



Lack of association between *RANTES-28*, *SDF-1* gene polymorphisms and systemic lupus erythematosus in the Malaysian population

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ABSTRACT. Regulated on activation, normal T-cell expressed and secreted (*RANTES*) and stromal cell-derived factor 1 (*SDF-1*) are members of the CC- and CXC-chemokine families, respectively. Both genes have been postulated to be involved in the pathogenesis of systemic lupus erythematosus (SLE). We analyzed position 28 of the *RANTES* gene promoter region, as well as the SNP observed in the 3' UTR of the *SDF-1* gene at position 801, in 130 patients presenting SLE at the Malaya University Medical Centre. Screening of 130 healthy volunteer controls using RFLP was also performed. *RANTES-28* polymorphism analysis showed no significant ($P = 0.3520$) relationship, even though homozygous C/C was more frequent in SLE patients (OR = 1.4183) and heterozygous C/G was more frequent in healthy controls (OR = 0.7051). There were no significant ($P = 0.2650$) associations between A/A (OR = 0.783), G/G (OR = 1.5914) and G/A (OR = 0.8289) genotypes in the *SDF-1* gene polymorphism with SLE. We conclude

that there is no significant association of *RANTES-28* and *SDF-1* gene polymorphisms and occurrence of SLE in Malaysia.

Key words: RANTES; SDF; Polymorphism; SLE; Malaysia

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that manifests as severe inflammation of multiple organs. The usual affected organs include the brain, heart, skin, joints, kidneys, lungs, and blood vessels (Katsiari and Tsokos, 2006). SLE is characterized by pathogenic autoantibodies in the systemic circulation, which damage the organs upon deposition of immune complexes. Physicians often have difficulties diagnosing SLE accurately at initial stages due to clinical symptoms and complications that are similar to other autoimmune diseases, e.g., rheumatic arthritis and multiple sclerosis. Furthermore, the severity of SLE is highly variable, ranging from being mild to deadly. The symptoms in SLE patients include fever, multiple joints pain, skin rashes, malaise, extreme fatigue, and kidney problems. The butterfly-shaped rash that presents over the nose-bridge is a distinctive feature of SLE. Unfortunately, medications only relieve symptoms, reduce inflammation and slow down the disease's progression; there is no cure for this disease (Wallace and Hann, 2002).

Broadly, the exact cause of SLE remains unknown, despite extensive studies carried out all over the world to investigate the etiology of this disease. Researchers have postulated that initiation of SLE is possibly due to interaction of three major factors, these being genetic, endocrine-metabolic, and environmental. It is hard to draw a clear cut conclusion on how these factors affect the onset of SLE due to the poorly understood pathogenesis of SLE and the mechanisms involved in its initiation. There is no single gene reported to be responsible for the disease. It is suggested that a complex interaction of multiple genes may be involved, triggering the onset of SLE. SLE is a gender-biased disease that affects mostly females (approximately nine females to one male), more so during their child-bearing age. This is believed to occur due to hormonal changes in women during puberty (Danchenko et al., 2006). Also, the prevalence rate of SLE is at least 2- to 4-folds higher in Afro-Americans, Afro-Caribbeans, and Asians, when compared to Caucasians (Hochberg, 1985). In Malaysia, the prevalence rate of SLE is more common in Chinese, than in Malay and Indian ethnicities (57, 33, and 14 per 100,000 persons, respectively; Wang et al., 1997). The mean mortality rate for patients with SLE in Malaysia is 20.2% (Yeap et al., 2001).

Regulated on activation normal T-cell expressed and secreted (RANTES) is a member of the CC-chemokine family that selectively attracts T-cells, monocytes, eosinophils, and basophils (Ortiz et al., 1996). It has been extensively studied in allergic and infectious diseases (Nickel et al., 2000). RANTES is expressed in airway epithelial cells, platelets, fibroblasts, activated T-lymphocytes, renal epithelial, and mesangial cells (Nickel et al., 2000). The T-lymphocytes are attracted to the site of inflammation after early and transient RANTES activation by cells in injured tissues (Ortiz et al., 1996). T-lymphocytes will then encounter the antigen, fully differentiate and produce large amounts of RANTES, through which the inflammatory response is amplified (Ortiz et al., 1996). The *RANTES* gene is located on chromosome 17q11.2-q12, spanning 8.8 kb (An et al., 2002). It consists of three exons and two introns (An et al., 2002). There are seven single nucleotide polymorphisms (SNPs) in the *RANTES* gene;

four are in the promoter regions, two in the first intron, and one in the 3' untranslated region (UTR). One of the SNPs that is present at position 28 in the promoter region of the *RANTES* gene, has a cytosine (C) to guanine (G) variation. This polymorphism is proposed to elevate the promoter activity of *RANTES*, increasing the expression of *RANTES* in humans (Ye et al., 2005a).

Stromal cell-derived factor 1 (SDF-1) is a member of the CXC-chemokine family that is found on chromosome 4 (Bleul et al., 1996). It is also known as CXCL12, which was originally identified as a growth factor for murine pre-B cells (Ye et al., 2005b). SDF-1 plays an important role in the regulation of migration, proliferation, differentiation of hematopoietic cells, as well as being involved in the homeostatic and inflammatory traffic of leukocytes (Lima et al., 2007). The receptor for SDF-1 is CXCR4, and interaction between SDF-1 and its receptor plays a vital role in CD4⁺ T-cell accumulation in the synovium in patients with rheumatoid arthritis. SDF-1 is also known to inhibit activation-induced apoptosis of T-cells (Ye et al., 2005b). This condition can lead to production of pathogenic autoantibodies (Lima et al., 2007). An SNP was found in the 3' UTR of the *SDF-1* gene at position 801 (Lima et al., 2007). The polymorphism is characterized by a G to adenine (A) variation that can increase the transcriptional activity of the *SDF-1* gene, resulting in production of larger quantities of SDF-1 proteins (Ye et al., 2005b). Here, we examined the SNPs in both the promoter region of *RANTES* and 3' UTR of the *SDF-1* genes. We also looked at possible association of these SNPs with SLE in the Malaysian population.

MATERIAL AND METHODS

Sample collection and genomic DNA extraction

Two hundred and sixty blood samples were collected with informed consent from patients attended at the University Malaya Medical Centre (UMMC), Kuala Lumpur. These consisted of 130 SLE patients and 130 healthy volunteer controls. In general, the patients ranged in age from 16 to 50 years and their clinical manifestations were renal disorder with proteinuria (>0.5 g/day), malar rash, arthritis, and photosensitivity with production of anti-dsDNA at >200 IU/mL. Blood samples were collected in EDTA tubes and genomic DNA was extracted via a conventional phenol-chloroform extraction method. Both the quality and quantity of the extracted DNA were then determined using spectrophotometry.

Amplification of the *RANTES* gene

Amplification of the promoter region of the *RANTES* gene was carried out via PCR with primers, as described in a previous study (Ye et al., 2005a). The 20- μ L amplification reaction contained 10 ng genomic DNA, 2 μ L 10X *Taq* buffer with KCl, 1.5 mM MgCl₂, 0.075 mM dNTP mixture, 0.375 μ M of each forward and reverse primers, and 0.75 U *Taq* DNA polymerase. The primer sequences used for the analysis of *RANTES-28* polymorphisms in this study were as follows: 5'-ACAGAGACTCGAATTCGGA-3' and 5'-CCACGTGCTGTCTTGATCCTC-3'. PCR amplification was carried out at 95°C, for 5 min in the initial denaturation, followed by 35 cycles of 94°C for 40 s, 65°C for 40 s, 72°C for 40 s, and a final extension at 72°C for 10 min. The PCR product (173 bp) was then subjected to overnight digestion with 3 U *MnII* at 37°C.

The digested products were then electrophoresed on 3% (w/v) ethidium bromide-stained agarose gels and observed under ultra-violet (UV) light. C and G alleles were indicated by the presence of 126 and 146 bp fragments, respectively (Figure 1).

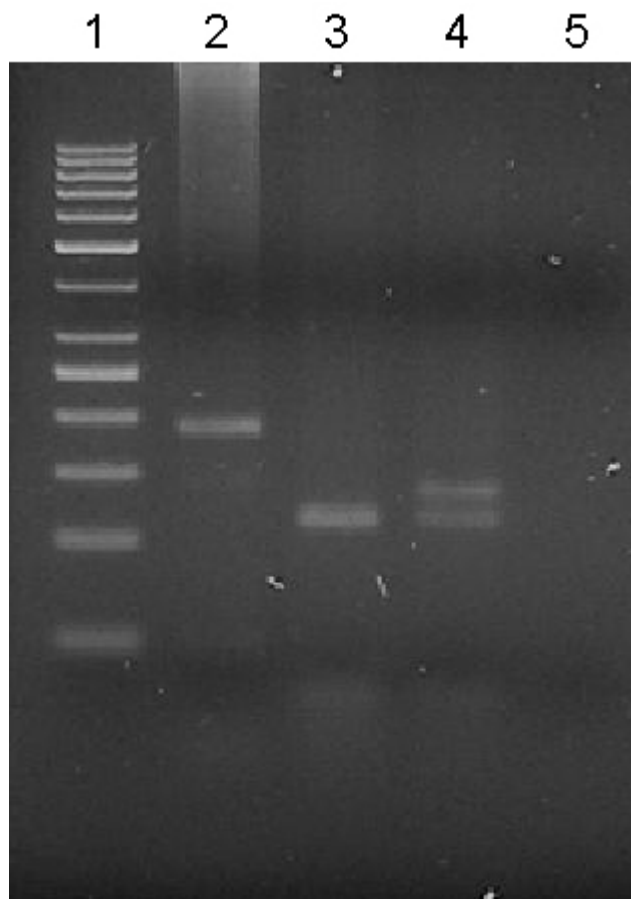


Figure 1. Amplified and digested products of the *RANTES-28* polymorphisms on an agarose gel. Lane 1 = 50-bp DNA ladder; lane 2 = undigested PCR product; lane 3 = digested PCR product (homozygous C/C); lane 4 = digested PCR product (heterozygous C/G); lane 5 = DNA blank.

Amplification of the *SDF-1* gene

Amplification of the *SDF-1* 3' UTR was carried out using primers described by Lima et al. (2007). The 20- μ L amplification reaction contained 10 ng genomic DNA, 2 μ L 10X *Taq* buffer with 500 mM KCl, 1.5 mM MgCl₂, 0.075 mM dNTP mixture, 0.375 μ M each for forward and reverse primers, and 0.75 U *Taq* DNA polymerase. The primer sequences were: 5'-AGTCAACCTGGGCAAAGCC-3' and 5'-AGCTTTGGTCCTGAGAGTCC-3'. The PCR cycling program was set at 95°C for initial denaturation, followed by 35 cycles of 95°C for 40 s, 57°C for 40 s, 72°C for 40 s, and a final extension at 72°C for 10 min. The PCR product (301

bp) was then digested overnight with 2 U *MspI* at 37°C. Following that, the digested products were electrophoresed on 2% (w/v) agarose gels. The A allele was indicated by an undigested fragment (301 bp), whereas, cleaved fragments (99 and 202 bp) indicated presence of the G allele (Figure 2).

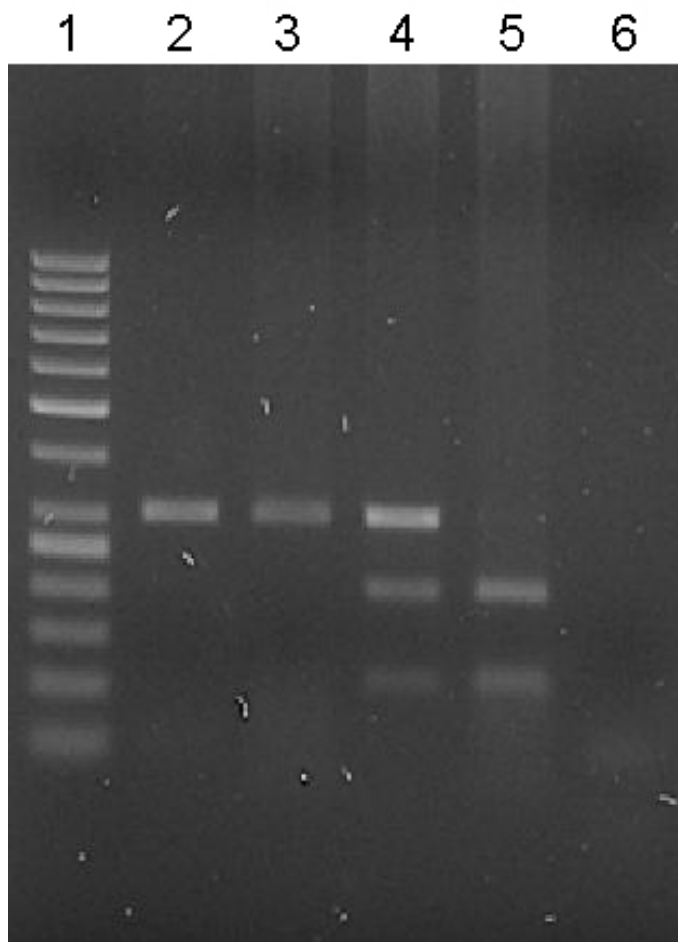


Figure 2. Amplified and digested products of the *SDF-1* gene polymorphisms on agarose gel. *Lane 1* = 50-bp DNA ladder; *lane 2* = undigested PCR product; *lane 3* = digested PCR product (homozygous A/A); *lane 4* = digested PCR product (heterozygous G/A); *lane 5* = digested PCR product (homozygous G/G); *lane 6* = DNA blank.

The chi-square test was carried out for statistical analysis; allele frequencies were also estimated by the gene-counting method. The frequencies of the alleles and genotypes were compared between patient and control groups by the chi-square test, when appropriate. The odds ratio (OR) and 95% confidence intervals (95%CI) were also estimated. The chi-square test was used to examine the deviation of genotype distribution from the Hardy-Weinberg equilibrium.

RESULTS

Table 1 shows the allelic frequencies of *RANTES-28* polymorphisms; both the C and G alleles were observed. The frequency of C alleles was higher in both SLE patients and healthy controls. However, there was no significant difference in the frequency of C and G alleles in the comparison between SLE patients and healthy controls ($\chi^2 = 0.809$, $P = 0.3684$). Neither the C (OR = 1.3853, 95%CI = 0.6791 to 2.8257) nor G alleles (OR = 0.7219, 95%CI = 0.3539 to 1.4725) were significantly associated with this disease. The homozygous C/C genotype was more common than the heterozygous C/G genotype. The frequency of the heterozygous C/G genotype was relatively low in both SLE patients and healthy controls. Surprisingly, no homozygous G/G genotypes were observed in the SLE patients or healthy controls. The distribution of the different genotypes was similar in both the cohorts of SLE patients and healthy controls. There was no significant association of homozygous C/C and heterozygous C/G genotypes with either SLE patients or healthy controls ($\chi^2 = 0.868$, $P = 0.3520$). Furthermore, there was no significant association between C/C homozygotes (OR = 1.4183, 95%CI = 0.6782 to 2.9661) and C/G homozygotes (OR = 0.7051, 95%CI = 0.3372 to 1.4764) with SLE disease.

Table 1. Allelic frequency (N), χ^2 (P) value, odds ratio (OR), and 95% confidence interval (95%CI) of *RANTES-28* polymorphisms in Malaysian systemic lupus erythematosus (SLE) patients and healthy controls.

<i>RANTES-28</i>	Frequency		χ^2 value (P value)	OR value (95%CI)
	SLE patients (N = 130)	Healthy controls (N = 130)		
Genotype				
C/C	116	111	0.868 (0.3520)	1.4183 (0.6782-2.9661)
C/G	14	19		
G/G	0	0		
Allele				
C	246	241	0.809 (0.3684)	1.3853 (0.6791-2.8257)
G	14	19		

In the study of *SDF-1* 3' UTR polymorphisms (Table 2), the frequency of the A allele was higher in healthy controls. On the other hand, the G allele was more commonly observed in Malaysian SLE patients. However, there were no significant differences in the frequencies of A and G alleles between SLE patients and healthy controls ($\chi^2 = 1.973$, $P = 0.1601$). The A (OR = 0.7811, 95%CI = 0.5533 to 1.1027) and G alleles (OR = 1.2802, 95%CI = 0.9068 to 1.8073) were not significantly associated with SLE disease in the Malaysian population. The heterozygous G/A genotype was most commonly observed in both Malaysian SLE patients and healthy controls. On the other hand, the frequency of the homozygous A/A genotype was higher in healthy controls, while the homozygous G/G genotype was frequently scored in SLE patients. However, the distribution of each of the genotype was similar between SLE patients and healthy controls. There was no significant difference in the distribution of the three genotypes between SLE patients and healthy controls ($\chi^2 = 2.660$, $P = 0.2650$). Moreover, there was also no significant association between the homozygous A/A genotype (OR = 0.7830, 95%CI = 0.4235 to 1.4478), the heterozygous G/A genotype (OR = 0.8289, 95%CI = 0.5075 to 1.3537) and the homozygous G/G genotype (OR = 1.5914, 95%CI = 0.8961 to 2.8262) with SLE. Statistical analysis also showed that the distribution of genotypes in both the SLE and healthy controls were in Hardy-Weinberg equilibrium.

Table 2. Allelic frequency (N), χ^2 (P) value, odds ratio (OR), and 95% confidence interval (95%CI) of *SDF-1* 3' UTR polymorphisms in Malaysian systemic lupus erythematosus (SLE) patients and healthy controls.

<i>SDF-1</i> 3' UTR	Frequency		χ^2 value (P value)	OR value (95%CI)
	SLE patients (N = 130)	Healthy controls (N = 130)		
Genotype				
G/G	37	26	2.660 (0.2650)	1.5914 (0.8961-2.8262)
G/A	70	76		
A/A	23	28		
Allele				
G	144	128	1.973 (0.1601)	1.2802 (0.9068-1.8073)
A	116	132		

DISCUSSION

The distribution of both allelic and genotypic frequencies of the *RANTES-28* polymorphisms showed no significant association between the SLE patient and healthy controls in the Malaysian population. Only two genotypes, homozygous C/C and heterozygous C/G, were found. The homozygous G/G genotype was not observed. A similar observation was made in studies carried out on Mexican and Han Chinese populations (Ye et al., 2005a,b). Interestingly, an opposite trend was reported for children of the Han Chinese population (Liao et al., 2004); children with C/G and G/G genotypes were found to have an increased risk of more than double to develop SLE when compared to those with the C/C genotype. Thus, the effect of *RANTES-28* polymorphisms on the onset of SLE may vary in different age groups.

On the other hand, the *RANTES-28* polymorphisms have also been studied in various other inflammatory diseases, e.g., asthma, severe acute respiratory syndrome (SARS), atopic dermatitis, and juvenile rheumatoid arthritis (JRA). The G allele of the *RANTES-28* polymorphisms has a significant association with late-onset asthma in the Japanese population (Hizawa et al., 2002). This finding was further supported by the increased production level of RANTES *in vitro* in individuals with the G allele (Zhernakova et al., 2006). The G allele elevates promoter activity and thus increases the expression of RANTES in T-cells, which can lead to cell damage and organ dysfunction. In another study of the association of *RANTES-28* polymorphisms with susceptibility to SARS in Hong Kong and Beijing citizens, individuals having G alleles were shown to have a 3-fold increased risk of developing the disease when compared to individuals possessing C alleles (Ng et al., 2007). The high level of RANTES is believed to predispose individuals with the G allele to SARS. In a study of *RANTES-28* polymorphisms in Japanese patients with atopic dermatitis, the G allele exhibited a strong relationship with disease due to its up-regulating effect on the expression of RANTES (Tanaka et al., 2006). Furthermore, G alleles were also shown to decrease the remission duration of Taiwan patients, with JRA to 49%, in comparison with patients with the C allele (Yao et al., 2009). Based on the various studies made of different inflammatory diseases, we suggest that up-regulation of the G allele of *RANTES-28* plays a role in the onset of SLE by amplifying the immune response, which leads to organ damage.

SDF-1 is a protein that acts as pro-inflammatory factor in the immune system; it activates and attracts inflammatory cells (such as monocytes and lymphocytes) to the site of inflammation (Robak et al., 2007). We did not observe significant association of *SDF-1* 3' UTR polymorphisms with susceptibility to SLE in Malaysian patients. Similar results were also

obtained in studies carried out by researchers on other populations (Liao et al., 2004; Ye et al., 2005b). Both studies demonstrated that the *SDF-1* polymorphisms did not associate with SLE. In addition, our results are consistent with Warchol's study, who found no significant differences in *SDF-1* 3' UTR variants between Polish SLE patients and healthy controls (Warchol et al., 2010). However, they found a significant association of homozygous A and heterozygous G/A with SLE patients who had renal manifestations. In another study that investigated association of serum levels of SDF-1 rather than association of the *SDF-1* gene with SLE, it was found that serum levels of SDF-1 were higher in SLE patients than in controls. There was no significant difference between active SLE and inactive disease (Robak et al., 2007).

It has been reported that individuals with *SDF-1* 3' A have higher levels of the SDF-1 protein due to the up-regulating effect of this allele (Tashiro et al., 1993). Moreover, the A allele has also been shown to increase mobilization of CD34⁺ progenitor cells into peripheral blood in humans (Benboubker et al., 2001). As multiple sclerosis is an autoimmune disease that involves damage by autoantibodies of the fatty myelin sheaths around the central nervous system, *SDF-1* 3' A has been demonstrated to play a role in the microvascular manifestation in multiple sclerosis and thus may be one of the susceptibility factors that lead to disease (Manetti et al., 2009). *SDF-1* 3' A variants have also been shown to play a role in metastasis of breast cancer (Hassan et al., 2008). The expression level of SDF-1 was found to be high in specific organs in breast cancer patients bearing the A allele. It serves as a chemoattractant that attracts primary breast cancer cells to adhere to the organs and thus promote earlier onset of metastasis in breast cancer. In another study carried out in polycythemia vera patients, individuals with homozygous A genotypes were found to have an 8-fold higher risk to develop polycythemia vera when compared to other genotypes (G/A + G/G) (Gerli et al., 2005). Despite the fact that *SDF-1* 3' A variant is known to contribute to the onset of several diseases, it has been reported to convey a protective effect against human immunodeficiency virus (HIV) infection (Winkler et al., 1998). This is because SDF-1 and HIV share the same receptor, CXCR4, for entry into immune cells. Therefore, high level of SDF-1, induced by the *SDF-1* 3' A variant, compete with HIV for binding to receptors and delay the onset of AIDS in affected patients.

We did not observe any significant association between *RANTES-28* and *SDF-1* 3' UTR polymorphisms and SLE in Malaysia. To the best of our knowledge, this is the first study relating these SNPs to susceptibility for SLE in Malaysia. Other studies based on complement components, interleukins and lymphocyte antigen also failed to demonstrate any significant correlations (Puah et al., 2007; Chew et al., 2008; Chua et al., 2009a,b, 2010). Onset of SLE might be a result of interaction and involvement of various factors and genes. More studies should be conducted to elucidate the mechanisms that are involved in the onset and progression of SLE disease.

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