RHEUMATOLOGY RESEARCH JOURNAL

Vol. 1, No. 1, October 2016, 11-16
Webpage: http://rheumres.org
Email: editor@rheumres.org
ISSN: 2476-5856
doi: 10.22631/rr.2016.40685

Research Article **Open Access**

Determination of the association of *ETS1* and *WDFY4* gene polymorphisms with systemic lupus erythematosus in an Iranian population

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Systemic Lupus Erythematosus (SLE) is a heterogeneous complex relapsing-remitting autoimmune disease. The role of genetics is obvious in predisposition of the disease. Several Single Nucleotide Polymorphisms (SNPs) in *ETS1* and *WDFY4* showed association with SLE in genome-wide association studies. The aim of this study was to examine the association of the SNPs in *ETS1* and *WDFY4* genes with SLE in an Iranian population. This study was performed on 280 patients that were not related to one another, and 281 healthy control subjects matched based on age, sex, and ethnicity, all of which were of Iranian origin. Rs10893872 and rs1128334 in the *ETS1* gene, and rs877819 and rs707397 in the *WDFY4* gene were genotyped using MGB TaqMan Allelic Discrimination Real-Time PCR. Our results showed no association in all mentioned SNPs with the susceptibility and clinical features of SLE in the Iranian population. The results were not consistent with genome-wide association studies performed on Asian and Caucasian populations.

Keywords: *ETS1*, systemic lupus erythematosus, *WDFY4*.

Introduction

Systemic Lupus Erythematous (SLE) is a relapsing-remitting autoimmune disorder which involves many different organs and can be characterized by several immunological abnormalities. These include the presence of hyper-reactive T and B cells and the production of an array of auto-antibodies against serological, intra-cellular, nucleic acid and cell surface antigens [1, 2]. The prevalence of SLE is approximately 1 in 2,500 Europeans with a sex ratio of 9:1. The disease is more frequent in people with non-European ancestry [2, 3]. Davatchi et al. reported a prevalence of 0.04% for SLE in a WHO-ILAR COPCORD study conducted in Iran.

Considering the wide range of clinical manifestations and the heterogeneous nature of the SLE phenotype, the American College of Rheumatology (ACR) has defined Eleven clinical criteria to identify patients, namely malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, pleuritis, renal disorders, neurologic disorders, hematologic disorders, immunologic disorders and, positive antinuclear antibodies [4].

Despite the fact that the exact etiology of SLE remains unclear, strong genetic linkage has been well accepted for this disease. Its heritability is estimated to be approximately 66%, with concordance rates of 24% to 57% in monozygotic twins and 2% to 5% in dizygotic twins[5]. The role of genetic predisposition is highly attributable to the disease. According to recent studies, SLE is characterized as a polygenic genetic model. As many as 100 genes could be involved, and every gene may have only a moderate effect size [6-8]. According to recent genome-wide association studies (GWAS), *ETS1 and WDFY4* were introduced as novel predisposing genes for SLE [9, 10].

V-ets avian erythroblastosis virus E26 oncogene homolog 1 (ETS1) is a negative regulator of B-cell differentiation and T helper 17 (Th17) cell proliferation. It has been shown that Patients with SLE present a reduced expression of *ETS1*, which might contribute to abnormal B-cell differentiation into auto-antibody secreting plasma cells and increased number

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Received: 24 May 2016; **Accepted:** 18 September 2016

of Th17 cells 3. Moreover, two recent genome-wide association studies on an Asian population (SLE patients from Hong Kong, Mainland China, Thailand, and China Han population) indicated that, variants (rs6590330, rs7932088, rs10893872, rs4937333, rs1128334) of the *ETS1* gene have significant association with SLE [9, 10], confirming the SLE-like disease observed in *ETS1*-deficient mice [11].

WDFY family member 4 (WDFY4) is a huge protein with unknown functions. WDFY4 is expressed predominantly in immune tissues such as lymph nodes, the spleen, the thymus and the tonsils (http://www.ncbi.nlm.nih.gov/UniGene/ESTProfileViewer.cgi?uglist=Hs.287379). Two recent genome-wide studies in Asia have identified several variants (rs7097397, rs10857650, rs877819) of this gene associated with SLE [9, 10].

Considering the differences in genetic and environmental factors affecting different populations, as well as the need for replication studies in various populations, in this study, we have investigated the association of *ETS1* (rs10893872, rs1128334) and *WDFY4* (rs877819, rs707397) polymorphisms with SLE susceptibility in the Iranian population. We have also investigated the association of these polymorphisms with different clinical features of the patients.

Materials and Methods

Subjects

The study population was made up of 280 patients (who were not related to one another) with SLE who were recruited from the outpatient clinic of the Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences. All SLE patients met the revised 1982 American College of Rheumatology (ACR) classification criteria for SLE.

281 healthy control subjects had no clinical evidence or family history of any types of rheumatologic or autoimmune disorders 4. The SLE patient group had a mean age of 36.77±11.72 years (244 females and 36 males) and the healthy control group had a mean age of 38.04±12.71 years (246 females and 35 males). All patients and healthy controls had Iranian ancestry. Healthy controls were matched with patients with regard to their gender, ethnicity, and age. To determine the association between two SNP variations and clinical features of SLE, all of the clinical manifestations of the patients were recorded. Informed consent was obtained from all of the subjects. The Ethical Committee of Tehran University of Medical Sciences approved this study.

Genotyping (DNA preparation and analysis)

Genomic DNA was extracted from peripheral blood leukocytes using a phenol-chloroform method [12]. The extracted DNA was stored at -20°C until it was analyzed. Approximately 30ng of the genomic DNA of each sample was used for genotyping. Amplification was performed in 10µl reaction volume, containing 5µl of the TaqMan Genotyping master mix (PN, 4371355), 0.25µl of the TaqMan Genotyping assay mix (PN, 4351376), 0.25µl of distilled water, and 4.5µl of genomic DNA. The genotyping of *ETS1* (rs10893872, rs1128334) and *WDFY4* (rs877819, rs707397) were performed using Real Time PCR using the TaqMan allelic discrimination method (Applied Biosystems, Foster City, CA, USA). The characteristics of the selected SNPs are summarized in Table 1.

Statistical analysis

The distribution of genotypes in the control subjects was examined for deviation from Hardy Weinberg equilibrium using the χ^2 test. Analysis of the data was carried out using the IBM™ SPSS version 20 (SPSS Inc., USA). The genotypic and allelic distribution between patients and controls was assessed by the χ^2 test and by binary logistic regression. The Odds Ratio (OR), with 95% Confidence Intervals (95% CI), was calculated from logistic regression analysis. *P*-values of less than 0.05 were considered statistically significant. The association of SNPs to clinical manifestations was also determined by the χ^2 test. We used the Benjamini- Hochberg method to control false discovery rate (FDR) for multiple comparisons.

Results

Distribution of ETS1 and WDFY4 SNP genotypes among patients and controls

Distribution of rs10893872 and rs1128334 genotypes

Table 1. Characteristics of selected SNPs

Genes	SNPs	Minor allele	Polymorphism Type	Location/Exon	Position GRCh37
ETS1	rs10893872	C	C/T, Transition Substitution	Intragenic region	Chr.11 128325553
ETS1	rs1128334	T	C/T, Transition Substitution	UTR-3	Chr.11 128328959
WDFY4	rs877819	A	A/G, Transition Substitution	Intron	Chr.10 50042951
WDFY4	rs7097397	A	A/G, Transition Substitution	Missense Mutation	Chr.10 50025396

in the *ETS1* gene and rs877819 and rs7097397 genotypes in the *WDFY4* gene did not show any significant deviation from the Hardy-Weinberg equilibrium in the healthy control subjects. None of the SNPs in either gene had significant distribution in patients by comparison to the control group (Table 2), however, we observed a mild shift to G allele and GG genotype in *WDFY4* (rs7097397) in comparison to the control group.

We next investigated the association of these four SNPs with the clinical manifestations of SLE. Such manifestations include photo-sensitivity, malar rash, discoid rash, oral ulcers, arthritis, pleuritis, pericarditis, proteinuria, seizures, leucopenia, anti-ds DNA, and ANA. After a false discovery rate (FDR) test, we did not detect any correlation between these SNPs and the mentioned clinical manifestations (Table 3 and 4).

Discussion

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, which is clinically heterogeneous with a wide range of clinical manifestations, which differ from patient to patient [13]. It is now widely accepted that genetic components play important roles in the abnormal immune responses and pathogenesis of SLE, thus, people carrying the special genes are susceptible to the disease. Studies in animal models have also confirmed that a large part of susceptibility to SLE is due to genetic predisposition [14]. However, SLE does not follow the simple Mendelian inheritance and no major single gene governs the pathogenesis, instead a polygenic model is expected, as genome-wide association studies have identified more than 30 associated loci [3, 15].

ETS1 is a member of the ETS family of transcription factors defined by the conserved DNA-binding domain known as ETS, which is a winged helix-turn-helix motif, located on chromosome number [11]. The protein contains 485 amino acids, which function as transcriptional activators and suppressors of numerous genes (http://www.ncbi.nlm.nih.gov/gene/2113) [16]. ETS1 regulates lymphocyte differentiation and development through regulating the B-cell differentiation and T helper-17 proliferation [16, 17]. ETS1 deficient Th-1 cells show increased and reduced secretion of IL-10 and IL-2 respectively. ETS1 deficient B-cells show enhanced differentiation to IgM secreting plasma cells and are hyper-responsive to TLR9, which indicates the possible involvement of ETS1 in the pathogenesis of SLE [18].

Kathleen et al. showed that a microsatellite repeat polymorphism in *ETS1* 3` flanking region is associated with SLE phenotypes [19]. Two genome-wide association studies on an Asian population also demonstrated a high association of rs6590330 and rs10893872 with SLE [9, 10].

Table 2. Distribution of ETS1 and WDFY4 SNP alleles and genotypes among patients and controls

Odds Ratio (CI 95%)	Adj.Pa	P	Controls N (%)	Patients N (%)	Alleles/ Genotypes	SNPs	Genes
1		Reference	278 (49.46)	277 (49.46)	T		
0.99 (0.79-1.26)	0.96	0.96	284 (50.53)	283 (50.53)	C		
1		Reference	74 (26.3)	73 (26.1)	TT	rs10893872	ETS1
1.02 (0.682-1.530)	0.99	0.918	130 (46.3)	131 (46.8)	CT		
1.00 (0.636-1.573)	0.99	0.998	77 (27.4)	76 (27.1)	CC		
			0.21	0.28	HWE		
1		Reference	512 (91.10)	497 (88.75)	C		
1.30 (0.88-1.19)	0.38	0.19	50 (8.89)	63 (11.25)	T		
1		Reference	233 (82.9)	220 (78.6)	CC	rs1128334	ETS1
1.31 (0.854-2.017)	0.43	0.215	46 (16.4)	57 (20.4)	CT		
1.59 (0.263-9.598)	0.82	0.614	2 (0.7)	3 (1.1)	TT		
			0.87	0.74	HWE		
1		Reference	240 (42.70)	228 (40.71)	G		
1.08 (0.86-1.38)	0.66	0.50	322 (57.29)	332 (59.28)	A		
1		Reference	56 (19.9)	45 (16.1)	GG	rs877819	WDFY4
1.34 (0.847-2.126)	0.43	0.211	128 (45.6)	138 (49.3)	AG		
1.24 (0.768-2.017)	0.60	0.375	97 (34.5)	97 (34.6)	AA		
			0.25	0.73	HWE		
1		Reference	289 (51.42)	318 (56.78)	G		
0.81 (0.64-1.02)	0.28	0.07	273 (48.57)	242 (43.21)	A		
1		Reference	71 (25.3)	94 (33.6)	GG	rs7097397	WDFY4
0.67 (0.453-0.985)	0.34	0.042	147 (52.3)	130 (46.4)	AG		
0.671 (0.418-1.078)	0.39	0.099	63 (22.4)	56 (20.0)	AA		
			0.43	0.37	HWE		

Table 3. Distribution of the ETS1 (rs1128334) and (rs10893872) genotypes among SLE phenotypes

Adj.P*	P	rs10893872 Genotype TT (%)	CT (%)	CC (%)	Adj.P*	P	rs1128334 Genotype CC (%)	CT (%)	TT (%)	Frequency N (%)	Clinical features
0.33	0.25	54 (26.0)	96 (47.1)	56 (26.9)	0.33	0.25	159 (76.4)	46 (22.1)	3 (1.4)	208 (74.3)	Photo-sensitivity
0.09	0.03	33 (28.9)	51 (44.7)	30 (26.3)	0.09	0.03	81 (71.1)	31 (27.2)	2 (1.8)	114 (40.9)	Malar rash
0.49	0.41	5 (33.3)	5 (33.3)	5 (33.3)	0.49	0.41	10 (66.7)	5 (33.3)	0 (0.0)	15 (5.4)	Discoid rash
0.89	0.89	20 (25.0)	38 (47.5)	22 (27.5)		0.89	64 (80.0)	15 (18.8)	1 (1.3)	80 (28.7)	Oral ulcer
0.09	0.01	52 (25.5)	95 (46.6)	57 (27.9)	0.89	0.01	162 (79.4)	42 (20.6)	0 (0.0)	204 (72.9)	Arthritis
0.74	0.68	16 (30.8)	22 (42.3)	14 (26.9)	0.09	0.68	42 (80.8)	9 (17.3)	1 (1.9)	52 (18.6)	Pleuritis
0.14	0.08	5 (33.3)	5 (33.3)	5 (33.3)	0.74	0.08	12 (80.0)	2 (13.3)	1 (6.7)	15 (5.4)	Pericarditis
0.14	0.08	37 (30.3)	53 (43.4)	32 (26.2)	0.14	0.08	98 (80.3)	21 (17.2)	3 (2.5)	122 (43.0)	Proteinuria
0.14	0.07	5 (25.0)	8 (40.0)	7 (35.0)	0.14	0.07	12 (60.0)	8 (40.0)	0 (0.0)	20 (7.2)	Seizures
0.09	0.03	27 (23.5)	56 (48.7)	32 (27.8)	0.09	0.03	99 (86.1)	15 (13.0)	1 (9.0)	115 (41.1)	Leukopenia
0.33	0.25	66 (25.0)	125 (47.3)	73 (27.7)	0.33	0.25	207 (78.4)	54 (20.5)	3 (1.1)	264 (95.3)	Anti-dsDNA
0.09	0.03	73 (26.4)	128 (46.2)	76 (27.4)	0.09	0.03	217 (78.3)	57 (20.6)	3 (1.1)	277 (98.9)	ANA

Table 4. Distribution of the WDFY4 (rs877819) and (rs7097397) genotypes among SLE phenotypes

Clinical features frequency	rs877819 Genotype N (%)	GG (%)	GA (%)	AA (%)	P	Adj.P*	rs7097397 Genotype GG (%)	GA (%)	AA (%)	P	Adj.P*
Photo-sensitivity	208 (74.3)	34 (16.3)	102 (49.0)	72 (34.6)	0.97	0.97	67 (32.2)	99 (47.6)	42 (20.2)	0.70	0.85
Malar rash	114 (40.9)	19 (16.7)	55 (48.2)	40 (35.1)	0.94	0.97	29 (25.4)	66 (57.9)	19 (16.7)	0.005	0.06
Disciod rash	15 (5.4)	4 (26.7)	7 (46.7)	4 (26.7)	0.49	0.65	6 (40.0)	4 (26.7)	5 (33.3)	0.23	0.69
Oral ulcer	80 (28.7)	15 (18.8)	31 (38.8)	34 (42.5)	0.07	0.24	29 (36.3)	36 (45.0)	15 (18.8)	0.83	0.90
Arthritis	204 (72.9)	34 (16.7)	102 (50.0)	68 (33.3)	0.73	0.87	67 (32.8)	88 (43.1)	49 (24.0)	0.019	0.11
Pleuritis	52 (18.6)	7 (13.5)	23 (44.2)	22 (42.3)	0.43	0.65	19 (36.5)	21 (40.4)	12 (23.1)	0.61	0.85
Pericarditis	15 (5.4)	0 (0.0)	7 (46.7)	8 (53.3)	0.12	0.29	7 (46.7)	5 (33.3)	3 (20.0)	0.49	0.85
Proteinuria	122 (43.0)	19 (15.6)	56 (45.9)	47 (38.5)	0.08	0.24	39 (32.0)	56 (45.9)	27 (22.1)	0.71	0.85
Seizures	20 (7.2)	1 (5.0)	10 (50.0)	9 (45.0)	0.07	0.24	9 (45.0)	10 (50.0)	1 (5.0)	0.19	0.69
Leukopenia	115 (41.1)	15 (13.0)	50 (43.5)	50 (43.5)	0.033	0.24	38 (33.0)	55 (47.8)	22 (19.1)	0.91	0.91
Anti-dsDNA	264 (95.3)	45 (17.0)	126 (47.7)	93 (35.2)	0.17	0.34	87 (33.0)	124 (47.0)	53 (20.0)	0.61	0.85
ANA	277 (98.9)	45 (16.2)	137 (49.5)	95 (34.3)	0.46	0.65	92 (33.2)	129 (46.6)	56 (20.2)	0.42	0.85

Jing Zhang et al. also examined serum IL-17 levels from 283 SLE cases, and reported a significant correlation between previously determined risk variants in *ETS1* and the concentration of IL-17 in their serum [20]. It is also reported that genetic variants of *ETS1* affect STAT1 binding. The results of the genome-wide association study on an Asian population was replicated for a Caucasian population for *ETS1* 21. In our study, we adopted rs1128334 instead of rs6590330 because the study of Yang et.al. show that it is in 3`UTR and correlates with the expression of *ETS1* [10]. Rs10893872 has a high linkage disequilibrium (LD) with rs4937333 [10]. Our results did not confirm previously presented data in Asian and Caucasian populations. We observed no significant association between any of the selected SNPs and SLE in Iranian population (Table 2). There were also no significant correlation between the clinical features of SLE and the studied SNPs, which contrasts with the study performed on the Han population [22].

WDFY4 is a 3184 amino acid protein with unknown functions, which is expressed in secondary immune tissues. The protein includes WD40 and BEACH (Beige and Chediak-Higashi) domains (http://www.ncbi.nlm.nih.gov/gene/57705). WD40 is found in a number of eukaryotic proteins and has many functions including adaptor/regulatory modules in signal transduction, pre-mRNA processing, and cytoskeleton assembly. The domain typically contains a GH dipeptide near the N-terminus and a WD dipeptide at the C-terminus, between which a conserved core exists that creates a propeller-like platform to bind other proteins either stably or reversibly (http://www.ncbi.nlm.nih.gov/Structure/ cdd/ cddsrv.cgi?uid=100117). The BEACH domain is important in membrane trafficking (http://www.ncbi.nlm.nih.gov/Structure/cdd/cddsrv.cgi?uid=207648).

We decided to use rs7097397 and rs877819 in the study, due to the results of genome-wide association studies on Asian populations, in which both of the SNPs showed association with SLE [9, 10]. Rs7097397 is in the coding region Arg1816Gln of the gene and can be considered as a functional SNP, while rs877819 has been shown to change the binding affinity of the Yin Yang 1 transcription factor and down regulate *WDFY4* 10. Our results were not consistent with those of the GWA studies on an Asian population as there were no associations between both SNPs with the disease (Table 2).

In conclusion, our results did not confirm the results of other association studies performed on Asian and Caucasian populations. We did not observe correlation between the SNPs and Systemic Lupus Erythematous, or between the SNPs and SLE clinical features. This data indicates the genetic and environmental differences within different populations.

Conflict of interests

Authors have no conflict of interests.

Acknowledgment

This work was partially supported by a research grant [grant number: 90-04-41-14909] from the Deputy of Research, Tehran University of Medical Sciences.

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