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IL-18 105 A>C polymorphism contributes to renal manifestations in patients with SLE

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Keywords

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Summary

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder characterized by various aberrations including increased production of IL-18.

Since IL-18 105 A>C polymorphic variants have been linked to increased production of this cytokine, we investigated the prevalence of IL-18 105 A>C (rs549908) polymorphic variants in SLE patients (n=111) and controls (n=152).

There were no significant differences in the distribution of IL-18 105 A>C polymorphic variants in SLE patients and controls. However, there was a significant association between the IL-18 105 AA genotype (recessive model) and renal manifestations OR=3.360 (1.523-7.415, P=0.0039) and the P value remained statistically significant after Bonferroni correction ($P_{\text{corr}} = 0.0351$).

Our findings indicate that the IL-18 105 AA genotype variant can contribute to renal manifestations in patients with SLE.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder characterized by loss of self-tolerance causing immune-mediated tissue destruction and various clinical presentations [1, 2]. Defective function of CD4⁺ T cells and abnormal activation of B cells results in autoantibody production and immune complex formation [3-5].

Immune cells from SLE patients display various aberrations including abnormal cytokine production, reduction of cytotoxic T cell function, and enhancement of humoral response [3-7].

Interleukin-18 (IL-18) belongs to a pleiotropic proinflammatory cytokine that contributes to the cellular and humoral immune response [8], both innate and adaptive [9]. IL-18 induces biosynthesis of IFN- γ , TNF- α , IL-1, IL-2, as well as expression of adhesion proteins leading to increase in T-lymphocyte proliferation [8, 9]. This cytokine also promotes the lytic activity of NK-cells [8, 9]. IL-18 can contribute to the pathogenesis of various

disorders including liver cirrhosis, type I diabetes, rheumatoid arthritis, Crohn's disease and SLE [10-16]. It has been reported that IL-18 concentrations are significantly higher in blood plasma of SLE patients than in control subjects [14-16].

The significance of susceptibility genes in SLE incidence has been heavily researched. Many genes that encode proteins involved in the immune system have been designated as candidate susceptibility genes [17-21].

Investigation has revealed the relationship between IL-18 gene polymorphic variants and predisposition to various malignant viral and autoimmune diseases [22-33]. Recently, a significant association was found between SLE and the IL-18 105 A>C (rs549908) polymorphic variants [32].

Although this polymorphism does not result in amino acid changes, individuals with IL-18 AA, AC and CC genotypes differ in production of this cytokine [34]. Therefore, we analysed the distribution of IL-18 105 A>C polymorphic variants in SLE patients (n=111) and controls (n=152).

PATIENTS AND METHODS

Patients and controls

Data for 111 patients (women only) fulfilling the American College of Rheumatology Classification (ACRC) criteria for systemic lupus erythematosus (35, 36) were collected for investigation at Institute of Rheumatology Warsaw, Poland. The controls constituted of 152 healthy women of Polish Caucasian origin, enrolled from individuals who had a comprehensive examination at the Institute of Mother and Child in Warsaw.

The protocol of the study was approved by the Local Ethical Committee of Poznań University of Medical Sciences. Written consent was obtained from all participating subjects.

Both patients and control groups were of Polish Caucasian origin. The mean age of SLE patients at diagnosis was 38 ± 11 years, and the mean age of controls 37 ± 12 years.

Genotyping

DNA was isolated from peripheral blood lymphocytes by salt extraction. Polymorphic variants of IL-18 105 A>C (rs549908) were identified using PCR with the primer pair 5'GTT TAT TGT AGA AAA CCT GGA ATT 3' and 5'ACC CCT AGC AAT GTC TTA TTG 3' followed by TagI (T/CGA) restriction digestion. The underlined letter denotes the modified base necessary for the creation of this specific restriction site. The 105C allele was cleaved into 24bp and 326bp fragments, whereas the 105A allele remained uncut as 350bp. Digestion products were separated on 10% polyacrylamide gels and stained by silver method. Confirmation of polymorphism was performed by sequencing analysis.

Statistical analysis

The distribution of genotypes in all groups was tested for deviation from Hardy-Weinberg equilibrium. Fisher exact test was used to determine differences in the genotypic and allelic distribution between patients and controls. Moreover, the Odds Ratio (OR) and 95% Confidence Intervals (CI) were calculated. A p value $p < 0.05$ was considered statistically significant. Associations between clinical manifestations and polymorphism distribution in patients with SLE were determined by Fisher exact test.

Results

Analysis of IL-18 105 A>C genotypes revealed no significant deviation from Hardy-Weinberg equilibrium in any group. There was no significant difference in the distribution of IL-18 105 A>C polymorphic variants in SLE patients and controls (Table 1).

Odds ratio for SLE patients with the 105AA genotype was 0.8500 (95% CI=0.5205-1.388, P=0.5344), and OR of the 105AA and 105AC genotypes was 1.410 (95% CI=0.5757-3.452, P=0.5130) (Table 1).

However, there was a significant association between IL-18 105 AA genotype (recessive model) and renal manifestations OR=3.360 (1.523-7.415, P=0.0039), and the P value remained statistically significant after Bonferroni correction ($P_{\text{corr}} = 0.0351$) (Table 2).

Discussion

Despite increased levels of IL-18 in SLE patients, the role of IL-18 in SLE pathogenesis remains unclear [14-16].

To date, the genetic contribution of variants in IL-18 promoter regions has been demonstrated in allergic rhinitis, asthma, as well as SLE [27-30, 37-39]. Many polymorphic variants in IL-18 promoter regions influence expression of IL-18 and may affect the blood plasma level of IL-18 [22, 34, 40]. It has been reported that single nucleotide polymorphisms in the IL-18 gene promoter at -607 C→A and -137 G→C alter the affinity of binding sites for CREB transcriptional factors and the H4TF-1 nuclear factor [22]. The allele -137G is associated with increases in both spontaneous and stimulated IL-18 biosynthesis [34, 40]. Results from linkage disequilibrium investigations indicate a significant association between

IL-18 -137 G>C and IL-18 105 A>C polymorphic variants [34, 40]. Moreover, individuals bearing the IL-18 AA genotype exhibited a higher production of this cytokine than subjects bearing either the AC or CC genotype [34].

To date, the contribution of the IL-18 105 A>C polymorphism has been observed in asthma, rheumatoid arthritis, as well as in SLE. Higa *et al.* (2003) found that the frequency of the 105A allele was significantly higher in asthmatic patients than in controls [33]. Moreover, Lee *et al.* (2007) observed that the IL-18 105A allele was associated with rheumatoid arthritis in Chinese patients [31]. The IL-18 105A allele frequency was also significantly higher in Taiwanese patients with SLE [32].

We did not observe differences in the distribution of the IL-18 105 A>C polymorphism between patients with SLE and controls. However, we found a significant association of renal symptoms with the IL-18 105AA genotype.

Since the IL-18 105 AA genotype is associated with increased IL-18 biosynthesis, we presume that this cytokine can be over-produced in the kidney of individuals bearing the 105 AA genotype. This increased IL-18 production may initiate or augment inflammatory events in nephritic glomeruli by attraction of immune cells.

Our hypothesis may be supported by studies recently conducted by Tucci *et al.* (2008), who reported increased production of IL-18 in patients with lupus nephritis [41]. Moreover, they found that patients with severe lupus nephritis exhibit a high accumulation of IL-18 within glomeruli [41]. They suggested that IL-18 is biosynthesized by macrophages within nephritic glomeruli, and this cytokine may chemoattract plasmacytoid dendritic cells to kidney glomeruli, leading to renal damage [41]. Wong *et al.* (2002) also reported elevated

production of IL-18 in SLE patients with renal disease [42]. Moreover, increased expression of IL-18 was observed in nephritic kidneys in lupus-prone MRL/lpr mice [43].

However, our results are contradictory to the study of Lin *et al.* (2008) who reported the association of IL-18 105 A>C polymorphism with SLE incidence in Taiwanese SLE patients. They also observed a significantly higher A allele frequency in SLE patients with a central nervous system disorder [32].

The variability of the influence of the IL-18 105 A>C polymorphism on SLE manifestation and incidence in different populations can be due to genetic heterogeneity, which usually confounds the study of multigenic disorders. Furthermore, various environmental factors together with genetic heterogeneity may also modulate the effect of the IL-18 105 A>C polymorphism on clinical manifestations and/or incidence of SLE [44].

However, to more precisely determine the association of the IL-18 105 A>C polymorphism to SLE incidence and/or manifestation, further investigation of the distribution of these variants in other populations is required.

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References

1. Sekigawa I, Naito T, Hira K, Mitsuishi K, Ogasawara H, Hashimoto H, Ogawa H (2004) Possible mechanisms of gender bias in SLE: a new hypothesis involving a comparison of SLE with atopy. *Lupus* 13:217–222 [Medline](#). [doi:10.1191/0961203304lu1012ed](https://doi.org/10.1191/0961203304lu1012ed)
2. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH (1992) Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 35:630–640 [Medline](#). [doi:10.1002/art.1780350606](https://doi.org/10.1002/art.1780350606)
3. Tsokos GC, Liossis SN (1999) Immune cell signaling defects in lupus: activation, anergy and death. *Immunol Today* 20:119–124 [Medline](#). [doi:10.1016/S0167-5699\(98\)01395-4](https://doi.org/10.1016/S0167-5699(98)01395-4)
4. Januchowski R, Wudarski M, Chwalińska-Sadowska H, Jagodzinski PP (2008) Prevalence of ZAP-70, LAT, SLP-76, and DNA methyltransferase 1 expression in CD4(+) T cells of patients with systemic lupus erythematosus. *Clin Rheumatol* 27:21–27 [Medline](#). [doi:10.1007/s10067-007-0644-8](https://doi.org/10.1007/s10067-007-0644-8)
5. Stohl W, Metyas S, Tan SM, Cheema GS, Oamar B, Xu D, Roschke V, Wu Y, Baker KP, Hilbert DM (2003) B lymphocyte stimulator overexpression in patients with systemic

- lupus erythematosus: longitudinal observations. *Arthritis Rheum* 48:3475–3486 [Medline](#). doi:10.1002/art.11354
6. Gröndal G, Gunnarsson I, Rönnelid J, Rogberg S, Klareskog L, Lundberg I (2000) Cytokine production, serum levels and disease activity in systemic lupus erythematosus. *Clin Exp Rheumatol* 18:565–570 [Medline](#).
 7. al-Janadi M, al-Balla S, al-Dalaan A, Raziuddin S (1993) Cytokine profile in systemic lupus erythematosus, rheumatoid arthritis, and other rheumatic diseases. *J Clin Immunol* 13:58–67 [Medline](#). doi:10.1007/BF00920636
 8. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H (2001) Interleukin-18 is a unique cytokine that stimulates both Th1 and Th2 responses depending on its cytokine milieu. *Cytokine Growth Factor Rev* 12:53–72 [Medline](#). doi:10.1016/S1359-6101(00)00015-0
 9. Dinarello CA (1999) Interleukin-18. *Methods* 19:121–132 [Medline](#). doi:10.1006/meth.1999.0837
 10. Rothe H, Jenkins NA, Copeland NG, Kolb H (1997) Active stage of autoimmune diabetes is associated with the expression of a novel cytokine, IGIF, which is located near Idd2. *J Clin Invest* 99:469–474 [Medline](#). doi:10.1172/JCI119181
 11. Gracie JA, Forsey RJ, Chan WL, Gilmour A, Leung BP, Greer MR, Kennedy K, Carter R, Wei XQ, Xu D, Field M, Foulis A, Liew FY, McInnes IB (1999) A proinflammatory role for IL-18 in rheumatoid arthritis. *J Clin Invest* 104:1393–1401 [Medline](#). doi:10.1172/JCI7317
 12. Monteleone G, Trapasso F, Parrello T, Biancone L, Stella A, Iuliano R, Luzzza F, Fusco A, Pallone F (1999) Bioactive IL-18 expression is up-regulated in Crohn's disease. *J Immunol* 163:143–147 [Medline](#).
 13. Yamano T, Higashi T, Nouse K, Nakatsukasa H, Kariyama K, Yumoto E, Kobayashi Y, Yamamoto K, Iwagaki H, Yagi T, Tanimoto T, Kurimoto M, Tanaka N, Tsuji T (2000) Serum interferon-gamma-inducing factor/IL-18 levels in primary biliary cirrhosis. *Clin Exp Immunol* 122:227–231 [Medline](#). doi:10.1046/j.1365-2249.2000.01356.x
 14. Wozniacka A, Lesiak A, Narbutt J, McCauliffe DP, Sysa-Jedrzejowska A (2006) Chloroquine treatment influences proinflammatory cytokine levels in systemic lupus erythematosus patients. *Lupus* 15:268–275 [Medline](#). doi:10.1191/0961203306lu2299oa
 15. Panafidina TA, Popkova TV, Alekberova ZS, Mach ES, Aleksandrova EN, Nasonov EL (2008) Interleukin-18 in systemic lupus erythematosus: link with clinical symptoms and vascular atherosclerosis. *Ter Arkh* 80:41–46 [Medline](#).
 16. Ogata A, Kitano M, Fukamizu M, Hamano T, Sano H (2004) Increased serum interleukin-18 in a patient with systemic lupus erythematosus and T-cell large granular lymphocytic leukemia. *Mod Rheumatol* 14:267–270 [Medline](#). doi:10.1007/s10165-004-0306-5
 17. Wong M, Tsao BP (2006) Current topics in human SLE genetics. *Springer Semin Immunopathol* 28:97–107 [Medline](#). doi:10.1007/s00281-006-0031-6
 18. Harley JB, Kelly JA, Kaufman KM (2006) Unraveling the genetics of systemic lupus erythematosus. *Springer Semin Immunopathol* 28:119–130 [Medline](#). doi:10.1007/s00281-006-0040-5
 19. Imanishi T, Morinobu A, Hayashi N, Kanagawa S, Koshiha M, Kondo S, Kumagai S (2005) A novel polymorphism of the SSA1 gene is associated with anti-SS-A/Ro52

- autoantibody in Japanese patients with primary Sjögren's syndrome. *Clin Exp Rheumatol* 23:521–524 [Medline](#).
20. Al-Awadhi AM, Haider MZ, Sharma PN, Hasan EA, Botaiban F, Al-Herz A, Nahar I, Al-Enezi H, Al-Saeid K (2007) Angiotensin-converting enzyme gene polymorphism in Kuwaiti patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 25:437–442 [Medline](#).
 21. Burzynski M, Duriagin S, Mostowska M, Wudarski M, Chwalinska-Sadowska H, Jagodzinski PP (2007) MTR 2756 A > G polymorphism is associated with the risk of systemic lupus erythematosus in the Polish population. *Lupus* 16:450–454 [Medline](#). [doi:10.1177/0961203307077988](https://doi.org/10.1177/0961203307077988)
 22. Giedraitis V, He B, Huang WX, Hillert J (2001) Cloning and mutation analysis of the human IL-18 promoter: a possible role of polymorphisms in expression regulation. *J Neuroimmunol* 112:146–152 [Medline](#). [doi:10.1016/S0165-5728\(00\)00407-0](https://doi.org/10.1016/S0165-5728(00)00407-0)
 23. Bushley AW, Ferrell R, McDuffie K, Terada KY, Carney ME, Thompson PJ, Wilkens LR, Tung KH, Ness RB, Goodman MT (2004) Polymorphisms of interleukin (IL)-1 α , IL-1 β , IL-6, IL-10, and IL-18 and the risk of ovarian cancer. *Gynecol Oncol* 95:672–679 [Medline](#). [doi:10.1016/j.ygyno.2004.08.024](https://doi.org/10.1016/j.ygyno.2004.08.024)
 24. Pratesi C, Bortolin MT, Bidoli E, Tedeschi R, Vaccher E, Dolcetti R, Guidoboni M, Franchin G, Barzan L, Zanussi S, Caruso C, De Paoli P (2006) Interleukin-10 and interleukin-18 promoter polymorphisms in an Italian cohort of patients with undifferentiated carcinoma of nasopharyngeal type. *Cancer Immunol Immunother* 55:23–30 [Medline](#). [doi:10.1007/s00262-005-0688-z](https://doi.org/10.1007/s00262-005-0688-z)
 25. Imboden M, Nieters A, Bircher AJ, Brutsche M, Becker N, Wjst M, Ackermann-Liebrich U, Berger W, Probst-Hensch NM, SAPALDIA Team (2006) Cytokine gene polymorphisms and atopic disease in two European cohorts. (ECRHS-Basel and SAPALDIA). *Clin Mol Allergy* 4:1–9 [Medline](#). [doi:10.1186/1476-7961-4-9](https://doi.org/10.1186/1476-7961-4-9)
 26. Zhang PA, Wu JM, Li Y, Yang XS (2005) Association of polymorphisms of interleukin-18 gene promoter region with chronic hepatitis B in Chinese Han population. *World J Gastroenterol* 11:1594–1598 [Medline](#).
 27. Nieters A, Linseisen J, Becker N (2004) Association of polymorphisms in Th1, Th2 cytokine genes with hayfever and atopy in a subsample of EPIC-Heidelberg. *Clin Exp Allergy* 34:346–353 [Medline](#). [doi:10.1111/j.1365-2222.2004.01889.x](https://doi.org/10.1111/j.1365-2222.2004.01889.x)
 28. Shin HD, Kim LH, Park BL, Choi YH, Park HS, Hong SJ, Choi BW, Lee JH, Park CS (2005) Association of interleukin 18 (IL18) polymorphisms with specific IgE levels to mite allergens among asthmatic patients. *Allergy* 60:900–906 [Medline](#). [doi:10.1111/j.1398-9995.2005.00619.x](https://doi.org/10.1111/j.1398-9995.2005.00619.x)
 29. Kruse S, Kuehr J, Moseler M, Kopp MV, Kurz T, Deichmann KA, Foster PS, Mattes J (2003) Polymorphisms in the IL 18 gene are associated with specific sensitization to common allergens and allergic rhinitis. *J Allergy Clin Immunol* 111:117–122 [Medline](#). [doi:10.1067/mai.2003.43](https://doi.org/10.1067/mai.2003.43)
 30. Pawlik A, Kurzawski M, Czerny B, Gawronska-Szklarz B, Drozdik M, Herczynska M (2006) Interleukin-18 promoter polymorphism in patients with rheumatoid arthritis. *Tissue Antigens* 67:415–418 [Medline](#). [doi:10.1111/j.1399-0039.2006.00582.x](https://doi.org/10.1111/j.1399-0039.2006.00582.x)
 31. Lee CC, Lin WY, Wan L, Tsai Y, Lin YJ, Tsai CH, Huang CM, Tsai FJ (2007) Interleukin-18 gene polymorphism, but not interleukin-2 gene polymorphism, is

associated with rheumatoid arthritis. *Immunogenetics* 59:433–439 [Medline](#).
[doi:10.1007/s00251-007-0212-z](#)

32. Lin YJ, Wan L, Sheu JJ, Huang CM, Lin CW, Lan YC, Lai CH, Hung CH, Tsai Y, Tsai CH, Lin TH, Chen CP, Tsai FJ (2008) A/C polymorphism in the interleukin-18 coding region among Taiwanese systemic lupus erythematosus patients. *Lupus* 17:124–127 [Medline](#). [doi:10.1177/0961203307086031](#)
33. Higa S, Hirano T, Mayumi M, Hiraoka M, Ohshima Y, Nambu M, Yamaguchi E, Hizawa N, Kondo N, Matsui E, Katada Y, Miyatake A, Kawase I, Tanaka T (2003) Association between interleukin-18 gene polymorphism 105A/C and asthma. *Clin Exp Allergy* 33:1097–1102 [Medline](#). [doi:10.1046/j.1365-2222.2003.01739.x](#)
34. Arimitsu J, Hirano T, Higa S, Kawai M, Naka T, Ogata A, Shima Y, Fujimoto M, Yamadori T, Hagiwara K, Ohgawara T, Kuwabara Y, Kawase I, Tanaka T (2006) IL-18 gene polymorphisms affect IL-18 production capability by monocytes. *Biochem Biophys Res Commun* 342:1413–1416 [Medline](#). [doi:10.1016/j.bbrc.2006.02.096](#)
35. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271–1277 [Medline](#). [doi:10.1002/art.1780251101](#)
36. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 40:1725 [Medline](#). [doi:10.1002/art.1780400928](#)
37. Lin YJ, Wan L, Lee CC, Huang CM, Tsai Y, Tsai CH, Shin TL, Chao K, Liu CM, Xiao JW, Tsai FJ (2007) Disease association of the interleukin-18 promoter polymorphisms in Taiwan Chinese systemic lupus erythematosus patients. *Genes Immun* 8:302–307 [Medline](#). [doi:10.1038/sj.gene.6364387](#)
38. Xu Q, Tin SK, Sivalingam SP, Thumboo J, Koh DR, Fong KY (2007) Interleukin-18 promoter gene polymorphisms in Chinese patients with systemic lupus erythematosus: association with CC genotype at position -607. *Ann Acad Med Singapore* 36:91–95 [Medline](#).
39. Lan Y, Wei YS, Tang XS, Qin J, Wu J, Qin JM (2008) Association of interleukin-18 gene polymorphism with genetic susceptibility to systematic lupus erythematosus in Guangxi Zhuang population. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 25:434–437 [Medline](#).
40. Pavlovna KO, Sergeevna SN, Anatolievna LJ, Ivanovich KJ, Leonidovich FM, Alexandrovich KE (2008) L'vovich GE, Vladimirovna YE, Alexandrovich KV, Vitalievich SS (2008) Association of single nucleotide polymorphisms in the IL-18 gene with production of IL-18 protein by mononuclear cells from healthy donors. *Mediators Inflamm* 2008:309721 [Medline](#).
41. Tucci M, Quatraro C, Lombardi L, Pellegrino C, Dammacco F, Silvestris F (2008) Glomerular accumulation of plasmacytoid dendritic cells in active lupus nephritis: role of interleukin-18. *Arthritis Rheum* 58:251–262 [Medline](#). [doi:10.1002/art.23186](#)
42. Wong CK, Ho CY, Li EK, Tam LS, Lam CW (2002) Elevated production of interleukin-18 is associated with renal disease in patients with systemic lupus erythematosus. *Clin Exp Immunol* 130:345–351 [Medline](#). [doi:10.1046/j.1365-2249.2002.01989.x](#)
43. Faust J, Menke J, Kriegsmann J, Kelley VR, Mayet WJ, Galle PR, Schwarting A (2002) Correlation of renal tubular epithelial cell-derived interleukin-18 up-regulation with

disease activity in MRL-Faslpr mice with autoimmune lupus nephritis. Arthritis Rheum 46:3083–3095 [Medline](#). doi:10.1002/art.10563

44. Love LA (1994) New environmental agents associated with lupus-like disorders. Lupus 3:467–471 [Medline](#). doi:10.1177/096120339400300607

Table 1. Distribution of the IL-18 105 A>C polymorphism in patients with SLE and controls

	n	Genotype distribution absolute number (frequency %)			Allele absolute number (frequency %)			Odds ratio (95% CI)	P ^c
		A/A	A/C	C/C	A	C	P ^c		
IL-18 105 A>C	Controls Total 152	76 (50)	61 (40)	15 (10)	213 (70)	91 (30)	0.9235	1.410 (0.8500-2.388) ^a 3.452) ^b	0.5344
	SLE Total	51 (46)	52 (47)	8 (7)	154 (69)	68 (31)			0.5130

The Odds ratio was calculated for patients ^ahomozygous carrying risk allele AA vs heterozygous AC or homozygous CC or, ^bhomozygous AA or heterozygous AC carrying risk allele vs homozygous CC. ^cFisher exact test

Table 2. The association of polymorphism IL-18 105 A>C with clinical manifestations in patients with SLE

Characteristic	Genotype distribution			Odds ratio (95% CI), p ^c
	A/A (51) ^a	A/C (52) ^a	C/C (8) ^a	
Central nervous system	11	6	1	
Vascular	8	9	1	
Renal	36	23	2	3.360 (1.523-7.415, P=0.0039) ^b
Musculoskeletal	28	27	6	
Serosal	11	9	2	
Dermal	32	26	4	
Immunologic	20	25	4	
Fever	3	5	1	
Hematologic	19	20	3	

^a-represents absolute number of positive patients for A/A, A/C, and C/C genotypes respectively

^b-(A/A vs A/C and C/C). Comparison of patients with clinical manifestations with vs. patients without a manifestation was performed by ^cFisher exact test