible loci for CD in the Chinese population.

However, this study has several drawbacks. First, the sample size is relatively small and may not produce efficient statistical power to detect a small genetic effect, resulting in a fluctuated estimation. Second, limited polymorphisms of *RAGE* gene associated with susceptibility to CD were shown, and other unidentified polymorphisms that influence the development of CD still remain to be discovered. Therefore, further related studies of a large sample size from different ethnic origins and biological studies should be carried out to verify this association. Third, data on circulating soluble RAGE levels are unavailable, so RAGE levels cannot be compared across genotypes.

In conclusion, this study revealed that polymorphisms and haplotypes of the *RAGE* gene are significantly associated with susceptibility to CD in the Chinese population. Moreover, this study leaves open the question of divergent genetic profiles across different ethnic groups. This study provides supporting evidence for further investigation on pathophysiological mechanisms of *RAGE* genes in CD.

COMMENTS

Background

The incidence of Crohn's disease (CD) is rising in China, although the exact etiology of CD remains elusive. Genome-wide linkage analyses and association

studies have identified multiple candidate genes susceptible to CD. However, the susceptibility genes in CD may vary across different ethnic groups.

Research frontiers

The receptor for advanced glycation end products (RAGE) is a pattern recognition receptor involved in several pathophysiological processes associated with inflammation, including *CD-374T/A* polymorphism in RAGE which was found to be associated with CD in a German population, but not in the American population. In the present study, the authors demonstrated that RAGE rs1800624 and rs2070600 polymorphisms were associated with CD occurrence in a Chinese population.

Innovations and breakthroughs

Studies that investigate the association between *RAGE* gene polymorphisms and CD susceptibility risk are limited. This study is the first to investigate the association between the three most commonly studied polymorphisms in *RAGE* gene and CD risk in a Chinese population.

Applications

The present findings further support a genetically impaired innate defense immunity system as one predisposing factor in the etiology of CD, which is a prerequisite for development of new treatment strategies for CD.

Terminology

RAGE is a member of the immunoglobulin protein family of cell surface molecules that binds multiple structurally diverse ligands, leading to the activation of several proinflammatory signaling pathways. RAGE is a pattern recognition receptor involved in several pathophysiological processes associated with inflammation, and has important functions in innate defense mechanisms.

Peer review

This research is a well-designed case-control study demonstrating that RAGE rs1800624 and rs2070600 polymorphisms are associated with CD occurrence in a Chinese population. This study adds evidence for a genetically impaired innate defense immunity system as one predisposing factor in the etiology of CD.

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