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TNF-α − 308 G>A and *IFN-γ + 874* A>T gene polymorphisms in Egyptian patients with lupus erythematosus

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is associated with immunogenetic factors. This study was planned to test for the association of *TNF-α − 308* and *IFN-γ + 874* gene polymorphisms with susceptibility and severity of SLE in Egyptian cases.
Subjects and methods: This is a case controlled study including 125 Egyptian cases with SLE in addition to 112 healthy unrelated individuals from the same locality. For all participants, *TNF-α* − 308 G>A and *IFN-γ* + 874 A>T genetic polymorphisms were characterized using the PCR technique.
Results: Cases with SLE showed a significantly higher *TNF-α* − 308 A allele carriage rate (AA + GA genotypes) compared to controls (26.4% vs. 12.5%, $p = 0.009$, OR = 2.51, 95% CI = 1.26–4.99). These cases showed also a significantly higher carriage rate for the *IFN-γ* + 874 T allele (AT + TT genotypes) compared to controls (47.2% vs. 32.1%, $p = 0.02$, OR = 1.89, 95% CI = 1.11–3.21). Comparing age, gender, and disease severity presented by nephritis class, activity and chronicity indices in cases carrying the *TNF-α − 308 A* allele and in cases carrying *IFN-γ + 874 T* allele versus others showed no significant difference ($p > 0.05$).
Conclusions: TNF-α − 308 A and *IFN-γ* + 874 T allele carriage are associated with susceptibility but not severity of SLE in Egyptian subjects.

1. Introduction

Systemic lupus erythematosus (SLE) is the prototypic autoimmune complex disease which is characterized by excessive production of autoantibodies against a broad range of self-antigens (Gurevitz et al., 2013). Vital organs and tissues are often implicated, including kidney, brain, cardiovascular, joint and skin (Sánchez et al., 2006). One of its most severe manifestations is lupus nephritis (LN), which remains a cause of substantial morbidity and mortality, either secondary to kidney disease, or as a result of intense immunosuppressive drug toxicity (Sestak et al., 2007; Hiraki et al., 2012; Pons-Estel et al., 2011). Genes most likely contribute to the development of lupus have been identified particularly of the major histocompatibility complex (MHC) types HLA-A1, B8, and DR3 (Wakeland et al., 2001; Walport et al., 1982). In addition, there is a strong evidence supporting the role of cytokine genes in the pathogenesis of SLE (Lin et al., 2009). One of the major cytokines that has been intensely investigated is the tumor necrosis factor alpha (*TNF-α*), an important pro-inflammatory cytokine that plays an important role in the inflammatory and immune responses (Aggarwal et al., 2012). High serum levels of *TNF-α* have been reported in SLE that correlated well with the renal inflammatory activity (Studnicka-Benke et al., 1996; Aringer et al., 2002; Maury and Teppo, 1989; Postal and Appenzeller, 2011). Effects of *TNF-α* were found to be related to activation of a cascade of inflammatory events, enhancing expression of adhesion molecules, activation of neutrophils in addition to acting as a costimulator for T cell activation and antibody production (Serrano et al., 2006). The single-nucleotide polymorphism (SNP) *TNF-α − 308 G>A* (rs1800629) is located on chromosome 6p21.3, within the class III region of MHC. The *TNF-α − 308* A allele has been reported to be a stronger transcriptional activator in vitro than the common G allele. Therefore, the A allele frequency has been associated with the risk of autoimmune disorders (Zou et al., 2011; Santos et al., 2012).

Interferon-gamma (*IFN-γ*) is one of the main cytokines secreted by activated T lymphocytes and has antiproliferative, antiviral and immunomodulatory activities as it controls the development of T helper 1 (Th1) cells (Silva et al., 1992; Torrico et al., 1991). Several studies have indicated that expression of the *IFN-γ* level has significant effects into the susceptibility of various autoimmune diseases. There is a report showing significant increasing *IFN-γ* messenger ribonucleic acid expression in peripheral blood mononuclear cells of patients with SLE that might trigger inflammatory responses (Baccala et al., 2005;

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Csiszár et al., 2000). The human *IFN-γ* gene located on chromosome 12q24.1 has a SNP in the first intron at its 5′ end, adjacent to a CA repeat region (+874 A>T, rs2430561) which was known to influence the secretion of *IFN-γ* and had been implicated in numerous autoimmune and chronic inflammatory conditions (Chong et al., 2006; Pravica et al., 2000). Analysis of the biological role of this SNP suggested that +874 T allele carriers showed higher production of *IFN-γ* (Pravica et al., 2000; López-Maderuelo et al., 2003).

The aim of this study is to investigate the association between *TNF-α −308 G>A* and *IFN-γ +874 A>T* gene polymorphisms with the SLE susceptibility and severity among Egyptian subjects.

2. Subjects and methods

This is a case controlled study involving 125 adult patients with SLE all suffering from LN (72 females and 53 males, age mean ± SD = 23.4 ± 4.4 years) and 112 healthy unrelated subjects (46 males and 66 females, age mean ± SD = 28.3 ± 6.2 years). Patients were recruited from the Urology and Nephrology Center, Mansoura University, Egypt. The diagnosis of SLE in patients was according to the American College of Rheumatology (1982) revised criteria for SLE (Tan et al., 1982). Assessment of the severity of SLE was based upon the classification of LN (Weening et al., 2004) where class I: normal glomeruli (0 cases), class II: purely mesangial disease (8 cases), class III: focal proliferative glomerulonephritis (25 cases), class IV: diffuse proliferative glomerulonephritis (88 cases), and class V: membranous glomerulonephritis (4 cases). The study was approved by the ethical and scientific committees of Mansoura University. An informed consent was also obtained from all participants before the start of the study.

2.1. DNA extraction, purification and amplification

For all participants, genomic DNA from a peripheral blood was extracted and purified using the kit provided by Gentra Systems, USA. Typing of the *TNF-α* −308 G>A (rs1800629) SNP and *IFN-γ +874 A>T* (rs2430561) were performed using the polymerase chain reaction with amplification refractory mutation system (PCR-ARMS) as described by Perrey et al. (Perrey et al., 1999) and Pravica et al. (Pravica et al., 2000) respectively. The PCR amplification was carried out using Veriti® thermal cycler (Applied Biosystems, USA) in a 20 μl total volume containing about 100 ng of genomic DNA template, 2 pM of each primer, 2 mM of each dNTP, 1.5 mM of $MgCl_2$, 1× PCR buffer and 0.6 U of Taq DNA polymerase. *TNF-α* Primer sequences were as follows: *TNF-α* G forward primer: 5′-ATA GGT TTT GAG GGG CAT GG-3′; *TNF-α* A forward primer: 5′-AATA GGT TTT GAG GGG CAT GA-3′; and reverse primer, 5′-TCT CGG TTT CTT CTC CAT CG-3′. Reaction conditions were carried out in a thermocycler at 95 °C for 1 min followed by 10 cycles of 95 °C for 15 s, 65 °C for 50 s, and 72 °C for 40 s and then 20 cycles of 95 °C for 20 s, 56 °C for 50 s, and 72 °C for 50 s. On the other hand, primer sequences for INF-γ were as follows: reverse primer: 5′-TCA ACA AAG CTG ATA CTC CA-3′, INF-γ A forward primer: 5′-TTC TTA CAA CAC AAA ATC AAA TCA-3′, INF-γ T forward primer: 5′-TTC TTA CAA CAC AAA ATC AAA TCT-3′. The PCR conditions consisted of an initial denaturation step at 95 °C for 2 min, 10 cycles of incubation at 95 °C for 15 s, 62 °C for 50 s and 72 °C for 40 s, followed by 20 cycles of incubation at 95 °C for 20 s, 56 °C for 50 s and 72 °C for 50 s, with a final extension at 72 °C for 5 min. The amplified PCR products were analyzed by 2% agarose gel and ethidium bromide staining followed by ultraviolet visualization. The PCR product for *TNF-α* −308 was detected at 184 bp (Fig. 1) while that of *IFN-γ +874* was detected at 263 bp (Fig. 2).

2.2. Statistical analysis

Data were analyzed using the statistical package of social science (SPSS, version 17.0) software program. The frequencies of studied genotypic and allelic polymorphisms among cases were compared to those of controls using Fisher's exact test and odds ratio (OR) with the 95% confidence interval (95% CI). For statistical analysis, the significance of clinical parameters related to age, gender, SLE classes, severity index and chronicity index was determined by Fisher's exact test. Conformity with the Hardy Weinberg law of genetic equilibrium was tested by Chi square test comparing the observed versus expected genotype frequencies in both groups of cases and controls. A minimum level of statistical significance was considered at a p level of <0.05.

3. Results

Cases with SLE showed a significantly higher *TNF-α* −308 (GA + AA genotypes) compared to controls (26.4% vs. 12.5%, $p = 0.009$, OR = 2.51, 95% CI = 1.26–4.99) (Table 1). Similarly, cases showed a significantly higher carriage rate for the *IFNG-γ* +874 (AT + TT genotypes) compared to controls (47.2% vs. 32.1%, $p = 0.02$, OR = 1.89, 95% CI = 1.11–3.21) (Table 2).

This was mainly due to the higher frequency of the heterozygous *TNF-α* GA and *INF-γ* AT genotypes, consistent with the dominant mode of inheritance. On other hand, comparing the homozygous genotype frequency between cases and control (recessive model) did not yield any significant difference. The frequencies of TNF-α and IFN-γ genotypes were in agreement with Hardy-Weinberg equilibrium in both groups of SLE cases and controls ($p > 0.05$) (Tables 1 and 2). Cases of *TNF-α* GA + AA genotypes vs. those with the GG genotype

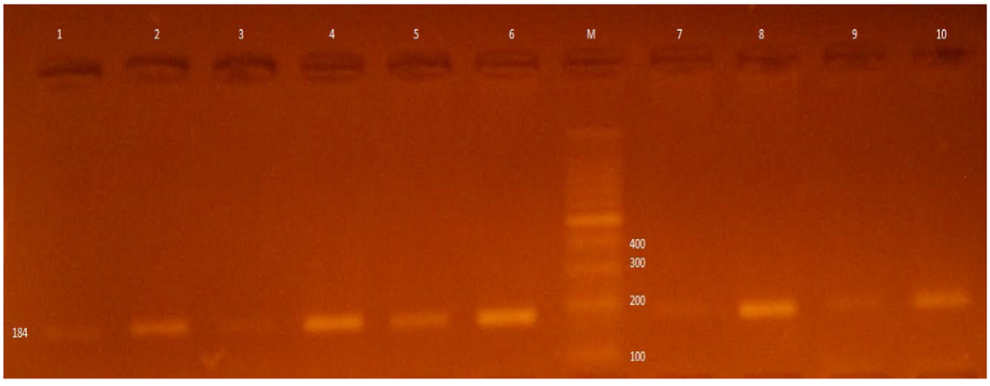

Fig. 1. The genotypes of TNF-α −308 G>A; lane M indicate DNA Ladder 100 bp, lanes (1 and 2) represent genotype GA, lanes (3 and 4) represent genotype GA, lanes (5 and 6) represent genotype GA, lanes (7 and 8) represent genotype GA, lanes (9 and 10) represent genotype GA, TNF-α −308 G>A was detected at 184 bp.

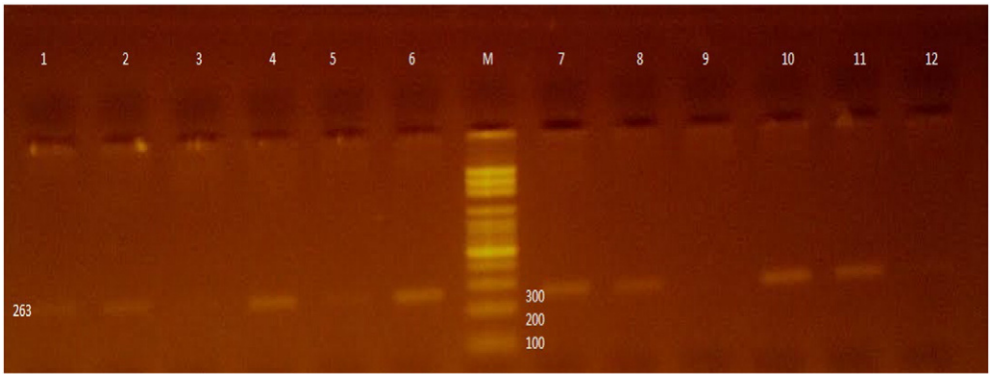

Fig. 2. The genotypes of IFN-γ +874 A>T; lane M indicate DNA Ladder 100 bp, lanes (1 and 2) represent genotype AT, lanes (3 and 4) represent genotype TT, lanes (5 and 6) represent genotype AT, lanes (7 and 8) represent genotype AT, lanes (9 and 10) represent genotype TT, lanes (11 and 12) represent genotype AT, IFN-γ +874 A>T was detected at 263 bp.

and those having the *INF-γ* AT + TT genotypes vs. those with the AA genotype revealed no significant difference regarding their age, gender and nephritis class, activity and chronicity indices ($p > 0.05$) (Table 3).

4. Discussion

This study tested the association of two important gene polymorphisms with SLE presenting mainly with nephritis. It showed clearly *IFN-γ +874 T* and *TNF-α −308 A* alleles are risk alleles for SLE in Egyptian subjects although apparently not affecting the clinical severity of the disease. In another study done among Egyptian SLE patients recruited from Upper Egypt, Ahmed et al. have found a high frequency of the *TNF-α −308 A* allele in the SLE patients but not in patients with nephritis (Ahmed et al., 2014).

Recent meta-analysis has shown also that individuals carrying *TNF-α −308 A* risk allele were significantly associated with SLE in European, South American and Mexican subjects but was not associated with SLE in Asian and African subjects (Pan et al., 2012). Similar conclusion regarding the association of *TNF-α −308 A allele* was also found among Brazilian (Angelo et al., 2012), Colombian (Guarnizo-Zuccardi et al., 2007), Mexican (Jiménez-Morales et al., 2009), North American (Parks et al., 2004), Spanish (Suárez et al., 2005), Asian (Lin et al., 2009) and Caucasian (van der Linden et al., 2001) patients. This might be explained by the fact that *TNF-α* is a pro-inflammatory cytokine involved in different immune-regulated diseases including autoimmune, infectious, and malignant ones (Lee et al., 2006).

Regarding the other polymorphism, we could find that a few number of articles were done to analyze the relationship between the *IFN-γ* +874 A>T SNP and susceptibility to SLE. For instance, Kim et al. found an association between the +874 A>T *IFN-γ* polymorphism and SLE patients in Korean patients (Kim et al., 2010). This might be also explained by the fact that *IFN-γ* is an important cytokine produced in response to inflammatory stimuli to regulate the human immune response. It was believed that the pathogenesis of SLE involves the over-production of *IFN-γ* (Bennett et al., 2003). It has been postulated that genetic polymorphisms affecting cytokine transcription exist in the regulatory regions of pro-inflammatory cytokine genes, and that such polymorphisms may control the level of inflammation (Baechler et al., 2003). In addition, the positive association was found between the amino acid polymorphism (Val14Met) within the *IFN-γ* receptor 1 gene and SLE. Several studies have indicated that alterable expression of the *IFN-γ* level has significant effects to the susceptibility of various autoimmune diseases, particularly in SLE (Csiszár et al., 2000; Tanaka et al., 1999). Nonetheless, other studies found contradictory results of no association of *TNF-α −308 G>A* polymorphism with SLE among Argentinean (Muñoz et al., 2014), Mexican (Zúñiga et al., 2001), Japanese (Takeuchi et al., 2005), Colombian (Tobón et al., 2005), African Americans (Parks et al., 2004), Italian (D'Alfonso et al., 1996), Chinese (Fong et al., 1996), Thai (Hirankarn et al., 2007) and Portuguese (Santos et al., 2012) patients. In spite of the above evidence, we have encountered two studies stating a non-association of *IFN-γ +874 T* allele and SLE among Thai and Brazilian subjects (Tangwattanachuleeporn et al., 2007; da Silva et al., 2014).

Table 1
Genotype frequencies of *TNF −308* in SLE cases compared to controls.

TNF −308 G>A	SLE % ($n = 125$)	Controls % ($n = 112$)
Genotypes		
GG	92 (73.6)	98 (87.5)
GA	28 (22.4)	13 (11.6)
AA	5 (4.0)	1 (0.9)
HWE	$\chi 2 = 2.15$, $p > 0.05$	$\chi 2 = 0.66$, $p > 0.05$
Alleles		
G	212 (84.8)	209 (93.3)
A	38 (15.2)	15 (6.7)
Statistics	*p*	OR (95% CI)
AA + GA vs. GG (dominant)	*0.009***	*2.51 (1.26–4.99)*
GA vs. GG + AA (overdominant)	*0.04**	*2.20 (1.08–4.49)*
AA vs. GG + GA (recessive)	*0.22*	*4.63 (0.53–40.21)*
A allele vs. G allele	*0.003***	*2.50 (1.33–4.68)*

* $p < 0.05$ = *significant.*
** $p < 0.01$ *highly significant.*

Table 2
Genotype frequencies of *IFNG +874* in SLE cases compared to controls.

IFNG +874 A>T	SLE % ($n = 125$)	Controls % ($n = 112$)
Genotypes		
AA	66 (52.8)	76 (67.9)
AT	52 (41.6)	29 (25.9)
TT	7 (5.6)	7 (6.2)
HWE	$\chi 2 = 0.62$, $p > 0.05$	$\chi 2 = 3.06$, $p > 0.05$
Alleles		
A	184 (73.6)	181 (79.9)
T	66 (26.4)	43 (20.1)
Statistics	*p*	OR (95% CI)
TT + AT vs. AA (dominant)	***0.02****	***1.89 (1.11–3.21)***
AT vs. AA + TT (overdominant)	***0.01****	***2.04 (1.17–3.54)***
TT vs. AA + AT (recessive)	*1.0*	*0.89 (0.30–2.62)*
T allele vs. A allele	*0.13*	*1.43 (0.93–2.20)*

* $p < 0.05$ = *significant.*
** $p < 0.01$ *highly significant.*

Table 3
Genotype frequencies of *TNF-α −308* and *IFN-γ +874* genotypes stratified by the clinical items of lupus nephritis.

	TNF-α −308 G>A		*p*	*INF-γ + 874* A>T		*p*
	GA + AA	GG		AT + TT	AA	
Age, years (M ± SD)	23.4 ± 4.6	23.5 ± 4.3	0.91	23.8 ± 3.7	24.6 ± 4.3	0.86
Gender, M/F (N%)	28.3%/25%	71.1%/75%	0.69	15.1%/9.8%	84.9%/90.2%	0.74
SLE class (M ± SD)	3.7 ± 0.6	3.5 ± 0.4	0.48	3.7 ± 0.5	3.9 ± 0.7	0.72
Activity index (M ± SD)	10.7 ± 4.6	11.4 ± 10.8	0.73	11.1 ± 4.2	17.2 ± 25.9	0.12
Chronicity index (M ± SD)	1.2 ± 0.9	2.8 ± 13.6	0.47	1.6 ± 1.2	1.1 ± 0.9	0.23

These contradictory results might be attributed to different ethnic origins in addition to diverse genetic and epigenetic interactions with different environmental effects. The relatively small sample size might also present other limiting factor. Lastly, we can conclude that *TNF-α* −308 G>A and *IFN-γ* +874 A>*T* gene polymorphisms might play a role in the susceptibility but not the severity and activity of lupus in Egyptian cases. However, taking into consideration the limiting factors, we recommend undertaking a wide-scale multicenter study into the entire genome sequence studying all cytokine gene polymorphisms and their expression status in cases of SLE.

Conflict of interest

The authors declare that they have no conflict of interest.

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