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Determination of *ETS1* gene single nucleotide polymorphism in Iranian patients with ankylosing spondylitis

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Ankylosing spondylitis (AS) is an inflammatory arthritis with unknown etiology. AS mostly affects the axial skeleton and peripheral joints. The genetic contribution is believed to be a major attributable reason of overall susceptibility to AS. *ETS1*, also known as the *avian erythroblastosis virus E26 (v-ets) oncogene homolog-1* gene, is essential in the development of immune cells in both adaptive and innate immunity. This study investigated the association of single nucleotide polymorphisms (SNPs) in the *ETS1* gene (rs1128334 and rs10893872) with ankylosing spondylitis in Iranian population. The study samples comprised 495 AS patients and 490 controls. All samples were selected from the Iranian population. Two SNPs were chosen from the *ETS1* gene (rs1128334 and rs10893872), and their association with AS was examined by applying the Real-time PCR allelic discrimination method. The results showed no significant associations between rs1128334 and rs10893872 SNPs and the risk of AS. However, the association between rs10893872 and the Bath Ankylosing Spondylitis Functional Index (BASFI) was significant (p=0.02) after Bonferroni correction, while BASFI was significantly increased in cases with CT in comparison to CC genotype. The results of this study on the Iranian population did not confirm the association of the *ETS1* gene SNPs with AS susceptibility; however, the association was significant in Han Chinese populations. The diversity in results among different populations is common in gene association studies of multifactorial diseases. Further investigations will be needed to identify other risk variants of the *ETS1* gene which are correlated with AS susceptibility.

Keywords: ankylosing spondylitis, *ETS1*, Single Nucleotide Polymorphism (SNP).

Introduction

Ankylosing spondylitis (AS) is an inflammatory rheumatologic disorder that primarily affects the spinal and, occasionally, peripheral joints. Inflammation and new bone formation, especially in the spine, can lead to severe disability and functional limitations [1]. It involves men three times more often than women. People of any age can develop AS, but it usually appears between the ages of 15 and 30 [2].

The etiopathogenesis of AS is not yet fully understood, but the pivotal role of genetic mechanisms has clearly been implicated by the strong association observed between disease risk and the human leukocyte antigen (HLA)-B27. HLA-B27 has been associated with risk of AS in approximately 70% of Iranian patients [3], while epidemiological investigations have demonstrated that nearly 90% of white AS patients in the United States and northern Europe harbor HLA-B27. Despite its strong association with AS, HLA-B27 may account for only 20% to 30% of the overall genetic risk of AS [4, 5].

Recent genome-wide association studies (GWASs) have identified several non-HLA loci associated with AS, including *ERAP1*, *IL23R*, *KIF21B*, *CYP2D6*, and two intergenic regions at 2p15 and 21q22 chromosomes [6, 7].

ETS1 (known as *avian erythroblastosis virus E26 (v-ets) oncogene homolog-1 gene*) knockout mice have a different pattern of deficiency in their immunologic pathways [8]. In adult humans, the *ETS1* gene is highly expressed mainly in immune tissues such as the thymus, spleen, and lymph nodes [9]. The association of this gene with SLE diseases has been documented in several studies [10-12]. GWASs of an Asian population revealed two susceptible SNPs, rs1128334 and rs10893872, for systemic lupus erythematosus (SLE) which had been previously reported as susceptible SNPs for this disease [13-15]. *ETS1* as a non-HLA gene has

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been associated with the proneness to AS, and the rs1128334 SNP of this gene was strongly associated with AS risk in Han Chinese people [7]. Given the essential role of the *ETS1* gene in the pathogenesis of autoimmune diseases and its frequently observed association with these diseases [16, 17], this study aimed to examine the association of the *ETS1* gene rs1128334 and rs10893872 SNPs with AS risk in an Iranian population.

Material and Methods

Patients and controls

The study group comprised 495 unrelated AS patients who were enrolled consecutively from the outpatient rheumatology clinic of Shariati Hospital, Tehran, Iran and 490 ethnically matched healthy controls (Table 1). The patient group consisted of 389 men and 106 women aged 38.3±10.4 years who met the modified New York criteria for AS [18]. The mean age of the 490 healthy controls (104 females and 386 males) was 38.1±10.6 years, and they had neither an autoimmune disorder nor spondyloarthropathies. All participants in the study were from the Iranian population, and they all signed an informed consent form for participation in this study. AS patients were evaluated for disease severity and functional abilities by a protocol based on the Assessment of Spondyloarthritis International Society (ASAS) core set [19], which consists of disease activity by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [20]; damage or deformity of the spine by Bath Ankylosing Spondylitis Metrology Index (BASMI) [21]; function by Bath Ankylosing Spondylitis Functional Index (BASFI) [22]; Bath Ankylosing Spondylitis Global Index (BAS-G); and pain score. Validated Persian versions of the BASFI and BASDAI questionnaires have been provided in the authors' previous studies [23]. To assess the quality of life, the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire was used [24]. This project was approved by the Human Research Ethics Committee of Tehran University of Medical Sciences.

SNP genotyping

Blood samples from cases and controls were collected in EDTA tubes, and genomic DNA was extracted using the phenol–chloroform method [25]. For genotyping the rs1128334 and rs10893872 SNPs, allelic discrimination approach was utilized using TaqMan MGB-based Real-time PCR (Applied Biosystems, Foster City, CA, USA). Genotyping was performed by approximately 30 ng of the genomic DNA of each sample according to the manufacturer's protocols provided by Applied Biosystems. PCR was carried out using 5 µl of the TaqMan Genotyping master mix (PN, 4371355), 0.25 µl of TaqMan Genotyping assay mix (PN, 4351376), 0.25 µl of distilled water, and 4.5 µl of genomic DNA in 10-µl reaction volumes.

Statistical analysis

The statistical package SPSS version 22 (SPSS Inc., Chicago, IL, USA) was used for analysis. Chi-square test was applied to assess genotype and allele frequencies between patients and controls. The genotype and allele distributions were determined in each group, and odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. The genotype distributions of rs1128334 and rs10893872 were tested for deviation from the Hardy-Weinberg equilibrium in controls [26]. To adjust for multiple comparisons, the Benjamini–Hochberg method was used to control the false discovery rate (FDR) [27]. SHEsis online software was used for haplotype construction, genotype analysis, linkage disequilibrium, and the Hardy-Weinberg equilibrium (HWE) [28].

Table 1. Ethnic groups

Ethnic	Case		Control	
	Count	Percent	Count	Percent
Fars	222	44.8	237	48.4
Turk	138	27.9	133	27.1
Kurd	56	11.3	50	10.2
Lor	42	8.6	37	7.6
Other	37	7.4	33	6.7
Total	495	100%	490	100%

Results

The current research aimed to genotype two SNPs (rs1128334 and rs10893872) in 495 AS patients and 490 healthy controls. No significant deviation from HWE was found in the control group. Analysis results did not show any significant association between the rs1128334 and rs10893872 SNPs of the *ETS*1 gene and risk of AS in the Iranian population. There was no significantly different distribution of either allele or genotype between AS patients and healthy subjects (Table 2). Furthermore, there was no significant association in haplotype frequencies between the case and control groups (Table 3). Next, the association between the two genotyped SNPs with clinical manifestations, namely BASMI, BASFI, BASDAI, ASQOL and NRSpain was investigated through the ANNOVA and Post-Hoc tests (Table 4). After ANNOVA test, associations between BASMI, and BASFI with rs10893872 were significant

(p= 0.04, p=0.03 respectivity). With Post-Hoc analysis only BASFI score was significantly different among AS patients with CC, CT, and TT genotypes of rs10893872 SNP (p=0.02). BASFI was significantly increased in AS patients with the rs10893872 CT genotype in comparison with those who had the rs10893872 CC genotype after adjustment with the Bonferroni method (Table 4).

Discussion

Several GWASs have identified numerous genetic factors influencing susceptibility in the risk of autoimmune disease. In the current study, one of the non-HLA loci, which was already observed to be contributing to AS susceptibility, was investigated. The first member of the ETS gene family was V-Ets, and it was identified as a fusion oncogene of the avian transforming retrovirus E26 that induces both erythroblastic and myeloblastic leukemia in chickens [29].

The *ETS1* gene encodes protein C-ets-1 which is a member of the ETS family of transcription factors. Most of the ETS family proteins have the ETS domain in their N-terminal regions, which can bind to DNA by the third α-helix at the helix–turn–helix structure of the ETS domain [9]. Moreover, ETS family proteins interact with other transcription factors, so they can act as regulators on gene expression. They regulate many important processes in cell life, such as mitosis, development, and death [30].

Some studies have revealed its developmental role even in immune cells. As an example, ETS1 is involved in signal transduction pathways during T cell differentiation, playing a role in the stimulation of an intense response to presented peptides [30]. Furthermore, the presence of ETS1 has essential impacts on B cell development and regular immunoglobulin pattern production [16].

Table 2. Allele and genotype distribution of *ETS1* in ankylosing spondylitis (AS) patients and healthy controls

dbSNP	Alleles/genotypes	AS (n=495) N (%)	Control (n=490) N (%)	*p*	OR (95% CI)
	C	514 (52)	478 (49)	0.2	1.1 (0.9-1.3)
	T	476 (48)	494 (51)	0.2	0.9 (0.7-1.1)
rs10893872	CC	130 (26.3)	122 (24.8)	0.6	1.08 (0.8-1.4)
	CT	256 (51.8)	234 (47.8)	0.2	1.1 (0.9-1.5)
	TT	109 (21.9)	134 (27.4)	0.06	0.7 (0.5-1.1)
HWE			0.51		
	C	867 (87.6)	878 (89.6)	0.15	0.8 (0.6-1.1)
	T	123 (12.4)	102 (10.4)	0.15	1.2 (0.9-1.6)
rs1128334	CC	420 (84.8)	393 (80.3)	0.56	1.1 (0.8-1.5)
	CT	71 (14.4)	92 (18.8)	0.06	0.7 (0.5-1.1)
	TT	4 (0.8)	5 (0.9)	0.7	0.8 (0.2-2.9)
HWE			0.78		

AS, ankylosing spondylitis; $p \leq 0.025$ was statistically significant after Bonferroni correction; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval.

Table 3. Haplotype analysis of rs10893872 and rs1128334 in ankylosing spondylitis (AS) patients and healthy controls

Haplotypes	Case (freq)	Control (freq)	Chi^2	*p*	Odds Ratio (95%CI)
C C	271 (52.7)	215 (48.2)	1.95	0.163	1.20 (0.93-1.54)
T C	202 (39.3)	185 (41.5)	0.47	0.492	0.91 (0.70-1.18)
T T	41 (8)	46 (10.3)	1.58	0.208	0.75 (0.48-1.17)

* Haplotypes with frequency more than 0.03 were selected for haplotype analysis

Table 4. Association of *ETS1* gene rs10893872 and rs1128334 genotypes with various clinical features of the 495 AS patients

Characteristic	rs10893872 CC	rs10893872 CT	rs10893872 TT	*p*	Post-Hoc	Corrected *p**
BASDAI	4.15 ± 2.15	4.82 ± 2.47	4.81 ± 2.09	0.11	CC *vs.* CT	0.14
					CC *vs.* TT	0.31
					CT *vs.* TT	1.00
BASFI	3.24 ± 2.36	4.21 ± 2.62	3.95 ± 2.50	0.03	CC *vs.* CT	0.02
					CC *vs.* TT	0.34
					CT *vs.* TT	1.00
BASMI	3.59 ± 1.65	4.13 ± 2.05	4.36 ± 1.64	0.04	CC *vs.* CT	0.14
					CC *vs.* TT	0.06
					CT *vs.* TT	1.00
ASQoL	6.61 ± 4.44	8.32 ± 5.48	7.67 ± 5.03	0.07	CC *vs.* CT	0.07
					CC *vs.* TT	0.75
					CT *vs.* TT	1.00
NRSPain	5.609 ± 0.66	5.58 ± 0.47	5.42 ± 0.71	0.18	CC *vs.* CT	0.42
					CC *vs.* TT	0.24
					CT *vs.* TT	1.00
Characteristic	**rs1128334 CC**	**rs1128334 CT**	**rs1128334 TT**	***p***	**Post-Hoc**	**Corrected *p****
BASDAI	4.62 ± 2.37	4.87 ± 2.41	5.75 ± 0.91	0.68	CC *vs.* CT	1.00
					CC *vs.* TT	1.00
					CT *vs.* TT	1.00
BASFI	3.88 ± 2.61	3.99 ± 2.43	4.95 ± 0.77	0.82	CC *vs.* CT	1.00
					CC *vs.* TT	1.00
					CT *vs.* TT	1.00
BASMI	4.02 ± 1.89	4.37 ± 1.94	5.00 ± 0.84	0.47	CC *vs.* CT	0.93
					CC *vs.* TT	1.00
					CT *vs.* TT	1.00
ASQoL	7.71 ± 5.07	8.28 ± 5.95	6.00 ± 5.65	0.74	CC *vs.* CT	1.00
					CC *vs.* TT	1.00
					CT *vs.* TT	1.00
NRSPain	9.07 ± 5.77	9.00 ± 4.58	8.50 ± 3.53	0.98	CC *vs.* CT	1.00
					CC *vs.* TT	1.00
					CT *vs.* TT	1.00

**p* value correction by Bonferroni method.

In addition to the adaptive immune response, ETS1 plays some pivotal roles in innate immunity, such as macrophage activation, NK cell and granulocyte differentiation [31, 32]. Based on a GWAS by Han et al., the *ETS1* was identified as a risk factor for SLE. This study reported the association of some variants of the *ETS1* gene including rs1128334, rs4937333, and rs6590330 with SLE [33]. Further studies examined the association of *ETS1* gene rs11221332 SNP in Caucasian subjects and a Chinese population with rheumatoid arthritis (RA), demonstrating significant relations in both mentioned diseases [34, 35]. In addition, the association of *ETS1* gene rs11221332 SNP was observed with celiac disease in a European population [36]. The contribution of *ETS1* to AS susceptibility in Han Chinese people was assessed through the evaluation of seven SNPs of *ETS1*, but only rs1128334 was significantly associated with AS [37]. The present study did not show any significant association between allele frequencies and genotype distributions of either rs1128334 or rs10893872 SNPs of the *ETS1* gene and AS susceptibility in the Iranian population. The association between clinical symptoms including BASDAI, ASQOL, NRSpain, BASMI, and BASFI (Table 4) with genotype distributions in AS patients was analyzed. A significant correlation was observed between the BASFI score of AS patients and rs10893872 genotypes. The association of rs1128334 SNP with AS in the current research contrasted with the results of Shan et al. [7]. This discrepancy might be due

to differences in sample size and ethnicity, which causes a diverse genetic background. Another conceivable explanation for this difference is patient exposure to various environmental factors, which is accompanied by different sets of clinical manifestations. Nonetheless, different findings should be noted, because it appeared that rs1128334 had a significant association with AS in the Han Chinese population, but it did not have in the Iranian population. The power of this study is the favorably large sample size. However, evaluation of a small number of SNPs might be the weak aspect of this research. Through the typical genetic analysis techniques, the identification of small effects of multiple SNPs was avoided. However, other approaches such as gene set analysis (GSA) may be advantageous in detecting additional genetic loci for complex disorders [38].

Conclusion

Overall, this study evaluated the *ETS1* gene rs1128334 and rs10893872 SNPs in association with AS. No significant associations were detected with regard to the alleles and genotypes of both positions. However, the BASFI score was significantly increased in AS patients with the rs10893872 CT genotype in comparison with those who have the rs10893872 CC genotype. Further studies are needed to identify other involved polymorphisms and genetic risk factors contributing to AS disease in the Iranian population.

Conflicts of interest

The authors declare no conflicts of interest.

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