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Association of rs2075876 polymorphism of AIRE gene with rheumatoid arthritis risk

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ABSTRACT

Background: Autoimmune regulator (AIRE), a protein encoded by AIRE gene, is a transcriptional factor primarily expressed in medullary thymic epithelial cells (mTECs). It has pivotal role in regulation of human immunology. The mutations of AIRE gene or protein level changes would alter the status of body immunity and therefore onset of diseases. Therefore we aimed at investigating the association of AIRE gene with the risk of rheumatoid arthritis (RA).
Methods: We genotyped 9 SNPs of AIRE gene of recruited 691 patients of rheumatoid arthritis and 800 healthy people in Chinese Han population.
Results: Our results indicated that a variant rs2075876 with minor allele A increased the risk of rheumatoid arthritis ($p_a = 0.008$, OR = 1.991, 95%CI 1.214–2.919). Other two SNPs rs933150 and rs760426 were borderline-associated with rheumatoid arthritis risk ($p_a = 0.055$; $p_a = 0.074$, respectively). Furthermore, in correlation analysis of SNPs in AIRE gene with clinical characteristics of rheumatoid arthritis, we found the SNP rs2075876 had significant correlation with CRP concentration ($p_a = 0.020$).
Conclusion: We might provide a new inside look into the AIRE gene variants in development and progression of rheumatoid arthritis.

1. Introduction

Rheumatoid arthritis (RA) is a type of chronic systematic inflammatory disease characterized with persistent synovitis and persistent existence of auto-antibody. In spite of the low prevalence of RA around the world, it would result in severe functional impairment and work-related disability, and finally burden hugely the economic and social cost [1–3]. Previous researches have demonstrated that RA was an autoimmune disease affected by multiple factors.

The combination of environmental and genetic effects influences the development and progression of RA. Several genome wide association studies (GWAS) in Europe and East Asia population have identified ethnic-restricted gene loci, such as CCR6 [4], inferred the functional effects of genes would be race specific.

Autoimmune regulator (AIRE) is a transcriptional regulator primarily expressed in medullary thymic epithelial cells (mTECs) and plays a pivotal role in thymocyte education and negative selection by controlling the expression of peripheral antigens in thymus [5,6]. The changes in transcriptional level of AIRE might alter the expression levels of various peripheral tissue antigens (PTAs). This would affect, probably invalidate, the negative selection in the thymus. And the termination effects would be the survival of auto-reactive T cells and the onset of autoimmune diseases [7–9].

It has been noticed that several autoimmune disorders, such as vitiligo [10], autoimmune hepatitis [11], type 1 diabetes mellitus [12], myasthenia gravis [13] and systemic sclerosis [14], might be affected by the genetic variability of AIRE gene. A recent GWA study in Japanese population has been identified two SNPs, rs2075876 and rs760426, in the AIRE gene was significant associated with RA risk [2]. Another study proposed the result that SNP rs878081 in AIRE gene had significant association with RA risk in Caucasian population, while result of the SNPs rs2075876 and rs760426 were negative [15]. It indicated that in AIRE gene region there might be ethnic-restricted loci for RA. Therefore, in the present research, we performed a hospital-based case-control study to investigate the association between selected 9 SNPs in AIRE gene and rheumatoid arthritis risk in Chinese Han population.

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2. Materials and methods

2.1. Study population

A total of 691 RA patients, mean age 52.3 ± 10.1 (age range from 33 to 74) were recruited from the Third Hospital of Hebei Medical University between 2009 and 2012. Diagnosis of RA was approved by at least two pathologists according to the American College of Rheumatology classification criteria. The unrelated 800 healthy people, mean age 53.9 ± 11.2 (27–78), were from the health examination center and confirmed they did not suffer any autoimmune diseases. All the recruited people were Chinese Han population, and bloods were drawn before they provided informed consent. All individuals participated in this study were given informed consents and this study was approved by ethical committee of the hospital.

2.2. DNA extraction

Genomic DNA was extracted from blood leukocytes using QIAmp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's recommendations and stored at −20 °C.

2.3. SNP selecting and genotyping

All the 9 SNPs with the MAF >0.05 were selected using Haploview Software based on the Chinese Han population data from International Hapmap Project Website (http://hapmap.ncbi.nlm.nih.gov/) [16]. Genotyping of these 9 SNPs from patients and healthy controls was performed by TaqMan® SNP Genotyping Assays (Applied Biosystems, Barcelona, Spain) in a LightCycler 480 (Roche, Barcelona, Spain).

2.4. Statistical analysis

Genotypic and haplotypic frequency distributions of 9 SNP between patients and healthy controls were examined using the chi square test. A difference of age and sex-adjusted p value (p_a) <0.05 was considered statistically significant. The Hardy–Weinberg equilibrium (HWE), linkage disequilibria (LD) and haplotype was analyzed with SHEsis software available on line http://analysis.bio-x.cn [17]. The correlation between these 9 SNPs and clinical pathological parameters was analyzed using chi square test and further logistical regression analysis.

3. Results

3.1. Clinical pathological parameters between cohorts of patients and healthy controls

Table 1 listed the characteristics of individuals in the case-control study. There were no significant differences in the distributions of age and gender status. The mean age of RA patients was 54.1 ± 11.2 (range from 30 to 66) and the mean age of healthy controls was 52.4 ± 11.8 (range from 24 to 68). Furthermore, some clinical parameters, including family history, DSA 28, ESR, anti-CCP antibody, CRP and RF were also listed in the column of cases.

Table 1
The characteristics of study population.

Clinical and laboratory parameters	Controls	RA patients	p-Value
Age (years)	54.1 ± 11.2	52.4 ± 11.8	>0.05
Gender status (male/female)	332/468	321/370	>0.05
Family history (+/−)	–	106/585	–
DSA 28	–	4.1 ± 1.3	–
ESR (mm/h)	–	44.0 ± 33.1	–
CCP (+/−)	–	390/301	–
RF (+/−)	–	452/239	–

3.2. Association between 9 SNPs of AIRE gene and rheumatoid arthritis risk

A total of 9 SNPs in AIRE gene were analyzed and results were summarized in Table 2. All SNPs fitted the Hardy–Weinberg equilibrium among controls. The SNP rs2075876 showed the only significant association with the risk of RA. The A allele of rs2075876 increased the risk of RA (p_a = 0.008, OR = 1.991, 95%CI 1.214–2.919), while the other 8 SNPs showed no significant association with RA risk. However, a borderline genotype distributions between cases and controls was observed in the SNP rs933150 (p_a = 0.055) and rs760426 (p_a = 0.074).

Then we evaluated the association of minor allele A of the SNP rs2075076 with the risk of RA in the dominant and recessive model in Table 3. And we found allele A account for higher proportion in the case and significantly increased the RA risk in codominant model (p_a = 0.001, OR = 1.328, 95%CI = 1.328–2.515) and dominant model (p_a = 0.028, OR = 1.621, 95%CI = 1.881–2.561).

3.3. Haplotype of SNPs in AIRE gene with the risk of rheumatoid arthritis

We estimated the linkage disequilibrium (LD) and show the LD plot in Fig. 1. The block 1 included 5 SNPs of AIRE (rs2075876, rs2075877, rs933150, rs1003854 and rs1078480) and block 2 included 2 SNPs (rs2256817 and rs760426) (Fig. 1). And we analyzed the haplotype of these 2 blocks based on the result of LD plot (Table 3). One haplotype of block 1 (p_a = 0.01, OR = 1.852) and another haplotype of block 2 (p_a = 0.02, OR = 1.950) increased the RA risk (Table 4).

3.4. Clinical correlation of clinical pathological parameters with SNPs of AIRE gene

9 clinical parameters of RA, including age, gender status, family history, DSA28, ESR, anti-CCP antibody, CRP, RF and ACPA, were analyzed with the SNP rs2075876, and CRP concentration had significant correlation with the rs2075876 (p_a = 0.020) (Table 5). There were no correlations between other 8 clinical parameters with rs2075876 (data not shown).

4. Discussion

In this association analysis between AIRE gene and rheumatoid arthritis risk, we demonstrated that the SNP rs2075876 with minor allele A increased the risk of RA (p_a = 0.008, OR = 1.991, 95%CI 1.214–2.919) in Chinese population. Meanwhile we observed in the dominant model that the genotype AA + AG was significantly associated with RA risk.

AIRE was closely related to the behavior of immunology of human organism. As we know it, a rare heritable disease, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type I (APS 1), was due to homozygocity or, rarely, heterozygocity of mutation of AIRE gene [18–20]. On the one hand, AIRE would promote and activate the expression of peripheral antigens in the process of thymocute education. It has been demonstrated that the AIRE expressed stromal cells within secondary lymphoid organs could express tissue-restricted self-antigens (TRAs), and furthermore allowed the negative selection of auto-reactive lymphocytes provided with high affinity for the recognized