Analysis of Systemic Sclerosis-associated Genes in a Turkish Population

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ABSTRACT. ***Objective.*** To evaluate the genetic background of systemic sclerosis (SSc) in the Turkish population.

Methods. There were 354 cases and 718 unaffected controls from Turkey genotyped for the most relevant SSc genetic markers (*IRF5*-rs10488631, *STAT4*-rs3821236, *CD247*-rs2056626, *DNASE1L3*-rs35677470, *IL12A*-rs77583790, and *ATG5*-rs9373839). Association tests were conducted to identify possible associations.

Results. Except for *ATG5*, all the analyzed genes showed either significant associations (*IRF5*: p = 1.32E–05, OR 1.76; *CD247*: p = 2.20E–03, OR 0.75) or trends of association (*STAT4*: p = 0.066, OR 1.21; *IL12A*: p = 0.079, OR 4.07; *DNASE1L3*: p = 0.097, OR 1.41) with the overall disease or with specific phenotypes.

Conclusion. The genetic component of SSc seems to be similar between Turks and Europeans. (J Rheumatol First Release May 1 2016; doi:10.3899/jrheum.160045)

Key Indexing Terms:
SYSTEMIC SCLEROSIS GENETICS TURKEY

Large-scale genetic analyses have represented a substantial step forward toward the understanding of the etiology of autoimmune processes[1]. One of the autoimmune diseases that has benefitted the most from this type of study is systemic sclerosis (SSc), a complex polygenic condition characterized by extensive fibrosis of the skin and internal organs, vascular damage, and presence of autoantibodies against nuclear antigens[2]. To date, around 20 genetic loci are firmly associated with SSc susceptibility[3]. However, most genetic studies on this disease have been performed in European populations, and additional studies in other ancestries are required to continue unraveling its genetic component. A clear example of a population for which no solid data regarding SSc genetics are available is the Turkish population. Although Turks show a genetic relatedness with Europeans, Middle Easterners, and South/Central Asians, it has been reported that their genetic structure is unique[4].

Considering the above, we decided to evaluate for the first time the population-specific relationship between the most relevant SSc risk genes outside the HLA region described in the 2 most powered large-scale studies [a genome-wide association study (GWAS) and an Immunochip study in Europeans][5,6] and disease predisposition in Turks. These include *IRF5*, *STAT4* (both crucial in the Type I interferon pathway), *CD247* (encoding the ζ chain of the T cell receptor), *DNASE1L3* (involved in DNA fragmentation during apoptosis), *IL12A* (encoding a subunit of the interleukin 12 that regulates different T cell responses), and *ATG5* (involved in autophagy processes)[7].

MATERIALS AND METHODS

Study population. In total, 354 patients with clinically defined SSc, i.e., diagnosed as having limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) according to LeRoy, *et al*[8], and 718 healthy individuals were included in our study. Both cases and controls were from Istanbul, Turkey. However, analysis of ancestry-informative markers was not performed, and

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therefore a population stratification could not be ruled out, which represents a limitation of our study. Informed written consent from all participants and approval from the responsible committee on human experimentation of all centers (Gaziantep Medical Faculty and Istanbul Bilim University) were obtained. All patients with SSc fulfilled the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for this disease[9,10].

The case set was further subdivided according to the degree of skin involvement into lcSSc and dcSSc, as well as according to the presence/absence of other relevant clinical manifestations such as anticentromere antibodies (ACA), antitopoisomerase antibodies (ATA), interstitial lung disease (ILD), and digital ulcers (DU). ACA were determined by their characteristic distinctive pattern on human epithelial cell line 2 cells, and ATA were detected using a line immunoassay (EUROLINE ANA Profile 3, Euroimmun) according to the manufacturer's protocol. ILD was diagnosed by high-resolution computed tomography (HRCT) and pulmonary function test (PFT) in all cases (forced vital capacity and/or diffusion capacity of the lung of < 75% of predicted was used as the cutoff value to define presence of ILD). Both methods were performed routinely in the first year, with a subsequent control by PFT and yearly chest radiograph (if abnormal PFT was detected during the followup, patients were then subjected to yearly HRCT). DU was defined as a loss of both epidermis and dermis in an area of at least 2 mm in diameter on the distal phalanx of the fingers. Table 1 shows the prevalence of each clinical feature in our study cohort.

Single-nucleotide polymorphism (SNP) selection criteria and genotype methods. We followed a candidate gene strategy by selecting the lead signals of the most associated non-HLA genes in Europeans described in both the GWAS by Radstake, *et al*[5] (*IRF5*-rs10488631, *STAT4*-rs3821236, and *CD247*-rs2056626) and the Immunochip study by Mayes, *et al*[6] (*DNASE1L3*-rs35677470, *IL12A*-rs77583790, and *ATG5*-rs9373839). The overall statistical power of our study for each analyzed marker is shown in Table 2.

DNA was extracted from peripheral white blood cells following standard procedures. The genotyping of the whole SSc sample set and part of the control group (219 samples) was performed using predesigned TaqMan assays in an ABI 7900HT (Applied Biosystems), whereas the remaining control data (499 samples) were obtained from a previously published Immunochip study[11] to increase the statistical power of our analyses.

Statistical analyses. Data analysis was performed using PLINK, v 1.07 (pngu.mgh.harvard.edu/purcell/plink)[12]. Association tests were conducted by performing 2 × 2 contingency tables, chi-square, and/or Fisher's exact tests when appropriate to obtain p values, OR, and 95% CI. The statistical threshold was set at 0.05. Benjamini and Hochberg step-up false discovery rate (FDR) control correction for multiple testing[13] was applied to the p values in the case/control analyses.

Table 1. Main clinical features of the Turkish cohort of patients with SSc included in this study. Values are n (%)* unless otherwise specified.

Features	Values
Age at diagnosis, yrs, median (IQR)	50 (41–62)
Women	327 (92.37)
Men	27 (7.63)
lcSSc	191 (53.95)
dcSSc	163 (46.05)
ACA+	73 (23.03)
ACA–	244 (76.97)
ATA+	166 (47.43)
ATA–	184 (52.57)
ILD+	212 (60.40)
ILD–	139 (39.60)
DU+	187 (53.28)
DU–	164 (46.72)

* Percentages refer to the total individuals with available data. SSc: systemic sclerosis; IQR: interquartile range; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ACA: anticentromere antibodies; ATA: antitopoisomerase antibodies; ILD: interstitial lung disease; DU: digital ulcers

RESULTS

No significant deviation from the Hardy-Weinberg equilibrium ($p < 0.05$) was observed for any of the analyzed SNP. In an initial approach, we compared the SSc group against controls to test for possible associations with the overall disease. Statistically significant differences between the allele frequencies of the global SSc group and the control set were observed for *IRF5*-rs10488631 (p = 1.32E–05, OR 1.76, 95% CI 1.36–2.28) and *CD247*-rs2056626 (p = 2.20E–03, OR 0.75, 95% CI 0.62–0.90). These association signals remained significant after adjusting for multiple testing (*IRF5*-rs10488631: p_{FDR} = 7.90E–05; *CD247*-rs2056626: p_{FDR} = 6.58E–03). Suggestive p values were also detected for *STAT4*-rs3821236 (p = 0.066, OR 1.21, 95% CI 0.99–1.48), *DNASE1L3*-rs35677470 (p = 0.097, OR 1.41, 95% CI 0.94–2.12), and *IL12A*-rs77583790 (p = 0.079, OR 4.07, 95% CI 0.74–22.30; Table 3).

When the different SSc case subsets were compared against the control population, statistical significance was reached in the analysis of most phenotypes for *IRF5*-rs10488631 and *CD247*-rs2056626 (Table 3). Additionally, evidence of association was observed for *STAT4*-rs3821236 (lcSSc vs controls: p = 0.041, OR 1.30,

Table 2. Overall statistical power of our study at the 5% significance level according to previously published data in European populations.

Locus	Studied Polymorphism	Reported DAF in Europeans, %	Reported OR in Europeans	Reference	Statistical Power Considering European OR	Statistical Power Considering OR = 1.5
IRF5	rs10488631	14.5	1.50	5	0.91	0.91
STAT4	rs3821236	24.7	1.30	5	0.72	0.98
CD247	rs2056626	37.0	0.82	5	0.56	0.99
DNASE1L3	rs35677470	10.0	1.47	6	0.76	0.81
IL12A	rs77583790	1.7	2.57	6	0.91	0.21
ATG5	rs9373839	24.1	1.19	6	0.37	0.98

DAF: disease allele frequency.

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Table 3. Analysis of established risk polymorphisms for SSc by comparing the different case sets against the control population. The allele frequencies (%) of the 2 control subsets included in the study (TaqMan/Immunochip) are as follows: *IRF5* = 11.81/10.22, *STAT4* = 22.58/25.60, *CD247* = 44.29/42.48, *DNASE1L3* = 4.34/4.11, *IL12A* = 0.23/0.10, and *ATG5* = 10.96/10.62.

Variant	1/2	Subgroup, n	Genotype, n (%)			MAF, %	Allele Test		
			1/1	1/2	2/2		p	p_{FDR}*	OR (95% CI)**
rs10488631 (*IRF5*)	C/T	Controls, n = 715	7 (0.98)	139 (19.44)	569 (79.58)	10.70			
		SSc, n = 353	10 (2.83)	103 (29.18)	240 (67.99)	17.42	**1.32E–05**	**7.90E–05**	1.76 (1.36–2.28)
		lcSSc, n = 191	5 (2.62)	52 (27.23)	134 (70.16)	16.23	**2.98E–03**	**0.0179**	1.62 (1.18–2.23)
		dcSSc, n = 162	5 (3.09)	51 (31.48)	106 (65.43)	18.83	**5.43E–05**	**3.26E–04**	1.94 (1.40–2.68)
		ACA+, n = 73	3 (4.11)	24 (32.88)	46 (63.01)	20.55	**4.03E–04**	**2.42E–03**	2.16 (1.40–3.34)
		ATA+, n = 165	4 (2.42)	61 (36.97)	100 (60.61)	20.91	**4.77E–07**	**2.86E–06**	2.21 (1.61–3.02)
		ILD+, n = 211	7 (3.32)	65 (30.81)	139 (65.88)	18.72	**1.22E–05**	**7.32E–05**	1.92 (1.43–2.59)
		DU+, n = 187	5 (2.67)	61 (32.62)	121 (64.71)	18.98	**1.52E–05**	**9.13E–05**	1.96 (1.44–2.66)
rs3821236 (*STAT4*)	A/G	Controls, n = 715	44 (6.15)	265 (37.06)	406 (56.78)	24.69			
		SSc, n = 354	33 (9.32)	135 (38.14)	186 (52.54)	28.39	0.0658	0.1169	1.21 (0.99–1.48)
		lcSSc, n = 191	18 (9.42)	78 (40.84)	95 (49.74)	29.84	**0.0406**	0.0812	1.30 (1.01–1.67)
		dcSSc, n = 163	15 (9.20)	57 (34.97)	91 (55.83)	26.69	0.4516	0.6095	1.11 (0.85–1.46)
		ACA+, n = 73	4 (5.48)	27 (36.99)	42 (57.53)	23.97	0.8490	0.8490	0.96 (0.65–1.43)
		ATA+, n = 166	16 (9.64)	59 (35.54)	91 (54.82)	27.41	0.3030	0.6060	1.15 (0.88–1.51)
		ILD+, n = 212	17 (8.02)	76 (35.85)	119 (56.13)	25.94	0.5992	0.7190	1.07 (0.83–1.37)
		DU+, n = 187	19 (10.16)	74 (39.57)	94 (50.27)	29.95	**0.0384**	0.0767	1.30 (1.01–1.68)
rs2056626 (*CD247*)	G/T	Controls, n = 718	144 (20.06)	330 (45.96)	244 (33.98)	43.04			
		SSc, n = 353	48 (13.60)	159 (45.04)	146 (41.36)	36.12	**2.20E–03**	**6.58E–03**	0.75 (0.62–0.90)
		lcSSc, n = 190	33 (17.37)	83 (43.68)	74 (38.95)	39.21	0.1794	0.2153	0.85 (0.68–1.08)
		dcSSc, n = 163	15 (9.20)	76 (46.63)	72 (44.17)	32.52	**4.91E–04**	**1.47E–03**	0.64 (0.49–0.82)
		ACA+, n = 73	9 (12.33)	32 (43.84)	32 (43.84)	34.25	**0.0405**	0.1215	0.69 (0.48–0.99)
		ATA+, n = 165	21 (12.73)	73 (44.24)	71 (43.03)	34.85	**6.49E–03**	**0.0195**	0.71 (0.55–0.91)
		ILD+, n = 211	28 (13.27)	94 (44.55)	89 (42.18)	35.55	**6.01E–03**	**0.0180**	0.73 (0.58–0.91)
		DU+, n = 186	23 (12.37)	78 (41.94)	85 (45.70)	33.33	**6.98E–04**	**2.09E–03**	0.66 (0.52–0.84)
rs35677470 (*DNASE1L3*)	A/G	Controls, n = 718	0 (0.00)	60 (8.36)	658 (91.64)	4.18			
		SSc, n = 354	1 (0.28)	39 (11.02)	314 (88.70)	5.79	0.0974	0.1169	1.41 (0.94–2.12)
		lcSSc, n = 191	1 (0.52)	22 (11.52)	168 (87.96)	6.28	0.0816	0.1224	1.54 (0.94–2.50)
		dcSSc, n = 163	0 (0.00)	17 (10.43)	146 (89.57)	5.22	0.4086	0.6095	1.26 (0.73–2.19)
		ACA+, n = 73	1 (1.37)	9 (12.33)	63 (86.30)	7.53	0.0620	0.1241	1.87 (0.96–3.64)
		ATA+, n = 166	0 (0.00)	16 (9.64)	150 (90.36)	4.82	0.6038	0.7033	1.16 (0.66–2.04)
		ILD+, n = 212	0 (0.00)	26 (12.26)	186 (87.74)	6.13	0.0923	0.1846	1.50 (0.93–2.41)
		DU+, n = 187	0 (0.00)	18 (9.63)	169 (90.37)	4.81	0.5904	0.7085	1.16 (0.68–1.99)
rs77583790 (*IL12A*)	A/G	Controls, n = 718	0 (0.00)	2 (0.28)	716 (99.72)	0.14			
		SSc, n = 354	0 (0.00)	4 (1.13)	350 (98.87)	0.57	0.0793	0.1169	4.07 (0.74–22.30)
		lcSSc, n = 191	0 (0.00)	3 (1.57)	188 (98.43)	0.79	**0.0321**	0.0812	5.68 (0.95–34.09)
		dcSSc, n = 163	0 (0.00)	1 (0.61)	162 (99.39)	0.31	0.5079	0.6095	2.21 (0.20–24.40)
		ACA+, n = 73	0 (0.00)	0 (0.00)	73 (100.00)	0.00	0.6518	0.7822	N/A
		ATA+, n = 166	0 (0.00)	1 (0.60)	165 (99.40)	0.30	0.5182	0.7033	2.17 (0.20–23.96)
		ILD+, n = 212	0 (0.00)	2 (0.94)	210 (99.06)	0.47	0.1942	0.2913	3.40 (0.48–24.20)
		DU+, n = 187	0 (0.00)	2 (1.07)	185 (98.93)	0.53	0.1469	0.2203	3.86 (0.54–27.46)
rs9373839 (*ATG5*)	C/T	Controls, n = 718	11 (1.53)	132 (18.38)	575 (80.08)	10.72			
		SSc, n = 353	3 (0.85)	74 (20.96)	276 (78.19)	11.33	0.6719	0.6719	1.06 (0.80–1.42)
		lcSSc, n = 190	2 (1.05)	42 (22.11)	146 (76.84)	12.11	0.4444	0.4444	1.15 (0.81–1.63)
		dcSSc, n = 163	1 (0.61)	32 (19.63)	130 (79.75)	10.43	0.8763	0.8763	0.97 (0.65–1.44)
		ACA+, n = 72	1 (1.39)	16 (22.22)	55 (76.39)	12.50	0.5142	0.7714	1.19 (0.71–2.00)
		ATA+, n = 166	1 (0.60)	36 (21.69)	129 (77.71)	11.45	0.7033	0.7033	1.08 (0.74–1.57)
		ILD+, n = 212	2 (0.94)	40 (18.87)	170 (80.19)	10.38	0.8388	0.8388	0.96 (0.68–1.37)
		DU+, n = 186	2 (1.08)	38 (20.43)	146 (78.49)	11.29	0.7543	0.7543	1.06 (0.74–1.52)

* Benjamini and Hochberg[13] step-up FDR control. ** OR and 95% CI for the minor allele. Significant p values are in bold face. MAF: minor allele frequency; SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ACA: anticentromere antibodies; ATA: antitopoisomerase antibodies; ILD: interstitial lung disease; DU: digital ulcers; N/A: not applicable; FDR: false discovery rate.

95% CI 1.01–1.67; DU+ vs controls: p = 0.038, OR 1.30, 95% CI 1.01–1.68) and *IL12A*-rs77583790 (lcSSc vs controls: p = 0.032, OR 5.68, 95% CI 0.95–34.09; Table 3).

A case-case analysis between the SSc subjects with and without the different clinical features was then conducted to dissect those putative associations. Interestingly, pheno-

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type-specific associations were either observed or suggested for some polymorphisms. That is, *IRF5*-rs10488631 was significantly associated with the presence of ATA (ATA+ SSc vs ATA– SSc: p = 0.031, OR 1.54, 95% CI 1.04–2.28), and *CD247*-rs2056626 showed evidence of association with the diffuse form of the disease (dcSSc vs lcSSc: p = 0.065, OR 0.75, 95% CI 0.55–1.02). On the other hand, *STAT4*-rs3821236 and *IL12A*-rs77583790 lost their suggestive associations with specific phenotypes in this analysis (data not shown).

DISCUSSION

To our knowledge, our study represents the first evaluation of established SSc risk polymorphisms in the Turkish population. Except for *ATG5*, we found evidence of association either with the overall disease or with a particular phenotype for all the investigated genes. The lower statistical significance observed in our Turkish cohort was most likely due to a considerably reduced statistical power in comparison with the studies performed in Europeans. Indeed, the allele frequencies and the effect sizes on disease susceptibility of the analyzed SNP were consistent with those described for the European population in all analyzed variants, with only the exception of *ATG5*, in which the minor allele frequencies (MAF) in Turks (MAF case/control = 0.113/0.107) were half the ones reported for Europeans (MAF case/control = 0.241/0.185)[5,6]. However, it should be noted that *ATG5* represents the SSc marker with a lower effect on the susceptibility (reported OR for Europeans = 1.19) among those included in our study[6]. In addition, the OR observed in the Turkish cohort had the same direction toward risk (1.06). Therefore, a larger case series would be needed to definitively discard a possible influence of this gene in SSc risk in Turkey.

On the other hand, our data are also in agreement with the reported phenotype-specific associations of the Immunochip study[6] because *IL12A*-rs77583790 and *DNASE1L3*-rs35677470 showed trends of association with lcSSc and ACA positivity, respectively, when the case subgroups were compared against the control population. The loss of these tendencies after comparing cases with and without the corresponding features was probably a consequence of insufficient power in the stratified analyses. Indeed, *DNASE1L3*-rs35677470 is a low-frequency variant (MAF < 5%) and *IL12A*-rs77583790 can be considered a rare variant (MAF < 1%)[6].

Altogether, our results suggest that the genetic background of SSc in Turks is similar to that in Europeans. Confirmation of identified associations in other populations than those of European ancestry (with different genetic structures) is not only necessary to validate initial findings, but also to have a broader overview of the genetic basis of human disease[14]. In this context, considering that the causal variants of most SSc associations and their specific relationship with the clinical outcomes remain unknown[7], studies such as the one reported here may be useful in the challenging endeavor of identifying reliable diagnostic and prognostic markers for a better management of this severe condition.

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