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ORIGINAL ARTICLE

Association of autoimmune regulator gene polymorphism with susceptibility to rheumatoid arthritis in Egyptian population

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Abstract

The autoimmune regulator (*AIRE*) gene controls autoimmunity via its transcript AIRE protein that suppresses naïve T cells during central selection. The role of *AIRE* polymorphism in rheumatoid arthritis (RA) autoimmunity remains elusive. This study aimed to investigate the association of two selected SNPs, namely, rs760426 and rs2075876, with RA susceptibility in the Suez Canal Zone population. The study population included 100 RA patients, and the control group included 100 healthy subjects who were age- and sex-matched to the RA group. SNP genotyping was performed using real-time polymerase chain reaction-based allelic discrimination assay, the odds ratio was defined to assess the strength of the association. For rs760426, combining genotypes data revealed a significant increase for A/G genotype in the RA cases (47%, $n = 47$) than in the control group (27%, $n = 27$) in both co-dominant and over-dominant models ($P = 0.013$ and 0.003 respectively). In addition, rs760426 correlated to duration of RA ($P = 0.031$) and anti-cyclic citrullinated peptide antibody ($P = 0.021$). For rs2075876, there was a significant increase in the A/A genotype in RA patients compared with control subjects. In the co-dominant model, the frequency of A/A was 14% and 7% respectively ($P = 0.02$). In contrast to rs760426, rs2075876 associated with the risk of increased body mass index ($P = 0.014$) and the positivity of rheumatoid factor (RF) ($P = 0.043$). The frequency of minor alleles, G allele in rs760426 SNP, and A allele in rs2075876 was higher in RA patients than in control. The haplotype frequency of both G and A alleles in rs760426 and rs2075876 receptively was 11% in RA group with statistically significant difference ($P = <0.001$) between RA patients and healthy control. SNPs rs760426 and rs2075876 in the AIRE gene may contribute to the risk for RA susceptibility. These two polymorphisms were associated with variable risk factors and predictive biomarkers for RA. The mutant allele (G) of rs760426 SNP has significant indication of poor prognosis.

Keywords Gene · AIRE · Polymorphism · Haplotype

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that can lead to functional impairment as a result of the poly-articular arthritis combined with extra-articular complications. It has an estimated worldwide prevalence of up to ~ 1% of the adult population [1, 2].

The root cause of RA is unknown; however, both genetic and environmental factors are believed to have a role in the disease pathogenesis [3]. The genetic contribution to RA susceptibility in humans has been proven through twin and family studies [4, 5]. It is estimated that ~ 60% of RA disease variability are inherited [4].

Among the key genes that regulate immune tolerance is the autoimmune regulator (*AIRE*) gene. *AIRE* gene, discovered in 1997, is located in the 21q22.3 region [6]. It is ~ 12.5 kb long

and encodes a 545 amino acid protein of 58 kDa by 14 exonial sequences [7–9]. The AIRE protein is a transcription factor that has a pivotal role in the negative selection of naive T cells during central tolerance [1], making AIRE a good candidate gene for autoimmune diseases.

In humans, mutations in *AIRE* cause autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) or autoimmune polyendocrine syndrome type 1 (APS1) [10]. Moreover, AIRE gene polymorphism is found to be associated with susceptibility to multiple diseases of autoimmune response such as alopecia areata, myasthenia gravis, hepatocellular carcinoma, myocardial infarction, pediatric acute lymphoblastic leukemia, melanoma, vitiligo, type 1 diabetes (T1D), Hashimoto's thyroiditis (HT), and RA [7, 11–15]. Among the studied diseases, only RA has been analyzed by multiple case-control studies and, therefore, seems to be optimal to analyze positive or negative associations [7].

Single-nucleotide polymorphisms (SNPs) in the gene sequence are believed to alter the *AIRE* transcription and functional activity. They also decrease the presentation of self-antigens, thus resulting in a less efficient negative selection, propagating higher survival of autoimmune T cells, which will eventually elevate the susceptibility to autoimmune diseases [16]. The SNPs thereby alter the functional activity of AIRE and potentially elevate disease susceptibility. Several SNPs in the *AIRE* genetic sequence were identified, while only a fewer studies have been done to assess an association between gene polymorphism and susceptibility to diseases [7].

The genome-wide association (GWA) studies were done in a Japanese population in 2011 and have recognized the AIRE as a novel susceptibility gene for RA, and two SNPs, rs2075876 (G > A) located in Intron 5 and rs760426 (A > G) located in Intron 12, have shown evidence of association with genome-wide significance [17–19]. Furthermore, in silico analysis using the Gene Expression Omnibus (GEO) database showed that the risk allele of rs2075876 was found to decrease the transcription level of AIRE, indicating that rs2075876 might be a functional SNP [6].

So far, the association between AIRE polymorphisms and genetic susceptibility to RA in Egyptian population still has to be clarified. Thus, we conducted this case-control study to investigate whether AIRE rs2075876 and rs760426 polymorphisms are often involved in the genetic conditions of RA in Egyptian population.

Patients and methods

This study was carried out as a case-control study in which 100 RA patients were recruited from the outpatient clinics at Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Suez Canal University Hospital. RA patients were enrolled in the study, according to the American College of Rheumatology (ACR)/the European League Against Rheumatism (EULAR) (ACR/EULAR) 2010 classification criteria for rheumatoid arthritis, and the age of the patients was more than 16 years old. Patients with other autoimmune diseases (spondyloarthropathies, systemic lupus erythematosus, dermatomyositis, polymyositis, sarcoidosis, and systemic sclerosis) were excluded. RA patients underwent a careful medical history and examination. Disease activity assessment with DAS-28 score was also done. One hundred healthy persons who were age- and gender-matched to RA patients were assigned as a control group.

Laboratory assessment

Laboratory investigations included complete blood count (CBC) by using an automated cell counter (CELL-DYN 1700, Abbott diagnostic, USA). Measuring serum rheumatoid factor (RF), C-reactive protein (CRP), and anti-citrullinated protein/peptide antibody (ACPA) (Elecsys anti-cyclic citrullinated peptide (anti-CCP) antibody assay) was done by COBAS e411 (Roche diagnostics, Germany). Measuring erythrocytes sedimentation rate (ESR) was done by using the Westergren method. Antinuclear antibodies (ANA) were evaluated by Bio-Rad; HEp-2 cell immunofluorescence assay was conducted at the Clinical Pathology Department, Suez Canal University.

AIRE SNPs (rs2075876 (G > A), rs760426 (A > G)) genotyping

DNA extraction: DNA was purified from EDTA blood using the spin column technique following the manufacturer's instruction (GeneJet, Thermo Fisher scientific).

Real-time PCR: the extracted DNA was used for TaqMan SNP genotyping assays (Applied biosystems, Thermo Fisher Scientific Inc., Foster city, CA, USA), use TaqMan 5′ nuclease assay chemistry, to amplify and detect AIRE SNPs alleles (rs2075876 (G > A), rs760426 (A > G)) by allelic discrimination assay [16]. PCR was performed using two primers flanking the SNP. Two allele-specific TaqMan minor groove-binding (MGB) probes containing distinct fluorescent dyes and a PCR primer pair were used to detect specific SNP targets. These TaqMan probe and primer sets (assays) uniquely align with the genome to provide unmatched specificity for the allele of interest. The assay was conducted with the Rotor-Gene 6000 instrument (Corbett Life Science), and the software Rotor-Gene 6000 series version 1.7 was used to analyze the results.

Statistical analysis

The data was analyzed by using the IBM SPSS.25 software (IBM SPSS Inc., Armonk, NY, USA). The data was presented as frequencies and percentages for qualitative variables and mean and standard deviation for quantitative variables. Chi-square test was used to compare alleles, genotypes, and haplotype frequency distributions and other categorical variables. ANOVA and *t* test was used to evaluate the relationship of the SNP genotyping and alleles with different quantitative variables. The logistic regression analysis was done for alleles and genotypes under different genetic models, and the odds ratios (ORs) and 95% confidence intervals were calculated to assess the risk of RA disease susceptibility. Significance is considered at P value of < 0.05, and P value was adjusted by Bonferroni for multiple comparisons.

Results

The clinical characteristics, demographic data, and biochemical parameters of RA patients are summarized in Table 1. One hundred RA patients were included in the study with mean age of 42.26 ± 11.88, 88.0% were females. Mean disease duration for RA patients was 3.97 ± 2.5 years. About 41% of patients tested positive for anti-CCP antibody. Other clinical parameters, including family history, body mass index (BMI), treatment taken, mean and percent of RF, and mean CRP, as well as DAS28, CRP, and ESR are also illustrated in Table 1.

Table 1 Demographic, clinical, and laboratory data of RA patients

Characteristics	RA ($n = 100$)
Age (years) mean ± SD	42.26 ± 11.88
Gender	
Male no. (%)	12 (12.0%)
Female no. (%)	88 (88.0%)
Duration of disease (years) mean ± SD	3.97 ± 2.5
Family history	
Negative	79 (79%)
Positive	21 (21%)
BMI kg/m^2 mean ± SD	29.26 ± 5.48
No. of tender joint mean ± SD	9.53 ± 8.1
No. of swollen joint mean ± SD	2.05 ± 1.74
Treatment no. (%)	
Monotherapy	36 (36%)
Ditherapy	48 (48%)
Tritherapy	13 (13%)
Biology	3 (3%)
Steroid no. (%)	
Yes	52 (52%)
No	48 (48%)
Rheumatoid factor (IU/mL)	
Mean ± SD	58.17 ± 25.35
Rheumatoid factor	
Positive no.(%)	31 (31%)
Negative no. (%)	69 (69%)
Anti-CCP (U/mL)	
Positive no. (%)	41 (41%)
Negative no. (%)	59 (59%)
CRP (mg/L) mean ± SD	13.35 ± 12.04
ESR (mL/h) mean ± SD	57.84 ± 27.61
DAS28.CRP mean ± SD	4.55 ± 1.7
DAS28.ESR mean ± SD	4.82 ± 1.61

BMI, body mass index; *Anti-CCP*, antibody to cyclic citrullinated peptide; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *DAS28*, disease activity score 28 joints

Genotype distribution and Hardy–Weinberg equilibrium

The Hardy–Weinberg equilibrium (HWE) was evaluated. Genotype frequencies in RA patients and healthy controls were in accordance with the HWE for the two selected SNPs. No significant differences were observed between the observed and expected values relative to genotype distribution from both the control ($P = 0.10$) and the RA groups of patients ($P = 0.22$) in rs760426, as well as from the control ($P = 0.15$) and the RA groups of patients ($P = 0.27$) in rs2075876. This confirms that the study sample excluded selection bias for the polymorphisms analyzed.

Allele frequencies and genotype distribution of rs760426 polymorphisms in healthy control and RA patients

We investigated the possibility to predict rheumatoid arthritis disease under co-dominant, dominant, recessive, over-dominant, additive, and allelic models (Table 2). Significant evidence was found under the co-dominant (additive) model. A/G genotype was more frequent in RA patients (47/100, 47%) than in healthy control (27/100, 27%), with statistically significant difference A/G (OR = 2.36, 95% CI = 1.29–4.31, $P = 0.013$). In addition, under the over-dominant model, A/G (OR = 2.40, 95% CI = 1.33–4.33, $P = 0.003$; Table 2) showed a significant association with high risk of RA disease, where the gene is over-expressed in the presence of two alleles together as in the heterozygous person compared with the homozygous one. No significant difference in the allelic distribution of AIRE rs760426 polymorphism between cases and controls was detected (A versus G, $P = 0.106$).

Table 2 Genotype and allele frequencies for AIRE (rs760426 and rs2075876) in RA patients and control cases

AIRE polymorphism	Controls = 100 *N* (%)	RA patients = 100 *N* (%)	*P* value	OR (95% CI)
SNP rs760426				
Genotype				
A/A	65 (65%)	48 (48%)		1.00 (reference)
A/G	27 (27%)	47 (47%)	0.013*	2.36 (1.29–4.31)
G/G	8 (8%)	5 (5%)		0.85 (0.26–2.75)
Allele				
A	157(78%)	143 (72%)		1.00 (reference)
G	43(22%)	57 (28%)	NS	1.45(0.92 to 2.29)
Dominant model				
A/A	65 (65%)	48 (48%)		1.0 (reference)
A/G-G/G	35 (35%)	52 (52%)	0.015*	2.01 (1.14–3.55)
Recessive model				
A/A-A/G	92 (92%)	95 (95%)		1.00 (reference)
G/G	8 (8%)	5 (5%)	NS	0.61 (0.19–1.92)
Over-dominant				
A/A+G/G	73 (73%)	53 (53%)		1.00 (reference)
A/G	27 (27%)	47 (47%)	0.003*	2.40 (1.33–4.33)
SNP rs2075876				
Genotype				
G/G	66 (66%)	47 (47%)		1.00 (reference)
G/A	27 (27%)	39 (39%)	0.02*	2.03(1.09–3.76)
A/A	7 (7%)	14 (14%)		2.81(1.05–7.49)
Allele				
G	159 (79.5%)	133 (66.5%)		1.00 (reference)
A	41 (20.5%)	67 (33.5%)	0.003*	1.95 (1.24 to 3.06)
Dominant model				
G/G	66 (66%)	47 (47%)		1.00 (reference)
G/A-A/A	34 (34%)	53 (53%)	0.006*	2.19 (1.24–3.87)
Recessive model				
G/G-G/A	93 (93%)	86 (86%)		1.00 (reference)
A/A	7 (7%)	14 (14%)	NS	2.16 (0.83–5.61)
Over-dominant				
G/G-A/A	73 (73%)	61 (61%)		1.00 (reference)
G/A	27 (27%)	39 (39%)	NS	1.73 (0.95–3.14)

OR, odds ratio; *CI*, confidence interval

*Statistically significant

Association between AIRE rs2075876 polymorphism and risk of RA

We evaluated the association between the minor allele A of AIRE rs2075876 polymorphism and the risk of RA under several genetic models; significant evidence was found under the co-dominant model. A/A genotype was more frequent in RA patients (14/100, 14%) than in healthy control (7/100, 7%), with a statistically significant difference (A/A, OR = 2.81, 95% CI = 1.05–7.49, $P = 0.02$) (Table 2). Significant difference in the allele distribution of AIRE rs2075876 polymorphism between cases and controls was also detected as the A allele was more frequent in RA patients (33.5%) compared with healthy control (20.5%) (A versus G, $P = 0.003$) (Table 2). Interestingly, the presence of only one A allele in the genotype has the high risk of RA disease susceptibility under the dominant model (G/A-A/A, OR = 2.19, 95% CI = 1.24–3.87, $P = 0.006$).

Logistic regression analysis to predict RA by AIRE gene polymorphisms

The presence of allele G of rs760426 SNP or allele A of rs2075876 SNP could be considered as risk factors for the person to develop RA two times more.

Haplotype of SNPS rs760426 and rs2075876 in AIRE gene and the risk of developing RA

Considering frequencies and association of AIRE gene (rs760426 and rs2075876) haplotypes in the study group and the risk of developing RA, G allele (in rs760426 SNP) and A allele (in rs2075876 SNP) frequency was 11% in the RA group with significant difference from the control group (P value < 0.000; OR = 27.12 (26.22–28.65)) (Table 3). Linkage disequilibrium analysis revealed that there is no linkage between two studied AIRE gene SNPs (rs760426 and rs2075876).

Association of clinical parameters of RA patients with AIRE SNPS rs760426 and rs2075876

Fifteen parameters were analyzed for the possible association with either investigated SNPs including age, gender, stages of RA, BMI, family history, no. of tender joints, no. of swollen joint, RF, anti-CCP, CRP, ESR, DAS28 CRP, DAS ESR, and treatment. Among them, there was a significant positive association between both the duration of RA disease and positive anti-CCP in carriers of rs760426 SNP ($P = 0.031$ and 0.021 respectively). On the other hand, the presence of rs2075876 SNP in RA patients had a strong positive association only with increased BMI and high levels of RF ($P = 0.014$ and 0.043 respectively).

Discussion

The complexity of RA disorder is attributed to its multifactorial origin that encompasses a wide range of genetic and environmental causes resulting in its heterogenic nature. AIRE is a transcriptional regulator essential for clearing autoreactive T cells, maintaining central immune tolerance. In rheumatoid arthritis, the effector cells are activated fibroblast-like synoviocytes (FLS), which have the vital role in mediating insistent inflammatory condition and joint destruction. Bergström et al. studied the pathological mechanism for AIRE association with RA. They demonstrated the role of AIRE as a cytokine-induced RA risk gene in RA FLS and reported that AIRE could enhance the pro-inflammatory response induced by some cytokines as tumor necrosis factor and interleukin-1β. In addition, AIRE could increase the production of some chemokines such as CXCL10. Meanwhile, in RA podoplanin-positive FLS in synovial tissue, the AIRE is expressed. According to these findings, AIRE has a novel pro-inflammatory role in RA at peripheral inflammatory sites [20]. Therefore, mutations in AIRE genes increase the tendency of autoimmune diseases [21]. The genetic role in RA disease was reported in various genetic polymorphisms inside the AIRE in Japanese [6], Spanish [16], and Chinese populations [13, 18]. In the current investigation, we conducted an association study for two variants located in the AIRE gene region, namely rs2075876 and rs760426, with the susceptibility to RA in the Egyptians population living in the Suez Canal Zone.

Among the known AIRE SNPs, few association studies for rs760426 variant in RA disease were carried out only in two countries of Asian ethnicity, namely, in Japan [6] and in China [13, 18]. Our data showed that rs760426 has the potential to reflect RA activity and prognosis, as the heterogeneous allelic genotype (AG) of AIRE rs760426 had a significant evidence in both co-dominant heterogenous model (A/G) and over-dominant model. These results are in agreement with Teroa et al. [6] who reported a strong association between SNP rs760426 and RA risk in GWA study in Japanese population ($P = 4.4 \times 10–8$). Also, Shao et al. proved the association of the minor allele G of AIRE rs760426 polymorphism with RA risk, however, under the dominant model and the recessive model (GG versus GA+AA, $P = 0.02$, $P = 0.04$). In contrast to our findings, SNP rs760426 in AIRE gene had just a borderline genotype distribution between RA cases and controls ($P = 0.074$) [18]. The proposed explanations for these discrepancies could be contributed to (i) the effect of ethnic

Table 3 Frequencies and association of AIRE gene (rs760426 and rs2075876) haplotypes in study group

Haplotype	rs760426	rs2075876	Healthy control	RA patients	OR (95% CI)	P value
1	A	G	117(58.5%)	98 (49%)	1.00	-
2	A	A	41 (20.5%)	45 (22.5%)	1.20 (0.74–1.96)	NS
3	G	G	42 (21%)	35 (17.5%)	0.95 (0.56–1.62)	NS
4	G	A	0 (0%)	22 (11%)	27.12 (26.22–28.65)	< 0.0001
	Global haplotype association P value 0.0013					
	Linkage disequilibrium analysis between rs760426 and rs2075876					
	$D = 0.0059$ $D' = 0.0347$ $r^2 = 0.0312$ P value = 0.6591					

differences between the studied populations, Chinese population, and Egyptian one, and (ii) the relatively small sample size of the studied patient's cohort. Further replication in larger cohorts to investigate the functional role of rs760426 on the expression pattern of the gene in disease and health is warranted. The association of the rs760426 SNP and disease severity was evident by the significant positive correlation of the mutant allele (G) of rs760426 SNP with the positive anti-CCP antibody and the duration of the RA disease as well (P value = 0.021 and 0.031 respectively). This suggests that SNP rs760426 polymorphism may be a candidate biomarker for predicting joint damage and poor prognosis in Egyptian patients with RA disease.

The association of AIRE rs2075876 with the RA risk was previously confirmed in Chinese population [13, 18]. Similar data was reproduced in the Egyptian population we studied. Our results revealed that the minor allele A of AIRE rs2075876 polymorphism was significantly associated with the risk of RA. Moreover, a significant evidence was found under the co-dominant model (A/A), and dominant model as well. Additionally, the current study showed that the risk of RA is higher with homogenous allelic genotype (AA) of AIRE rs2075876, compared with heterogeneous allelic genotype (GA), suggesting the partial protective effect of G allele against A allele in AIRE rs2075876 polymorphism. Finally, we showed that rs2075876 is significantly correlated with positive RF and increased BMI in RA patients. The rs2075876 risk allele (A) decreases AIRE transcription [6].

Since the reduction in AIRE transcription contributes to the failure of negative selection in the thymus and hence increases the survival of autoimmune T cells that will subsequently increase RA susceptibility, this could in part support our finding that AIRE rs2075876 SNP significantly correlated with RF titer, which is an auto-antibody that attacks healthy tissue. In contrast to our findings, Garcia-Lozano et al. [16] reported no association of this polymorphism with RA presumably to the different studied ethnic group, European (Spanish) population versus our Egyptian or the previously reported Chinese populations [13, 18].

On testing the association of AIRE gene (rs760426 and rs2075876) haplotypes in the study group and the risk of developing RA, and in agreeing with Feng et al. [18], we found that carriers of the mutant G allele (in rs760426 SNP) and mutant A allele (in rs2075876 SNP) showed a highly significant difference in RA patients compared with the control group ($P < 0.0001$), further supporting the notion that AIRE rs2075876 and rs760426 polymorphisms are involved in the genetic background of RA in the Egyptian population.

To the best of our knowledge, this is the first study establishing a relationship between the AIRE gene and the susceptibility to RA in Egyptian cohort. Our findings replicate previous studies associating SNPs rs760426 and rs2075876 in AIRE gene to RA heritability, disease activity, and severity in different ethnic groups. These two SNPs could be considered as RA susceptibility biomarkers potentially useful in disease screening. Future validation studies using larger cohorts are recommended to address mechanisms of *AIRE* polymorphisms in the pathogenesis of RA.

Authors' contribution All authors have seen and approved the manuscript and contributed significantly to the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement The study was approved by the Ethics Committee at the Faculty of Medicine, Suez Canal University, Egypt.

References

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet (London, England). 2010;376(9746):1094–108.
2. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res. 2002;4(Suppl 3):S265–72.
3. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet (London, England). 2001;358(9285):903–11.
4. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum. 2000;43(1):30–7.
5. Bali D, Gourley S, Kostyu DD, Goel N, Bruce I, Bell A, et al. Genetic analysis of multiplex rheumatoid arthritis families. Genes Immun. 1999;1(1):28–36.
6. Terao C, Yamada R, Ohmura K, Takahashi M, Kawaguchi T, Kochi Y, et al. The human AIRE gene at chromosome 21q22 is a genetic determinant for the predisposition to rheumatoid arthritis in Japanese population. Hum Mol Genet. 2011;20(13):2680–5.
7. Colobran R, Gimenez-Barcons M, Marin-Sanchez A, Porta-Pardo E, Pujol-Borrell R. AIRE genetic variants and predisposition to polygenic autoimmune disease: the case of Graves' disease and a systematic literature review. Hum Immunol. 2016;77(8):643–51.
8. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, et al. Positional cloning of the APECED gene. Nat Genet. 1997;17(4):393–8.
9. Consortium F-GA. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet. 1997;17(4):399–403.
10. Abramson J, Husebye ES. Autoimmune regulator and self-tolerance-molecular and clinical aspects. Immunol Rev. 2016;271(1):127–40.
11. Tazi-Ahnini R, McDonagh AJ, Wengraf DA, Lovewell TR, Vasilopoulos Y, Messenger AG, et al. The autoimmune regulator gene (AIRE) is strongly associated with vitiligo. Br J Dermatol. 2008;159(3):591–6.
12. Wengraf DA, McDonagh AJ, Lovewell TR, Vasilopoulos Y, Macdonald-Hull SP, Cork MJ, et al. Genetic analysis of autoimmune regulator haplotypes in alopecia areata. Tissue Antigens. 2008;71(3):206–12.
13. Shao S, Li XR, Cen H, Yin ZS. Association of AIRE polymorphisms with genetic susceptibility to rheumatoid arthritis in a Chinese population. Inflammation. 2014;37(2):495–9.

14. Ferrera F, Rizzi M, Sprecacenere B, Balestra P, Sessarego M, Di Carlo A, et al. AIRE gene polymorphisms in systemic sclerosis associated with autoimmune thyroiditis. Clinical immunology (Orlando, Fla). 2007;122(1):13–7.
15. Conteduca G, Ferrera F, Pastorino L, Fenoglio D, Negrini S, Sormani MP, et al. The role of AIRE polymorphisms in melanoma. Clin Immunol. 2010;136(1):96–104.
16. Garcia-Lozano JR, Torres-Agrela B, Montes-Cano MA, Ortiz-Fernandez L, Conde-Jaldon M, Teruel M, et al. Association of the AIRE gene with susceptibility to rheumatoid arthritis in a European population: a case control study. Arthritis Res Ther. 2013;15(1): R11.
17. Li X, Li T, Chen M, Chai Y. Association of AIRE gene polymorphisms with susceptibility to rheumatoid arthritis among ethnic Han Chinese from Shaanxi. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2016;33(3):373–7.
18. Feng ZJ, Zhang SL, Wen HF, Liang Y. Association of rs2075876 polymorphism of AIRE gene with rheumatoid arthritis risk. Hum Immunol. 2015;76(4):281–5.
19. Berczi B, Gerencser G, Farkas N, Hegyi P, Veres G, Bajor J, et al. Association between AIRE gene polymorphism and rheumatoid arthritis: a systematic review and meta-analysis of case-control studies. Sci Report. 2017;7(1):14096.
20. Bergstrom B, Lundqvist C, Vasileiadis GK, Carlsten H, Ekwall O, Ekwall AH. The rheumatoid arthritis risk gene AIRE is induced by cytokines in fibroblast-like synoviocytes and augments the pro-inflammatory response. Front Immunol. 2019;10:1384.
21. Zhao B, Chang L. The role of autoimmune regulator (AIRE) in peripheral tolerance. 2018;2018:3930750.