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Analysis on the interaction between IL-1F7 gene and environmental factors on patients with ankylosing spondylitis: a case-only study

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Abstract To examine the interaction between IL-1F7 gene and environmental factors in patients with ankylosing spondylities (AS). 150 AS Han Chinese patients (all human leukocyte antigen-B27 positive) were genotyped using a panel of single-nucleotide polymorphism markers within IL-1F7 gene (rs3811047) by ligase detection reactions. Polymerase chain reaction with sequence-specific primer was used to determine HLA-B27 subtypes. We analyzed the interaction between IF-1F7 gene and eight environmental factors in AS patients by using a case–only study. The genetic polymorphism and environmental factors were considered as dependent variables in logistic models, and *P*-values, OR_i and 95% confidence intervals were used for estimating the effects of interaction. The different frequency of A/G between drinking group and non-drinking group was significant (OR_i 3.163, 95% CI 1.368–7.317, $P = 0.006$). Within the cooking oil group, odds ratio for interaction of G × E between main plants fats and half plants -half animal fats subunits was 4.273 (95% CI 1.590–11.479, $P = 0.004$). Our data show that there was no interaction between IL-1F7 alleles and the other six environmental factors in AS patients (all $P > 0.05$). We observed that there was an interaction between IF-1F7 gene and drinking in AS patients. Thus, drinking may be a risk exposure factor to take combined action with predisposing genes in AS patients. This action may increase the incident risk of AS. Also, main plants fats may be protective factors to AS.

Keywords IL-1F7 gene · Environmental factors · Case-only study · Interaction

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Introduction

Ankylosing spondylitis (AS) is one of chronic inflammatory autoimmune diseases with an estimated prevalence of 0.1–0.9%. In this disease, axial skeleton, along with peripheral joints, tendons ligament attachment points, is injured, studies showed that AS is associated with complex genetic factors, environmental factors and autoimmune disorders, yet the pathogenesis are still unclear so far. It is known that AS has familial aggregation, and the fact that family members share susceptibility to AS could be environmental or genetic. Substantial evidence revealed that AS can be triggered by a common environmental pathogen, while studies also provided strong evidence that AS is highly heritable [1]. The extent of inflammation of AS could be affected by polymorphisms which modify the inflammatory response. Furthermore, it is possible that there are interactions between such polymorphisms and environmental risk factors in AS. The genetic association between AS and human leukocyte antigen (HLA)-B27 has been identified in different races, but twin studies indicate that HLA-B27 contributes only 16% of the total genetic risk for the disease [2]. It is proposed that the genetic predisposition between non-major histocompatibility

complex (non-MHC) genes and AS existed [3]. Genome-wide scans demonstrated that several areas from non-MHC regions like 2q, 6p, 6q, 10, 11, 16, 17, and 19q are related to AS [4],however candidate gene studies for non-MHC has its limitation. Interleukin-1 (IL-1) family gene cluster is located on chromosome 2q13, within a 36-kb region, including IL-1(IL1A), IL-1(IL1B), IL-1F7, IL-1F9, IL-1F6, IL-1F8, IL-1F5, IL-1F10, and IL-1RN genes. IL-1 molecule has extensive biological effects, among which it can partly or entirely activate and enhance mononuclear cells-neutrophils, phagocytosis function of destruction and promote them to release inflammatory mediators' protein, immune response and inflammation. Clinical studies showed that IL-1 is related to several autoimmune diseases, such as AS, and the family-based association studies came to the same conclusion [5]. Our previous work found the SNP (rs3811047) of the IL-1F7 gene is associated with susceptibility to AS in Han Chinese population, and this polymorphism is an independent susceptible risk factor to AS in addition to HLA-B27 [6].

To date, most of the epidemiological advances in AS have come from the ascertainment of novel genetic associations, while few environmental risk factors have been studied [7], and most of them just simply confirmed the association with AS from genetic angle although there have been some intensive studies[8]. To examine whether the effects of exposure are influenced by genetic polymorphism within the IL-1F7 gene, we performed an association study by examining gene × environment (G × E) interaction between genetic polymorphisms at the IL-1F7 gene and measures of exposure.

Materials and methods

Subject

We studied 150 unrelated AS patients (122 males and 28 females) with mean age of 29.91 years (SD = 9.606). All the cases were Han Chinese and HLA-B27 positive. Patients were diagnosed at Department of Rheumatology, First Affiliated hospital, Anhui Medical University, in accordance with New York criteria [8]. Permission was obtained from all individuals who were enrolled in our study. All the samples in our study answered the questionnaire, which including individual essential information (e.g. name, age, sex, and address), habits and customs (smoking, drinking and diet), past medical history, etc. The IL-1F7 gene SNP was selected from NCBI dbSNP (dbSNP home page). SNP rs3811047 (A/G transition) is located in exon 2 (Amino acid position 42). The SNP is the missense mutation resulting in different amino acid codon (rs3811047: Thr/Ala).

Definition of environmental factors

Environmental factors include eight aspects: (1) Smoking (yes or no). (2) Drinking (yes or no). (3) Type of cooking oil (absolute plants fats, main plants fats, half plants -half animal fats, animal fats). (4) Type of salt consumption (light, moderate, salty). (5) Type of meat products consumption (fat,fat and lean, lean). (6) Type of vegetable consumption (less than six times per week, once per day, 2–3 times per day, more than three times per day). (7) Having heavy noise source around (yes or no). (8) Sleep quality (well, normal, bad).

Genotyping

The genotyping of SNP (rs3811047) was conducted by the Shanghai Biowing Applied Biotechnology Company (http://www.biowing.com.cn) using ligase detection reactions (LDR) [6].

Statistical analysis

EpiData 3.0 was used for inputting questionnaire information and SPSS 11.0 for analyzing data. This data were sampled according to one case-only study design. We put the patients into different groups according to their genotype and exposure. Binary non-conditional Logistic Model was used for analyzing the interaction between IL-1F7 gene (rs3811047) and environmental factors. The genetic polymorphism was considered as the dependent variable in all logistic models. The non-carriers of the variant allele were coded as 0 while carriers of at least one copy of the variant allele were coded as 1. Environmental variables were included in different logistic equations as independent variables. All the parameters, alleles and genotype frequencies, Hardy–Weinberg equilibrium analysis were computed online using http://analysis.bio-x.cn (Shi and He, 2005). Power calculations were performed using the G*Power program [9]. Odds ratios (OR) for interaction were estimated by logistic regression. We calculated two-sided 95% confidence intervals (CI) based on Wald's tests. Significance level was set at $\alpha = 0.05$.

Results

SNP rs3811047 polymorphism has been found in our AS cases, including heterozygous A/G and wild type G/G genotypes. The mutant A/A genotype has not been found in AS patients. Hardy–Weinberg test showed that SNP rs3811047 was in Hardy–Weinberg equilibrium (Table 1). The results of interaction between IL-1F7 gene (rs3811047) and environmental factors are shown in Table 2. As shown in

Table 1 Distribution of genotypes in samples

Marker ID	*N*	Genotype			Fisher's *P* *
rs3811047	150	A/A	A/G	G/G	0.060
		0(0.00)	40(0.267)	110(0.733)	

* Hardy–Weinberg equilibrium test for samples

Table 2 Odds ratios (95% CI) and *P*-values for interaction between IL-1F7 gene (rs3811047) and eight environmental factors in AS patients

Environmental factors	Genotype		OR_i	95% CI	*P*
	A/G	G/G			
Smoking					
Yes	14	33	1.256	0.583–2.706	0.559
No	26	77			
Drinking					
Yes	14	16	**3.163**	**1.368–7.317**	**0.006**
No	26	94			
Cooking oil					
Main plants fats	8	47	Reference		
Absolute plants fats	11	32	2.020	0.732–5.575	0.175
Half plants–half animal fats	16	22	4.273	**1.590–11.479**	**0.004**
Animal fats	5	9	0.306	0.081–1.153	0.071
Salt consumption					
Light	7	23	Reference		
Moderate	14	46	1.000	0.355–2.818	1.000
Salty	19	41	1.523	0.557–4.163	0.413
Meat products consumption					
Fat	1	4	Reference		
Fat and lean	13	29	1.793	0.182–17.651	0.617
Lean	26	77	1.351	0.144–12.636	0.792
Vegetable consumption					
Less than six times per week	2	15	Reference		
Once per day	15	35	0.311	0.063–1.533	0.151
2–3 times per day	21	59	0.375	0.079–1.778	0.217
More than three times per day	2	1	0.067	0.004–1.116	0.060
Having heavy noise source around					
Yes	7	19	1.016	0.391–2.637	0.974
No	33	91			
Sleep quality					
Well	19	54	Reference		
Normal	14	38	1.047	0.468–2.343	0.911
Bad	7	18	1.105	0.400–3.058	0.847

Bold values indicate *P* is significant

this table, no differences were observed in the distributions of rs3811047 polymorphisms between smoking and non-smoking AS cases using logistic regression ($P = 0.559$). However, the different frequency of A/G between drinking group and non-drinking group was significant (OR_i 3.163, 95% cI 1.368–7.317, $P = 0.006$). Within the cooking oil group, there may has an interaction of G × E between main plants fats and half plants -half animal fats subunits (OR_i 4.273, 95% cI 1.590–11.479, $P = 0.004$). Interaction between IL-1F7 alleles and the other five environmental factors in AS patients was not significant (all $P > 0.05$).

Discussion

As a complex disease, AS has a strong association with gene and environment. Interaction between G × E plays an important role in the disease process of AS. The study on the GxE interaction in epidemiologic studies is not only beneficial for a better understanding of the multifactorial causation of AS, but also useful for the design of prevention strategies in genetic high-risk subjects. In our study, we found that the different frequency of A/G between drinking group and non-drinking group was significant, revealing an interaction of IF-1F7 gene (rs3811047) and drinking in AS patients. Drinking may be a risk environmental factor to take combined action with predisposing genes, and this action may increase the incident risk of AS. We also found the interaction between rs3811047 polymorphisms and the cooking oils,. In particular, our study found that main plants fats may be protective factors to AS, The results of these studies is great significance to AS for prevention and control.

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