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ORIGINAL ARTICLE

Tumor necrosis factor gene polymorphisms are associated with systemic lupus erythematosus susceptibility or lupus nephritis in Mexican patients

Julian Ramírez-Bello[1,2] · Daniel Cadena-Sandoval[1,3] · Jorge Flavio Mendoza-Rincón[4] · Rosa Elda Barbosa-Cobos[5] · Fausto Sánchez-Muñoz[6] · Luis M Amezcua-Guerra[6] · Mónica Sierra-Martínez[7] · Silvia Jiménez-Morales[8]

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Abstract

The *TNF* -238G/A (rs361525) and -308G/A (rs1800629) polymorphisms have consistently been associated with systemic lupus erythematosus (SLE) in several populations; however, these findings have not been verified in all populations. Here, we aimed to examine whether the *TNF* -238G/A, -308G/A, -376G/A (rs1800750), and -1031T/C (rs1799964) polymorphisms confer SLE or lupus nephritis (LN) susceptibility in a Mexican population. Our study included 442 patients with SLE and 495 controls. For genotyping, we used the TaqMan 5′ allele discrimination assay. The *TNF* -238G/A and -1031T/C polymorphisms were associated with SLE susceptibility (odds ratio (OR) 2.1, $p = 0.0005$ and OR 1.4, $p = 0.003$, respectively). Gender stratification showed a strong association between *TNF* -238G/A and SLE in women (OR 2.2, $p = 0.00006$), while *TNF* -1031T/C had an OR of 1.5 ($p = 0.007$). With regard to the *TNF* -376G/A polymorphism, this also showed association with SLE susceptibility (OR 1.95, $p = 0.036$) and LN (OR 3.5, $p = 0.01$). In conclusion, our study provides the first demonstration of association between the *TNF* -376G/A polymorphism and SLE and LN susceptibility. In addition, our study is the second documenting an association of *TNF* -1031T/C with SLE susceptibility. We also observed a strong association between *TNF* -238G/A and SLE susceptibility. The *TNF* 308G/A polymorphism was not associated with SLE or LN.

Keywords Systemic lupus erythematosus · Rheumatoid arthritis · Tumor necrosis factor · Susceptibility

Introduction

The tumor necrosis factor (TNF) gene encodes the TNF cytokine, a multifunctional protein and one of the major regulators of inflammation that is involved in different normal immunological processes, including the optimal defense against pathogens, germinal center formation, resolution of inflammation, induction of tissue repair, apoptosis, proliferation, and necrosis [1, 2]. Moreover, this same cytokine plays an important role in pathological processes, e.g., it induces its own secretion in macrophages, orchestrates the tissue recruitment of immune cells, promotes tissue destruction, and stimulates the synthesis of inflammatory cytokines, chemokines, and different cell survival factors [1–3]. Additionally, TNF is involved in acute/chronic inflammation and has been associated with several inflammatory and autoimmune diseases (ADs)

✉ Julian Ramírez-Bello
dr.julian.ramirez.hjm@gmail.com

[1] Unidad de Investigación en Investigación en Enfermedades Metabólicas y Endócrinas, Hospital Juárez de México, Mexico City, Mexico

[2] Instituto Politécnico Nacional, Gustavo A. Madero, Magdalena de Las Salinas, 07760 Mexico City, Mexico

[3] Programa de Doctorado de la Escuela Superior de Medicina, Instituto Politécnico Nacional, Mexico City, Mexico

[4] Laboratorio de Oncología Molecular, Unidad de Diferenciacón Celular y Cáncer, FES-Zaragoza, UNAM, Mexico City, Mexico

[5] Servicio de Reumatología, Hospital Juárez de México, Mexico City, Mexico

[6] Departamento de Inmunología, Instituto Nacional de Cardiología, Mexico City, Mexico

[7] Laboratorio de Diagnóstico Molecular y Genética, Hospital Juárez de México, Mexico City, Mexico

[8] Laboratorio de Genómica del Cáncer, Instituto Nacional de Medicina Genómica, Mexico City, Mexico

such as systemic lupus erythematosus (SLE), autoimmune thyroid disease (AITD), rheumatoid arthritis (RA), and others, including lupus nephritis (LN), which is the most common disorders associated with SLE [1, 3–7].

The TNF promoter gene contains several single-nucleotide polymorphisms (SNPs), which are located at the positions -1031T/C (rs1799964), -376G/A (rs1800750), -308G/A (rs1800629), and -238G/A (rs361525) of the transcription start site [1]. In addition, some of these SNPs have been associated with SLE or LN susceptibility [8–13].

For example, the *TNF* -308G/A SNP is commonly associated with SLE susceptibility in different populations and has been identified as an important variant involved in the etiology of SLE [8]. However, the *TNF* -1031T/C and -238G/A SNPs have been scarcely explored in SLE patients from different populations and the associations found have been controversial [9–13]. As far as we know, the *TNF* -376G/A SNP has not been previously evaluated or associated with SLE susceptibility. The aim of our study was to determine whether the *TNF* -1031T/C, -376G/A, -308G/A, and -238G/A polymorphisms confer SLE susceptibility or risk for lupus nephritis (LN) in a sample of Mexican patients.

Materials and methods

Population study

All SLE patients as well as controls signed and dated an informed consent form. The protocol was previously approved by the Ethics, Research, and Biosecurity committee of the Hospital Juarez of Mexico (HJM) and the National Institute of Cardiology (NIC) of Mexico. Our study included 442 SLE patients (classified according to the 1997 American College of Rheumatology criteria) and 495 healthy individuals. The LN data were available for 262 SLE patients. Cases and controls were recruited from central Mexico and were comprised of unrelated individuals who were over 18 years old and of self-reported Mexican-Mestizo ancestry (for three generations). The SLE patients included in this study were recruited from the rheumatology (HJM) and immunology (NIC) departments. The healthy individuals, without a family history of autoimmune or chronic inflammatory disease (including asthma, obesity, arterial hypertension, cancer, type 2 diabetes, food and drug allergy, inflammatory bowel disease, chronic and acute urticaria) for three generations, were recruited from the Hospital Juarez of Mexico. The SLE patients were matched with healthy individuals by ethnicity.

Genomic DNA

The nuclear genome from each patient and control was isolated from whole blood samples (5 ml of EDTA-treated peripheral blood) using the Invisorb Blood Universal Kit (Stratec molecular GmbH, Berlin, Germany), according to the manufacturer's specifications. The isolated nuclear DNA was quantified, diluted (5 ng/μL), and stored at − 20 °C until needed.

Genotyping of polymorphisms

Genotyping of the *TNF* -1031T/C, -376G/A, -308G/A, and -238G/A SNPs was evaluated using the 5′ exonuclease allelic discrimination assay and TaqMan probes and a CFX96 Real-Time PCR system (Bio-Rad, California, USA), as previously reported [14].

Statistical analysis

Finetti software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) was used to estimate the Hardy Weinberg equilibrium (HWE) and the genetic associations between the *TNF* -1031T/C, -376G/A, -308G/A, and -238G/A SNPs and SLE susceptibility or LN. Finetti software estimates the odds ratios (ORs), 95% confidence intervals (CIs), and *p* values. Haplotype frequencies and linkage disequilibrium (LD) were evaluated as previously reported [15]. A *p* value of 0.05 or lower was considered statistically significant. The statistical power was estimated using Quanto software.

Results

Our study included 442 SLE patients, as well as 495 healthy individuals. The average age and the proportion of females/males and LN/non-LN are shown in Table 1.

The genotype distribution of the *TNF* -1031T/C, -376G/A, -308G/A, and -238G/A SNPs between cases and controls showed no deviations from HWE ($p > 0.01$) (data not shown). Under a recessive model, the statistical power for our study was 85%.

The GA genotype and A allele frequencies of *TNF* -238G/A were significantly higher in SLE patients versus controls and we identified an association with SLE susceptibility (GG vs GA, OR 2.3, $p = 0.0002$; G vs A, OR 2.1, $p = 0.0005$; Table 2). In

Table 1 Demographic characteristics in patients with SLE and controls

	Controls $n = 495$ (%)	SLE $n = 442$ (%)
Age (mean ± SD years)	50.0 (± 7.9)	39.5 (± 13.4)
Gender (Female, male)	459 (92.7)/36 (7.3)	414 (93.7)/28 (6.3)
LN/non-LN	–	115 (43.9)/147 (56.1) *

SLE systemic lupus erythematosus, *SD* standard deviation

*262 SLE patients with LN/non-LN were available

Table 2 Genotype and allele frequencies of *TNF* polymorphisms and association analysis in SLE patients and controls

SNP ID	Population	Allele	Genotype *n* (%)						Allele *n* (%)				
		1 2	1 1	1 2	2 2	OR (11 vs 12)	95% CI	*p*	1	2	OR (1 vs 2)	95% CI	*p*
TNF-α -238	Controls	G A	458 (92.7)	34 (6.9)	2 (0.4)	–	–	–	950 (96.2)	38 (3.8)	–	–	–
(rs361525)	SLE		377 (85.3)	63 (14.3)	2 (0.4)	2.3	1.45–3.49	0.0002*	817 (92.4)	67 (7.6)	2.05	1.36–3.09	0.0005*
TNF-α -308	Controls	G A	450 (90.9)	43 (8.7)	2 (0.4)	–	–	–	943 (95.3)	47 (4.7)	–	–	–
(rs1800629)	SLE		398 (90.0)	44 (10.0)	0 (0.0)	1.2	0.74–1.80	0.52	840 (95.0)	44 (5.0)	1.1	0.69–1.60	0.82
TNF-α -376	Controls	G A	479 (96.8)	16 (3.2)	0 (0.0)	–	–	–	974 (98.4)	16 (1.6)	–	–	–
(rs1800750)	SLE		415 (93.9)	27 (6.1)	0(0.0)	1.9	1.04–3.67	0.036*	857 (96.9)	27 (3.1)	1.9	1.03–3.58	0.038*
TNF-α -1031	Controls	T C	370 (74.8)	112 (22.6)	13 (2.6)	–	–	–	852 (86.1)	138 (13.9)	–	–	–
(rs1799964)	SLE		293 (66.3)	130 (29.4)	19 (4.3)	1.5	1.09–1.97	0.011*	716 (81.0)	168 (19.0)	1.4	1.13–1.85	0.003*

SLE systemic lupus erythematosus, *OR* odds ratio, *CI* confidence interval, *SNP* single-nucleotide polymorphism, *1* common allele, *2* not common allele, *p p* value

*Statistically significant at *p*

addition, the gender stratification showed a strong association among women with SLE (GG vs GA, OR 2.5, $p = 0.00006$; G vs A, OR 2.21, $p = 0.0001$) (Table 3). In addition, the *TNF* -238A allele showed a trend towards an association with LN susceptibility (OR 1.8, $p = 0.07$) (Table 4).

On the other hand, the genotype and allele frequencies for the *TNF* -308G/A SNP were similar between cases and controls and among control women and SLE women; thus, there was no evidence of a genetic association (Tables 2 and 3, respectively). The *TNF* -308G/A SNP also showed no association with LN (Table 4).

With respect to the *TNF*-376G/A SNP, the genotype GA and A allele frequencies were significantly higher in SLE patients than in controls and we observe an association with susceptibility (GG vs GA, OR 1.95, $p = 0.036$; G vs A, OR 1.9, $p = 0.038$) (Table 2), similar results were identified in SLE women and control women (GG vs GA, OR 1.9, $p = 0.038$; G vs A, 1.9, $p = 0.04$) (Table 3). In addition, we also identified an association between this polymorphism and LN susceptibility (GG vs GA, OR 3.6, $p = 0.01$; G vs A, OR 3.5, $p = 0.01$) (Table 4).

The genotype and allele frequencies of *TNF* -1031T/C were significantly higher in SLE patients versus controls (TT vs TC, OR 1.5, $p = 0.01$; C vs T allele, OR 1.5, $p = 0.003$, respectively; Table 2). Similar results were identified when patients were stratified by gender for SLE women (TT vs TC, OR 1.5, $p = 0.007$; T vs C, OR 1.5, $p = 0.003$) (Table 3). Finally, there was no evidence of an association between LN and non-LN patients (Table 4).

Allele combinations of the *TNF* -1031T/C, -376G/A, -308G/A, and -238G/A SNPs showed five haplotypes in SLE (Table 5). Some haplotypes showed association with SLE; however, after 100,000 permutations, only one (CAGA), which carried the three minor alleles; *TNF* -1031C, -376A, and -238A, showed association with SLE susceptibility (Table 5). On the other hand, no LD was found between these alleles (pairwise r^2 values < 0.8) (Fig. 1). In SLE patients, our data suggest that the three association signals (*TNF* -1031T/C, -376G/A, and -238G/A) are independent.

Discussion

TNF is a multifunctional proinflammatory cytokine produced mainly by monocytes and macrophages. It exerts a wide variety of pathological and normal physiologic effects, and it is a master switch for the initiation and perpetuation of inflammatory responses [1, 2]. Alterations in TNF signaling have been involved in several ADs such as SLE and RA [1–3, 16, 17]. Serum TNF levels in patients with active SLE were significantly higher than in patients with inactive SLE [18]. In addition, this cytokine is overexpressed in human LN [19, 20]. Therefore, TNF can serve as a biomarker of SLE activity and LN.

Table 3 Genotype and allele frequencies of *TNF-α* polymorphisms and association analysis in SLE women and control women

SNP ID	Population	Allele	Genotype *n* (%)						Allele *n* (%)				
		1 2	1 1	1 2	2 2	OR (11 vs 12)	95% CI	*p*	1	2	OR	95% CI	*p*
TNF-α -238	Controls	G A	425 (92.8)	31 (6.8)	2 (0.4)	–	–	–	881 (96.2)	35 (3.8)	–	–	–
(rs361525)	SLE		349 (84.3)	63 (15.2)	2 (0.5)	2.5	1.57–3.89	0.00006*	761 (91.9)	67 (8.1)	2.2	1.45–3.37	0.0001*
TNF-α -308	Controls	G A	418 (91.1)	39 (8.5)	2 (0.4)	–	–	–	875 (95.3)	43 (4.7)	–	–	–
(rs1800629)	SLE		373 (90.1)	41 (9.9)	0 (0.0)	1.2	0.74–1.87	0.48	787 (95.0)	41 (5.0)	1.1	0.68–1.64	0.79
TNF-α -376	Controls	G A	443 (96.5)	16 (3.5)	0 (0.0)	–	–	–	902 (98.3)	16 (1.7)	–	–	–
(rs1800750)	SLE		387 (93.5)	27 (6.5)	0 (0.0)	1.9	1.02–3.64	0.038*	801 (96.7)	27 (3.3)	1.9	1.02–3.55	0.04
TNF-α -1031	Controls	T C	342 (74.5)	104 (22.6)	13 (2.8)	–	–	–	788 (85.8)	130 (14.2)	–	–	–
(rs1799964)	SLE		271 (65.5)	125 (30.2)	18(4.3)	1.5	1.12–2.06	0.007*	667 (80.6)	161 (19.4)	1.5	1.14–1.88	0.003*

SLE systemic lupus erythematosus, *OR* odds ratio, *CI* confidence interval, *SNP* single-nucleotide polymorphism, *1* common allele, *2* not common allele, *p p* value
*Statistically significant at *p*

Table 4 Genotype and allele frequencies of *TNF* polymorphisms and association analysis in SLE patients with lupus nephritis

SNP ID	Population	Allele	Genotype *n* (%)			Allele *n* (%)							
		1 2	1 1	1 2	2 2	OR (11 vs 12)	95% CI	*p*	1	2	OR (1 vs 2)	95% CI	*p*
TNF-α -238	Non-LN	G A	129 (87.8)	18 (12.2)	0 (0.0)	–	–	–	276 (93.9)	18 (6.1)	–	–	–
(rs361525)	LN		93 (80.9)	20 (17.4)	2 (1.7)	1.5	0.77–3.07	0.21	206 (89.6)	24 (10.4)	1.8	0.95–3.38	0.07
TNF-α -308	Non-LN	G A	136 (92.5)	11 (7.5)	0 (0.0)	–	–	–	283 (96.3)	11 (3.7)	–	–	–
(rs1800629)	LN		100 (87.0)	15 (13.0)	0 (0.0)	1.9	0.82–4.21	0.14	215 (93.5)	15 (6.5)	1.8	0.81–3.99	0.15
TNF-α -376	Non-LN	G A	142 (96.6)	5 (3.4)	0 (0.0)	–	–	–	289 (98.3)	5 (1.7)	–	–	–
(rs1800750)	LN		102 (88.7)	13 (11.3)	0 (0.0)	3.6	1.25–10.5	0.01*	217 (94.3)	13 (5.6)	3.5	1.22–9.86	0.01*
TNF-α -1031	Non-LN	T C	93 (63.3)	49 (33.3)	5 (3.4)	–	–	–	235 (79.9)	59 (20.1)	–	–	–
(rs1799964)	LN		78 (67.8)	31 (27.0)	6 (5.2)	0.8	0.44–1.30	0.30	187 (81.3)	43 (18.7)	0.9	0.59–1.42	0.69

SLE systemic lupus erythematosus, *OR* odds ratio, *CI* confidence interval, *p p* value, *SNP* single-nucleotide polymorphism, *1* common allele, *2* not common allele
*Lupus nephritis (LN) data were not available in all cases

Table 5 *TNF*-α haplotypes (-1031T/C, -376G/A, -308G/A, and -238G/A) in SLE patients

	Haplotypes	Frequency		OR	95% CI	*p*	Pc
		Cases	Controls				
SLE ($n = 442$)	TGGG	75.9	80.7	0.77	0.61–0.97	0.01	NS
	CGGG	11.5	10.2	1.21	0.89–1.63	0.35	NS
	TGAG	5.0	4.7	0.99	0.63–1.55	0.82	NS
	CGGA	4.4	2.4	1.69	0.98–2.91	0.02	NS
	CAGA	3.1	1.3	1.96	0.96–4.00	0.009	0.048*

SLE systemic lupus erythematosus, *OR* odds ratio, *CI* confidence interval, *Pc p* corrected after 100,000 permutations

On the other hand, some variants, such as the *TNF* -308G/A SNP, have been identified as genetic biomarkers important in SLE and LN susceptibility. In fact, Yang et al., who performed a meta-analysis, found a differential association between the *TNF* -308A allele with LN in European and Asian populations [8]. However, our data are not in agreement with this finding, because we did not identify an association between this polymorphism and SLE or LN susceptibility. To note, similar results have been documented in other Latin-American population [21]. The discrepancies between our results with those published in various studies may have been due to the different genetic backgrounds among populations, sample size, low statistical power, etc. [22]. On the other hand, our LN data can be biased by the small sample size (115 patients with LN versus 147 patients without LN) and low statistical power (29%). With regard to this polymorphism, studies performed in adult and pediatric SLE Mexican patients showed controversial results, for example, Zuñiga et al. did not identify association in adult SLE patients; meanwhile, Jiménez-Morales et al. identified an association in pediatric SLE patients [23, 24]. Our information is in agreement with those published by Zuñiga et al. Although adult and pediatric patients are phenotypically similar, these discrepancies between adults and pediatrics in studies of Mexican patients with SLE may be because the pediatric SLE patients have higher incidences of renal, cardiac, neurological, and hematological disorders [25, 26]. This may result in a more severe form or more alleles affected or different allele combinations in pediatric SLE. For example, the functional *PTPN22* R620W SNP is not a risk factor for adult SLE patients while, in pediatrics, this variant conferred susceptibility [14, 27].

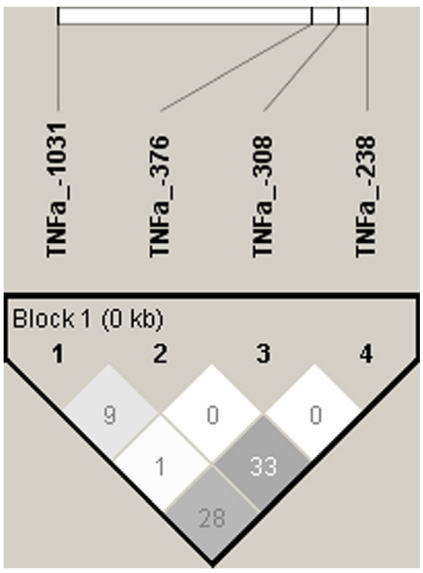

Fig. 1 Linkage disequilibrium (LD) of the *TNF* -238G/A, -308G/A, -376G/A, and -1031T/C polymorphisms in SLE. Each box represents the r^2 value between pairs of the four *TNF* SNPs. The analysis shown that the *TNF*-α -1031T/C, -376G/A, and -238G/A polymorphisms are not in LD in SLE

In our study, we identified the *TNF* -238G/A SNP associated with SLE susceptibility. In 2001, Zúñiga et al. evaluated a SLE sample from central Mexico (with a small sample size and low statistical power) [23]. Despite differences in the sample size and statistical power, our study also showed that this variant confers SLE susceptibility in Mexican patients. Although the *TNF* -238G/A variant has been evaluated in different populations, only a few studies have identified an association with SLE susceptibility, while others have not found an association [9–11, 13, 23, 28]. Some functional studies indicated that the *TNF* -238A allele or GA genotype affected gene expression, while other studies did not [11, 29, 30]. More studies are required to better understand the role of *TNF* -238G/A on SLE susceptibility.

The *TNF* -376G/A SNP, as far as we know, has not been previously evaluated for its association with SLE susceptibility. Our data suggest that this variant is a risk factor for SLE or LN. However, our study should be interpreted cautiously since the *p* value was close to 0.05. Functional studies indicate that the *TNF* -376A allele creates a binding site for OCT-1 (a transcription factor), which increases the TNF gene expression [31]. This is the first study to show that the *TNF* -376G/A polymorphism is associated with SLE and LN. Other studies in different populations should be performed to identify if this variant is a risk factor for SLE or LN.

On the other hand, *TNF* -1031C/T has been scarcely explored in different populations [10, 12, 32]. Only one study (with a small size sample and low statistical power) identified an association between this polymorphism and SLE

susceptibility [10]. Another study showed a trend towards an association with SLE susceptibility [12], while other work showed that the CCC haplotype, which carries the C allele of *TNF* -1031T/C, confers protection against SLE [32]. Our data showed that the *TNF* -1031C allele confers SLE susceptibility in the Mexican population. Our study is the second study documenting an association between this SNP and SLE susceptibility. There are no functional studies evaluating only this variant. However, a study identified that the haplotype CA, which carried the two minor alleles of the *TNF* -1031T/C and -863C/A SNPs, respectively, affects the transcriptional promoter activity (the expression was higher than that of the common alleles) [33]. Further investigations are required to better understand the biological role of this variant in immune cells.

The haplotype CAGA, which carried the three minor alleles: *TNF* -1031C, -376A, and -238A, showed an association with SLE susceptibility ($p = 0.048$, p corrected after 100,000 permutations). In addition, the haplotype analysis showed that these alleles were not in LD (including the *TNF* -308A allele); thus, our data suggest that the three association signals (*TNF* -1031T/C, -376G/A, and -238G/A) with SLE are independent.

We also identified associations between the *TNF* -1031T/C, -376G/A, and -238G/A SNPs and SLE in women. The associations with susceptibility loci observed in women with ADs are common, because these pathologies mainly affect women [14, 34–36].

A major limitation of our study is the lack of clinical features (except LN) and autoantibodies typical of SLE, which does not allow us to determine an association between *TNF* SNPs and any clinical or laboratory characteristic.

Our study provide the first demonstration of association between the *TNF* -376G/A SNP and SLE and LN susceptibility. In addition, our study is the second report documenting an association of *TNF* -1031T/C with SLE susceptibility. We also observed a strong association between *TNF* -238G/A and SLE susceptibility. Finally, the *TNF* 308G/A SNPs were not associated with SLE or LN in Mexican population.

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Compliance with ethical standards

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

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