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ORIGINAL ARTICLE

SDF-1(CXCL12) polymorphisms in Egyptian patients with systemic lupus erythematosus (SLE): a pilot study

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Abstract SDF-1(CXCL12) is a chemokine that plays an important role in the regulation of migration, proliferation, and differentiation of hematopoietic cells, as well as being involved in the homeostatic and inflammatory traffic of leukocytes. It was suggested that CXCL12 is a key molecule in the development of autoimmunity in the murine model of lupus. It has been demonstrated that SDF-1 has a G801A transition at position 801 in the 3′-untranslated region of the transcript, known as SDF-1-3′G801A. This polymorphism may have an important regulatory function via an increase in the biosynthesis of SDF-1 protein and has been reported in association with autoimmune diseases, such as type 1 diabetes and systemic sclerosis. We investigated the prevalence of SDF-1-3′ G801A genotype in Egyptian patients with systemic lupus erythematosus (SLE) (n=50) and healthy controls (HC) (n= 50) and its relation to SLE manifestations. We found a significant correlation between the SDF-1-3′G801A genotype and the following SLE features: photosensitivity, nephritis, serositis, and vasculitis, and also anticardiolipin antibodies. Our observations suggest that the SDF-1-3′-G801A genotype may be associated with some clinical and laboratory manifestations in patients with SLE.

Keywords SDF-1(CXCL12) · SLE · Chemokines · Polymorphism

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Introduction

Systemic lupus erythematosus (SLE) is a chronic and systemic autoimmune disease that is characterized by autoantibody production, abnormalities of immune-inflammatory system function, and inflammatory manifestations in several organs (Kyttaris et al. 2005). The prevalence of SLE is 20 to 150 cases per 100,000; both geography and race affect the prevalence of SLE and the frequency and severity of clinical and laboratory manifestations (Pons-Estel et al. 2010).

The etiology of SLE remains unknown and is clearly multifactorial. Many observations suggest a role for genetic, hormonal, immunologic, and environmental factors. There is no single gene polymorphism that creates high risk for SLE, except for the rare TREX1 mutation or deficiencies of early components of complement (Günther et al. 2009). A combination of susceptibility genes or presence of susceptibility genes plus the absence of protective genes are required for sufficient genetic susceptibility to permit disease development, and it is likely that environmental or epigenetic changes play a major role. Additionally, some of the single-nucleotide polymorphisms in SLE-risk genes predispose to particular clinical subsets of SLE (Crispín et al. 2013).

Directional movement of cells in the human body is orchestrated via chemokines. This migration was initially identified in pathological and immunological processes but quickly extended to homeostatic cell trafficking. One such chemokine is the ubiquitous CXCL12 (initially called SDF-1-α) which signals via the chemokine (C-X-C motif) receptors CXCR4 and CXCR7, and it has a ubiquitous expression in the bone marrow (Burger and Kipps 2006), lymph nodes, liver, lung, brain, heart, kidney, thymus, stomach, and most abundantly in the pancreas, spleen, ovary, and small intestine (Juarez et al. 2004). Its role was thought to be exclusively as a regulator of normal leukocyte recirculation, hematopoiesis,

and infection of the HIV virus. However, more recently, CXCL12 was discovered to be a participant in homing of progenitor leukocytes into the marrow microenvironment, as well as adaptive immune processes; for example, co-stimulation of $CD4^+$ T cells activation and survival (Werner et al. 2013).

In rheumatoid arthritis (RA), increased amounts of CXCL12 mRNA were found in RA synoviocytes, and elevated CXCR4 expression by synovial memory T cells was reported suggesting that CXCL12/CXCR4 play a role in the recruitment of inflammatory cells to the joint (Chung et al. 2010). CXCL12/CXCR4 interactions are also implicated in chronic lung inflammatory processes. In these disorders, CXCL12/CXCR4 were found to operate similarly to their mode of action in RA. CXCL12 was upregulated in the lung in both humans and animal models of lung inflammation. It exhibits pro-inflammatory influence as observed by increased influx of $CXCR4^+$ cells from the bone marrow to the lung. Small molecule inhibitors or neutralizing antibodies of CXCR4 attenuated lung inflammation, highlighting its critical involvement in the pathology of this disorder (Petty et al. 2007).

High expression of CXCL12 has been documented in patients with SLE. Moreover, in the study conducted by Balabanian et al., administration of antagonists of CXCL12/SDF-1 early in life prevented the development of autoantibodies, nephritis, and death in NZB/W mice. Meanwhile, initiation of anti-CXCL12/SDF-1 mAb treatment later in life, in mice with established nephritis, inhibited autoantibody production, abolished proteinuria and immunoglobulin (Ig) deposition, and reversed morphological changes in the kidneys. These results suggest that CXCL12 is a key molecule in the development of autoimmunity in the murine model of lupus (Balabanian et al. 2003). A common polymorphism variant, defined by a G/A mutation and located at position 801 in 3′ UTR in CXCL12 gene (designated CXCL12-3′G801A), has been shown to possess the ability of upregulating the expression of CXCL12 (Dommange et al. 2006). This polymorphism has been considered a factor in increased susceptibility to many different types of carcinomas, autoimmune diseases, and type 1 diabetes mellitus (Chang et al. 2009). It is worth noting that CXCL12/CXCR4 interactions are highly involved in leukocyte recruitment to areas of inflammation, resulting in end-organ damage, and blockade of this axis represents a potential therapeutic avenue for preserving peripheral organ function in SLE.

A few reports study the CXCL12-3′G801A polymorphism in SLE patients. We aimed by this study to clarify whether the (CXCL12-3′G801A) polymorphism is associated with increased SLE susceptibility and to study its impact on both clinical and laboratory characteristics in Egyptian patients. We therefore investigated the distribution of (CXCL12-3′ G801A) genotype in Egyptian patients with SLE comparing them with a group of unrelated healthy controls (HC) particularly that published data regarding susceptibility genes and disease biomarkers in this population are still insufficient.

Patients and methods

Patients A total of 50 adult Egyptian SLE patients (48 women, 2 men, mean age 28.88±7.51 years) were enrolled in the study; all were recruited from Rheumatology and Rehabilitation Department, Kasr El Aini Hospital, during the period from 2012 to the end of 2014. The diagnosis was established based on the 1987 American College of Rheumatology criteria for SLE (Hochberg 1997). A total of 50 age, sex, and ethnically matched unrelated healthy subjects were recruited as controls. Peripheral blood samples (5 mL) were obtained from all subjects after they provided a written informed consent. This pilot case control study was approved by the ethical committee.

Methods SLE patients were subjected to the following: full history taking, thorough clinical examination, assessment of disease activity using systemic lupus erythematosus activity measure (SLAM) (Rosalind and David. 2003), and laboratory investigations which included complete blood count (CBC), erythrocyte sedimentation rate (ESR), complete urine analysis, kidney function tests, serum complement level (C3 and C4), serum antinuclear antibodies (ANAs), serum anti-double-stranded deoxyribonucleic acid antibodies (dsDNA), and anticardiolipin antibodies. Lupus nephritis is assessed by doing ultrasound-guided renal biopsy when clinically indicated and staged according to the following classifications revised by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003: Class I: minimal mesangial lupus nephritis, Class II: mesangial proliferative lupus nephritis, Class III: focal lupus nephritis (active and chronic; proliferative and sclerosing), Class IV: diffuse lupus nephritis (active and chronic; proliferative and sclerosing; segmental and global), Class V: membranous lupus nephritis, and Class VI: advanced sclerosis lupus nephritis. All data were collected prospectively during assessment (Dooley 2007).

CXCL12-3'G801A polymorphism genotype evaluation Total genomic DNA of patients and healthy controls was extracted from about 2 mL anticoagulated whole blood on EDTA using QIAamp blood DNA isolation kits (Qiagen, Crawley, UK) according to the manufacturer's protocol. The genotyping for CXCL12-3′G801A was performed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. The primers used for genotyping were as follows: forward primer, 5′CAG TCA ACC TGG GCA AAG CC 3′; reverse primer, 5′AGC TTT GGT CCT GAG AGT CC 3′. Sample DNA (100 ng) was amplified by PCR

under the following conditions: an initial heat denaturation at 94 °C for 3 min and two loops of amplification. Loop 1 included 7 cycles with the following program: denaturation at 94 °C for 20 s, annealing at 67 °C for 45 s, and extension at 72 °C for 80 s. Loop 2 included 28 cycles with the following program: denaturation at 94 °C for 20 s, annealing at 60 °C for 30 s, and extension at 72 °C for 1 min. In the last cycle, extension was prolonged to 5 min at 72 °C. PCR reaction yielded a 302-bp product. Since CXCL12 mutant allele (A) eliminated an MspI restriction site, the PCR products were digested at 37 °C overnight with 0.6 μl MspI in the manufacturer's buffer (Helena Biosciences, Sunderland, UK). The digested products were then run in parallel on 2 % agarose gel using gel electrophoresis (electro-4, Thermal Hybaid, from Promega) and visualized on a UV transilluminator (wave length 312). Samples exhibiting 302-bp band were assigned as A/A genotype, and samples revealing two bands of 202 and 100 bp were typed as G/G genotype, and samples illustrating three bands of 302, 202, and 100 bp were assigned as G/A genotype.

Statistical analysis Data were analyzed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, USA) version 15 for Microsoft Windows. Numerical data were expressed as mean, standard deviation, range, and median. Qualitative data were expressed as frequency and percentage. Analysis of variance (ANOVA) test and Chi-square test were used to examine the relation between qualitative variables. A probability value (*P* value) less than 0.05 was considered statistically significant.

Results

Patients included in our study were 48 females (96 %) and 2 males (4 %), and their age ranged between 18 and 41 years with median age of 29 years (mean age 28.88±7.51 years). Healthy controls were 40 females (80 %) and 10 males (20 %), and their age ranged between 18 and 42 years with median age of 32 years (mean age 30.8±6.01 years).

Of the 50 SLE patients examined, 42 patients had skin rash (84 %); 34 patients had photosensitivity (68 %); 30 patients had arthritis (60 %); also 30 patients had oral ulcers (60 %); 25 patients had nephritis (50 %), where 2 had stage I lupus nephritis (LN), 10 patients had stage II LN, 10 patients had stage III LN, 1 patient had stage IV LN, 2 patients had stage V LN, and no patients had stage VI LN; 21 patients had serositis (42 %); 12 patients had vasculitis (24 %); 14 patients had cerebritis (28 %); 5 patients had low-grade fever not explained by infections (10 %); and by revising their laboratory data, we found 41 patients had anemia (82 %), 6 patients had leucopenia (12 %), and 10 patients had thrombocytopenia (20 %); all 50 patients had positive ANA (100 %), 38 patients had positive anti-DNA (76 %), 15 patients had positive anticardiolipin (30 %), 28 patients had low C3 (56 %), and 19 patients had low C4 (38 %).

The genotyping for CXCL12-3′G801A performed by PCR-RFLP assay of the studied SLE patients revealed that 34 patients had wild G/G genotype (68 %), 3 patients had homozygous mutant A/A genotype (6 %), and 13 patients had heterozygous mutant G/A genotype (26 %), as shown in Fig. 1.

The genotyping for CXCL12-3′G801A of the healthy controls (HC) revealed that 32 patients had wild G/G genotype (64 %), 2 patients had homozygous mutant A/A genotype (4 %), and 16 patients had heterozygous mutant G/A genotype (32 %), as shown in Fig. 2.

The comparison between patients and healthy control in genotyping pattern of CXCL12-3′G801A revealed insignificant correlation, as shown in Table 1.

We studied the correlation between patient's genotype and different clinical and laboratory parameters of the studied SLE patients, and we found statistically significant correlation between heterogeneous mutant G/A genotype and photosensitivity (*P* value 0.032), nephritis (*P* value 0.047), serositis (*P* value 0.045), and vasculitis (*P* value 0.022), and also anticardiolipin antibodies (*P* value 0.037), as shown in Table 2; the correlations between the other clinical and laboratory parameters in our studied SLE patients were insignificant as shown in Table 2.

Discussion

SLE is characterized by infiltration and accumulation of inflammatory leukocytes in different tissues which is a critical process in the pathogenesis of the tissue injury (Rovin 2008). The recruitment of inflammatory cells to lesions is an essential step in the development and progression of inflammation which facilitated by chemokines and cytokines (Kim et al. 2002). Chemokines such as SDF-1 has been involved in inflammatory pathologies.

SDF-1(CXCL12) protein is a critical molecule in the pathogenesis of SLE. Robak reported that serum concentration of CXCL12 was elevated significantly in SLE patients compared with that in control individuals (Robak et al. 2007). Also, it was found that CXCL12 and its receptor CXCR4 were significantly upregulated in nephritic kidney in murine models of lupus and SLE patients (Wang et al. 2009).

SDF-1(CXCL12)-3'-G801A gene variant has been considered a factor in increased susceptibility to lymphoma, oral and squamous carcinomas, and cancers of the breast, lung, and prostate (Khademi et al. 2008), and it has been observed that it is significantly associated with higher mortality in liver allograft recipients. Moreover, the *SDF-1-3'-G801A* allele has

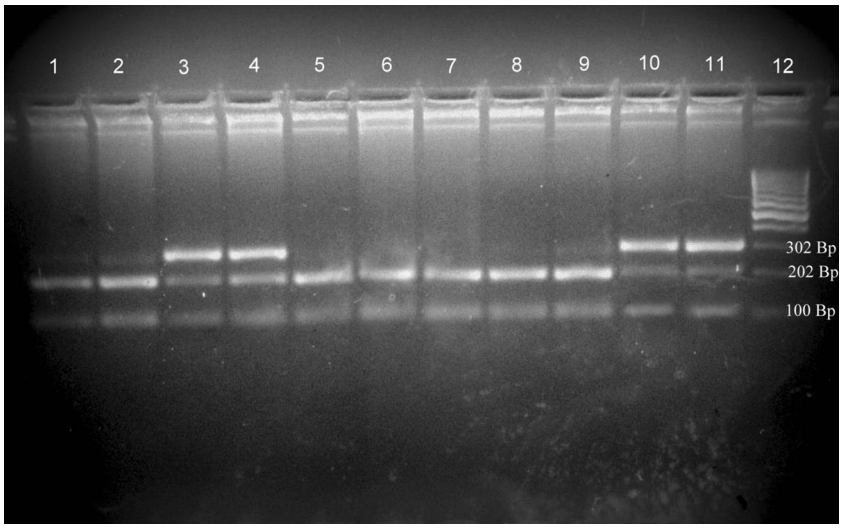

Fig. 1 Genotyping of CXCL12-3′G801A polymorphism in SLE patients which performed by PCR-RFLP assay. Lanes *1*, *2*, *5*, *6*, *7*, *8*, and *9* show bands at 202 and 100 bp denoting the wild type (G/G). Lanes *3*, *4*, *10*, and *11* show bands at 302, 202, and 100 bp denoting heterozygous mutant type (G/A)

been associated with the microvascular involvement in systemic sclerosis and with age-at-onset of type 1 diabetes mellitus in the Japanese population (Manetti et al. 2009).

In the present study, we assessed the association between CXCL12-3′G801A polymorphism and the SLE clinical/laboratory characteristics of a group of Egyptian patients comparing them with a group of unrelated healthy controls (HC). It revealed that no genotypic difference between SLE cases and HC group, and this indicates that CXCL12-3′G801A polymorphism might not contribute in susceptibility to SLE in Egyptian subjects.

Our result did not match the study of Lima et al. who had the CXCL12-3′G801A polymorphism genotyped in 242 Mexican SLE patients and found increased frequency of G/G genotype (71.5 vs. 64.5 %) (Lima et al. 2007) and Wu F-X et al. who investigated 422 patients from China and demonstrated a significant association of the G/G homozygous in CXCL12-3′G801A gene with SLE (60.0 vs. 52.7 %) (Wu et al. 2012). But on the other hand, our results matched studies by Ye et al., Warchol et al., and Lian LH who had genotyped the CXCL12-3′G801A polymorphism in Chinese, Poland, and Malaysian subjects, respectively, and found no association of CXCL12-3′G801A polymorphism with SLE (Ye et al. 2005; Warchol et al. 2010; Lian et al. 2011).

We found a statistically significant correlation between the presence of CXCL12-3′G801A polymorphism and SLE clinical and laboratory characteristics such as: photosensitivity (*P* value 0.032), nephritis (*P* value 0.047), serositis (*P* value 0.045), vasculitis (*P* value 0.022), and also anticardiolipin antibodies positivity (*P* value 0.037).

The data concerning the influence of CXCL12-3′G801A polymorphism on the clinical manifestations of SLE yielded conflicting results. Ye et al. did not find any association of CXCL12-3′G801A polymorphism with clinical features (Ye et al. 2005), but on the contrary, Warchol et al. observed that the CXCL12-3′G801A A/A and G/A genotypes contributed to renal manifestations of SLE (Warchol et al. 2010); Lima

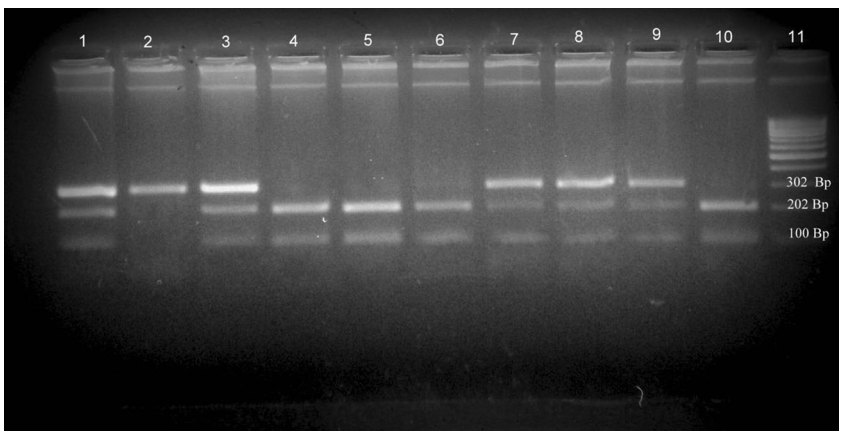

Fig. 2 Sample of the genotyping for CXCL12-3′G801A of the HC which performed by PCR-RFLP assay. Lanes *4*, *5*, *6*, and *10* show bands at 202 and 100 bp denoting the wild type (G/G). Lanes *1*, *3*, *7*, *8*, and *9* show bands at 302, 202, and 100 bp denoting heterozygous mutant type (G/A). Lane *2* shows band at 302 bp denoting homozygous mutant type (A/A)

Table 1 Comparison between SLE patients and controls in genotyping pattern of CXCL12-3′G801A

genotype	SLE (*n*)	SLE (%)	controls (*n*)	Controls (%)	*P* value
G/G	34	68	32	64	0.54
A/A	3	6	2	4	0.57
G/A	13	26	16	32	0.22

The comparison between patients and controls in genotyping pattern of CXCL12-3'G801A revealed insignificant correlation

et al. demonstrated that CXCL12-3′G801A homozygous A/A genotype is associated with the incidence of antiphospholipid syndrome (APS) in lupus patients (Lima et al. 2007), and also Wu et al. observed a significant association of CXCL12-3′G801A G/G genotype and a higher incidence of photosensitivity and nephritis of SLE in Chinese patients (Wu et al. 2012) which matched our finding in the Egyptian patient group.

The presence of autoantibodies in serum is a hallmark of SLE, and it is widely understood that inflammation and deposition of antibodies and complement exist in affected organs in SLE patients. And a large amount of retrospective studies have documented that autoantibodies associate to specific clinical manifestations of SLE (Su et al. 2011).

Table 2 Correlation between patient's genotype and different clinical and laboratory parameters of the studied SLE patients

	G/G *n*=34 (%)	A/A *n*=3 (%)	G/A *n*=13 (%)	*P* value
Skin rash	27 (79)	2 (66)	13 (100)	(0.679)
Photosensitivity	21 (61)	2 (66)	11 (84)	*(0.032)
Arthritis	34 (91)	2 (66)	12 (92)	(0.856)
Oral ulcer	23 (67)	2 (66)	5 (38)	(0.123)
Nephritis	17 (34)	2 (66)	6 (46)	*(0.047)
Serositis	15 (34)	1 (33)	5 (38)	*(0.045)
Vasculitis	8 (23)	1 (33)	3 (23)	*(0.022)
Cerebritis	12 (35)	0 (0)	2 (15)	(0.512)
Low-grade fever	4 (12)	0 (0)	1 (7.5)	(0.897)
Anemia	27 (79)	2 (66)	12 (92)	(0.866)
Leucopenia	5 (14)	0 (0)	1 (7.5)	(0.834)
Thrombocytopenia	7 (20)	0 (0)	3 (23)	(0.911)
ANA	34 (100)	3 (100)	13 (100)	(0.913)
Anti-dsDNA	25 (73)	2 (66)	11 (84)	(0.065)
Anticardiolipin antibodies	9 (36)	1 (33)	5 (38)	*(0.037)
C3	19 (56)	2 (66)	7 (54)	(0.657)
C4	20 (59)	1 (33)	10 (76)	(0.912)

Statistically significant correlation between heterogeneous mutant G/A genotype and photosensitivity (*P* value 0.032), nephritis (*P* value 0.047), serositis (*P* value 0.045), and vasculitis (*P* value 0.022), and also anticardiolipin antibodies (*P* value 0.037)

*Significant correlation

The data concerning the association of CXCL12-3′ G801A polymorphism with the occurrence of autoantibodies was not available in the studies conducted by Ye et al. (Ye et al. 2005).

While there was no association of CXCL12-3′G801A polymorphism with the production of autoantibodies was reported by Warchol et al. (Warchol et al. 2010), Wu et al. found a significant correlation between CXCL12-3′G801A polymorphism and SLE autoantibodies, anti-nucleosome and anti-smith (Wu et al. 2012), as well as our study in the Egyptian subjects, we found a statistically significant correlation between *SDF-1-3'-G801A* polymorphism and anticardiolipin antibodies positivity ($P<0.037$) which was supported by the finding of Lima et al. who found a relationship existing between A/A genotype and the presence of APS (Lima et al. 2007).

The functional role of the SDF-1-801 genotype seems to involve upregulation of the quantity of SDF-1 protein available. Similarly, SDF-1 increases the chemotaxis of inflammatory cells and contributes to the activation of platelets in the damaged area, which could result in thrombosis or an acceleration of the damage done to the vascular integrity (Ao et al. 2011). This could explain, at least partially, the association of the SDF-1-801 genotype with the clinical manifestations of APS (e.g., thrombosis, fetal loss) which only represented in our subjects by the positivity of anticardiolipin as a laboratory feature of APS.

Our observations suggest that the CXCL12-3′G801A genotype may be associated with some clinical and laboratory manifestations in patients with SLE, but the discrepancies in the influence of CXCL12-3′G801A polymorphism on the clinical manifestations and autoantibody production of SLE between others' and our findings could be due to ethnicity-specific factors that might be contributing to the conflicting results; this was to be expected, taking into account the concept that the influence of individual genes or environmental factors that alone or in interaction induce the expression of disease susceptibility may vary in populations, and also, the presence of CXCL12-3′G801A polymorphism could not be used as a marker for increased susceptibility to SLE, but additional studies in other populations and with a larger study number could help to define the true role of these polymorphisms as genetic markers in SLE patients.

Conflict of interest Sherif Yousry, Gehan Shahin, Doaa El Demerdash, and Noha EL Husseiny declare that they have no conflict of interest.

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Authors' contributions

Meticulous laboratory work was done under the supervision of Dr. Sherif Yousry and Dr. Gehan Shahin. Statistical work was done and reviewed by Dr. Noha EL Husseiny. Drafting of the article by Doaa El Demerdash, and all the authors revised it.