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ORIGINAL ARTICLE - GENES AND DISEASE

The association of interleukin-31 polymorphisms with interleukin-31 serum levels and risk of systemic lupus erythematosus

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Abstract Interleukin-31 (IL-31) is the most recently discovered member of the gp130/IL-6 cytokine family which is produced mainly by activated Th2 cells. IL-31 was proved to play a crucial role in autoimmune and inflammatory diseases such as atopic dermatitis, asthma, cutaneous T cell lymphomas, Kawasaki disease and allergic rhinitis. Previous studies have identified that IL-31 could significantly induce the release of proinflammatory cytokines IL-6. Moreover, a large number of studies have shown that IL-6 plays an important role in the pathogenesis of systemic lupus erythematosus (SLE). However, up to date, no study to data was reported on the relationship between IL-31 and SLE. Therefore, in the present study, we investigated the association between IL-31 polymorphisms and its serum levels with the risk of SLE in a Chinese population. We analyzed two single nucleotide polymorphisms of IL-31 gene rs7977932 C/G and rs4758680 G/T in 190 patients with SLE and 250 age- and sex-matched controls, using polymerase chain reaction-single base extension and DNA sequencing methods. Soluble IL-31 (sIL-31) levels were measured by ELISA. From this study, we found that there were significant differences in the genotype and allele frequencies of IL-31 gene rs7977932 C/G polymorphism between the group of patients with SLE and the control group ($P < 0.05$). sIL-31 levels were increased in patients with SLE compared with controls ($P < 0.01$). Moreover, genotypes carrying the IL-31 rs7977932 G variant allele were associated with increased IL-31 levels compared to the homozygous wild-type genotype in patients with SLE. The rs7977932 C/G polymorphism of IL-31 gene and its sIL-31 levels were associated with SLE in the Chinese population. Our data suggest that IL-31 gene may play a role in the development of SLE.

Keywords IL-31 · Gene · Polymorphism · SLE

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Introduction

Systemic lupus erythematosus (SLE) is a well-known autoimmune disease that involves in inflammation of various organs, characterized by deposition of immune complexes and uncontrolled B cell hyperactivity [1, 2]. Although there were many researches on the etiology of the disease, the exact cause of the onset of SLE is not yet fully understood. Many factors have been proposed in the pathogenesis of SLE, such as genetic factors, environmental factors and disorder of cytokine production factors. In the last few years, disorder of cytokine production factors seems to play a significant role in the pathogenesis of SLE. It has been proposed that the functional imbalance of T helper type 1 (Th1) and Th2 cells is possibly associated with immune responses in different kinds of immune disorders [3]. In SLE patients, Th1 levels are decreased, whereas Th2 levels are elevated [4]. So, scientists inferred that alteration of Th1 and Th2 lymphocyte functions may result in the upregulation of autoantibody production by B cells that can

lead to the pathogenesis of SLE [1]. Moreover, a number of cytokines which were associated with the pathogenesis of SLE such as IL-6, IL-21, IL-27, IL-12, IL-17 and TNF-α have been reported [4–9].

IL-31, produced mainly by activated $CD4^{+}$T cells, especially cells skewed toward a T help (Th) 2-phenotype, is a newly discovered cytokine, belonging to the gp130/IL-6 cytokine family that includes IL-6, IL-11, IL-27, oncostatin M, leukemia inhibitory factor, ciliary neurotrophic factor, neuropoietin, cardiotrophin-1 and cardiotrophin-like cytokine [10–12]. IL-31 signals through a heterodimeric receptor consisting of IL-31 receptor alpha (IL-31RA) and oncostatin M receptor (OSMR) [10]. IL-31RA has been identified as a gp130-like receptor showing 28 % homology to gp130, the common signaling receptor subunit of the family of IL-6-type cytokines [13–15]. Receptors for IL-31 were found on a variety of cells, such as keratinocytes, macrophages, eosinophils and participate in regulating immune responses in these cell types [10, 16, 17]. Therefore, IL-31 possesses potential pleiotropic physiological functions, including regulating hematopoiesis and immune response, causing inflammatory bowel disease, airway hypersensitivity and dermatitis [18–20].

Previous studies have demonstrated that IL-31 plays a crucial role in different autoimmune and inflammatory diseases, such as atopic dermatitis (AD), asthma, cutaneous T cell lymphomas, Kawasaki disease and allergic rhinitis [19–24]. However, up to date, no data in literature have examined the association between IL-31 and SLE. IL-6, one of the members of gp130/IL-6 cytokine family, was widely reported to play an important role in the pathogenesis of SLE [25–29]. Linker-Israeli et al. [25] reported that elevated plasma levels of IL-6 messenger RNA and protein could be detected in SLE patients. Serum IL-6 levels were reported to be sensitive markers for SLE activity [26]. Interestingly, previous studies have provided evidence that IL-31 was involved in the inflammatory response mediating by IL-6. Cheung et al. [30] reported that IL-31 can significantly induce the release of proinflammatory cytokines IL-6 (also inducing the release of AD-related chemokines CXCL1, CXCL8, CCL2 and CCL18) from eosinophils, via functional cell surface IL-31 receptor. Furthermore, they also demonstrated that IL-31 could delay the apoptosis of eosinophils and significantly stimulate eosinophils to secrete higher levels of proinflammatory cytokines IL-6. These data indicated that IL-31 seems to play a role in the pathogenesis of SLE and was likely a positional candidate gene for its risk. Thus, in the present study, we investigated the association between IL-31 gene rs4758680 G/T and rs7977932 C/G polymorphisms and their sIL-31 levels with the risk of SLE in a Chinese population.

Materials and methods

Study population

Our study was designed as a retrospective study. The study consisted of 190 patients with SLE (25 males and 165 females, aged between 30 and 75 years). All patients with SLE were consecutively selected. They were recruited from the Department of Dermatology, Affiliated Hospital of Youjiang Medical University for Nationalities, Guangxi, China, between January 2013 and June 2015. The 250 control subjects were matched to the patients on the basis of age and gender (30 males and 220 females, aged between 26 and 77 years). The control subjects underwent a routine medical checkup in the outpatient clinic of the Department of Internal Medicine, Affiliated Hospital of Youjiang Medical University for Nationalities, Guangxi, China, between March 2014 and November 2014. According to the thorough clinical and laboratory evaluation, none of them were found to have any medical condition or family history of any autoimmune disease. The study was approved by the local institutional ethics committee of the Affiliated Hospital of Youjiang Medical University for Nationalities. All procedures were conducted in accordance with the Declaration of Helsinki. The participants provided their written consent in order to participate in this study.

DNA extraction and PCR assay

For genetic studies, 5 mL of venous blood was collected from each patient. Genomic DNA was extracted from whole peripheral blood using a QIA Amp DNA Blood Mini Kit (Qiagen, Germany) according to the standard protocols. The DNA was subsequently stored at −20 °C until needed. Before use, the DNA was resolved using a 1 % agarose gel stained with the ethidium bromide. The PCR primers were designed based on the GenBank reference sequence (Accession No. NC_000012.11) (Table 1). PCR primers were designed using Primer 3 Input (version 0.4.0). The PCRs consisted of 10 × PCR buffer 2.0 μL, 0.3 mmol/L dNTPs mixture 2.0 μL, TaqDNA polymerase 1.0 U, forward and reverse primer 1.0 ml, respectively, genomic DNA 1.0 μL. Insufficient volume was make up to 20 ml by distilled water.

Determination of IL-31 genotype

PCR products were sequenced using the ABI PRISM SNaPshot Multiplex Kit according to the protocols. Detection and sequencing were carried out with a 3730XL ABI Genetic Analyzer. Results were analyzed using GeneMapper 4.1 (Applied Biosystems Co., Ltd., USA). To confirm

Table 1 Primer sequences used for detecting different IL-31 SNPs

SNP ID	PCR primer
rs7977932	F: 5′-GGTCAGTGTTGGGTTTGCAATG-3′
	R: 5′-TTGGTGATGGCACAGCCTCATA-3′
	EF: 5′-TTTTTTTTTTTTTTTTTTTTTTTTTTTGACATTGATCAGATAAATATATCAAC-3′
rs4758680	F: 5′-TTGTGCAAACCACACCTCTTCG-3′
	R: 5′-GATCACCCGGACTCAAAACGTG-3′
	EF: 5′-TTTTTTTTTTTTTTTTTTTTAATCTTGAGTCTACCAGCACCTATAT-3′

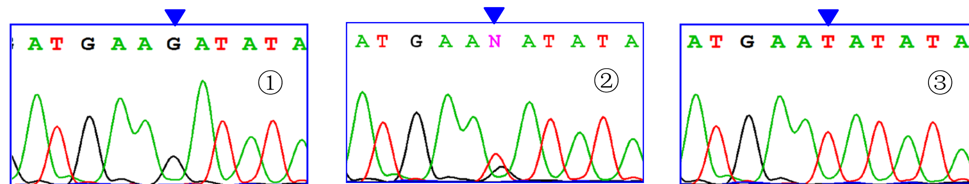

Fig. 1 Sequencing map of genotype for IL-31 gene rs4758680 G/T polymorphism. The *arrow* of ①–③ showed GG, GT and TT genotypes, respectively

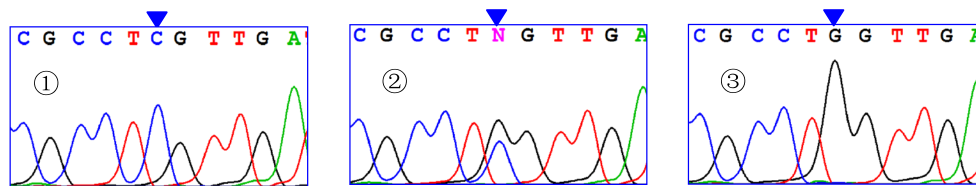

Fig. 2 Sequencing map of genotype for IL-31 gene rs7977932 C/G polymorphism. The *arrow* of ①–③ showed CC, CG and GG genotypes, respectively

the genotyping results, PCR-amplified DNA samples were examined by DNA sequencing, and the results were 100 % concordant (Figs. 1, 2).

Plasma IL-31 determination

Plasma samples from the patients and healthy controls were separated from venous blood at room temperature and stored at −70 °C until use. The quantity determination of plasma IL-31 levels was performed by enzyme-linked immunosorbent assay (ELISA) kits (Fermentas, Lithuania), following the manufacturer's protocol. Developed color reaction was measured as OD450 units on an ELISA reader (RT-6000, China). The concentration of plasma IL-31 was determined by using standard curve constructed with the kit's standards over the range of 0–1000 pg/ml.

Statistical analysis

Genotype and allele frequencies of IL-31 gene were compared between SLE cases and controls by using the χ^2 test and Fisher's exact test when appropriate, and odds ratios (OR) and 95 % confidence intervals (CIs) were calculated to assess the relative risk conferred by a particular allele and genotype. Demographic and clinical data between groups were compared by χ^2 test and by Student's *t* test. Hardy–Weinberg equilibrium was tested for with a goodness of fit χ^2 test with one degree of freedom to compare the observed genotype frequencies among the subjects with the expected genotype frequencies. The haplotypes and their frequencies were estimated based on a Bayesian algorithm using the Phase program [31]. Statistical significance was assumed at the $P < 0.05$ level. The SPSS statistical software package version 11.5 was used for all of the statistical analyses.

Results

Clinical characteristics of the study participants

There were no statistically significant differences in the age and percentage of males/females between the two study groups. The serum IL-31 levels were significantly

higher in the group of patients with SLE than those in the control group [(618.5 ± 305.7 pg/mL, $n = 190$) vs. (306 ± 113.4 pg/mL, $n = 250$); $P < 0.001$; Fig. 3].

The genotype and allele frequencies of IL-31 gene

The genotype and allele frequencies of the IL-31 gene rs4758680 G/T and rs7977932 C/G polymorphisms in the group of patients with SLE and in the control group are shown in Table 2. The genotype distributions of the two polymorphisms among the controls and the cases were in Hardy–Weinberg equilibrium. The frequencies of the CC, CG and GG genotypes of rs7977932 C/G were 73.2, 23.2 and 3.6 % in controls, and were 60.0, 32.1 and 7.9 % in cases, respectively. There were significant differences in the genotype and allele frequencies of the IL-31 gene rs7977932 C/G polymorphism between SLE patients and control groups ($P < 0.05$). The rs7977932 G allele was associated with a significantly increased risk of SLE as compared with the rs7977932 C allele (OR 1.757, 95 % CI, 1.251–2.466, $P = 0.001$). However, genotype and allele frequencies of the IL-31 gene rs4758680 G/T polymorphisms in SLE patients were not significantly different than those in controls ($P > 0.05$).

Haplotype analysis of the IL-31 gene

Haplotype analyses were performed, and the possible four haplotype frequencies are shown in Table 3. One major haplotype (rs7977932C/rs4758680G) accounted for 62.6 and 68.4 % of these four haplotypes in the cases and the controls, respectively. By haplotype analyses, we found rs7977932G/rs4758680T haplotype was associated with a significantly increased risk of SLE as compared with the control group (OR 2.569; 95 % CI, 1.091–6.053; $P = 0.026$).

Association between IL-31 gene polymorphisms and sIL-31 levels

Genotype at the rs7977932 C/G polymorphism was significantly associated with sIL-31 levels in patients with SLE. The plasma IL-31 levels were significantly higher in individuals with heterozygous CG genotypes (657.6 ± 295.4 pg/mL, $n = 61$) or homozygous of GG genotypes (663.2 ± 291.3 pg/mL, $n = 15$) than homozygous of CC genotypes (591.7 ± 307.2 pg/mL, $n = 114$, $P < 0.01$), respectively. However, there were no significant differences in the plasma IL-31 levels between CG and GG genotypes (Fig. 4). In addition, there were no significant associations of the IL-31 rs4758680 G/T polymorphism with plasma levels of IL-31 (data not shown).

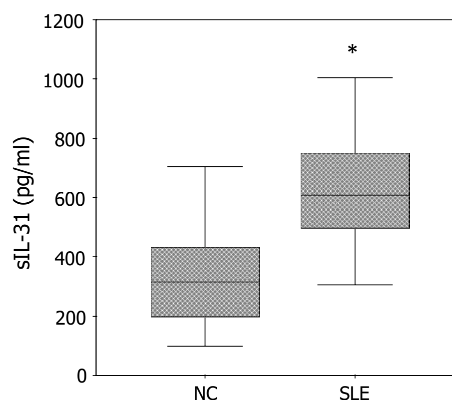

Fig. 3 The levels of IL-31 in patients with SLE and normal control subjects. The expression of IL-31 was significantly increased in patients with SLE compared to that in control subjects [(618.5 ± 305.7 pg/mL, $n = 190$) vs. (306 ± 113.4 pg/mL, $n = 250$); $P < 0.001$]

Table 2 The genotype and allele frequencies of IL-31 polymorphisms in SLE patients and controls

Polymorphism	Control subjects $n = 250$ (%)	SLE patients $n = 190$ (%)	χ^2	P value
rs7977932 C/G				
CC	183 (73.2)	114 (60.0)	9.603	0.008
CG	58 (23.2)	61 (32.1)		
GG	9 (3.6)	15 (7.9)		
C	424 (84.8)	289 (76.1)	10.744	0.001
G	76 (15.2)	91 (23.9)		
rs4758680 G/T				
GG	172 (68.8)	132 (69.5)	0.326	0.850
GT	66 (26.4)	47 (24.7)		
TT	12 (4.8)	11 (5.8)		
G	410 (82.0)	311 (81.8)	0.004	0.952
T	90 (18.0)	69 (18.2)		

Discussion

To our knowledge, this is the first report to determine whether the IL-31 gene polymorphism and its soluble levels were associated with SLE. In this study, we found that the rs7977932 C/G polymorphism of IL-31 gene and the levels of sIL-31 were significantly associated with the presence of SLE. The rs7977932 C/G polymorphism may affect the levels of sIL-31. One major haplotype (rs7977932C/rs4758680G) accounted for 62.6 and 68.4 % of these four haplotypes in the cases and the controls, respectively. By haplotype analyses, we found rs7977932G/rs4758680T haplotype was associated with a significantly increased risk of SLE as compared with the control groups (OR 2.569;

Table 3 Haplotype distribution in the patients with SLE and controls

IL-31 gene (rs7977932/rs4758680) haplotypes	Controls $2n = 500$ (%)	SLE patients $2n = 380$ (%)	OR (95 % CI)	P value
C–G	313 (62.6)	260 (68.4)	1.294 (0.976–1.716)	0.074
C–T	75 (15.0)	59 (15.5)	1.042 (0.719–1.509)	0.830
G–G	89 (17.8)	54 (14.2)	1.307 (0.905–1.889)	0.153
G–T	23 (4.6)	7 (1.8)	2.569 (1.091–6.053)	0.026

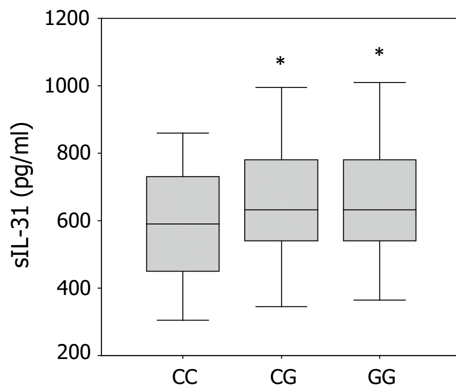

Fig. 4 Association between the levels of IL-31 and the rs7977932 C/G polymorphism of IL-31 gene was observed in patients with SLE. Plasma IL-31 levels with CC homozygous (591.7 ± 307.2 pg/mL, $n = 114$) were significantly lower than that of the GG (663.2 ± 291.3 pg/mL, $n = 15$) homozygous or CG (657.6 ± 295.4 pg/mL, $n = 61$) heterozygotes, respectively. However, there were no significant differences in the plasma IL-31 levels between CG and GG genotype

95 % CI, 1.091–6.053; $P = 0.026$). Our data suggest that IL-31 may play an important role in the development of SLE. Thus, IL-31 gene rs7977932 C/G polymorphism may serve as novel genetic markers of susceptibility to SLE in the Chinese population.

SLE is a chronic, systemic, autoimmune disease that is characterized by a diverse array of autoantibody production, complement activation and immune-complex deposition, which causes tissue and organ damage. The etiology and pathogenesis of SLE have not been fully elucidated. IL-31 is a newly discovered member of the gp130/IL-6 cytokine family. IL-31 mRNA is preferentially expressed by the activation of Th2 cells and is also expressed in testis, bone marrow, skeletal muscle, kidney, colon, thymus, small intestine, trachea [10] and dorsal root ganglia [12]. Its receptor is a heterodimer receptor consisting of IL-31RA and OSMR and is co-expressed in a wide range of tissues such as lung, skin, brain, thymus, trachea, testis, ovary, skeletal muscle, prostate, placenta, spleen, and also in bone marrow and blood leukocytes [11, 32]. Binding of IL-31 to its receptor activates JAK/STAT, PI3 K/AKT and MAPK pathways and finally results in induction of proinflammatory cytokines (IL-6, IL-32 and IL-16), chemokines (GRO-α, IL-8, MCP-3, CXCL3, CCL13 and CCL15), matrix metalloproteinases (MMP-1, MMP-3, MMP-7 and MMP-25), regulating hematopoiesis, inflammation and immune response [10, 33].

IL-31 has been frequently implicated in the pathogenesis of different autoimmune and inflammatory diseases owing to its central role in regulating immune and inflammatory response. Sonkoly et al. [12] reported that the plasma levels of IL-31 were significantly elevated in atopic dermatitis (AD) patients compared with healthy controls and correlated positively with disease severity. Similarly, previous study has demonstrated that transgenic mice overexpressed IL-31 and developed severe pruritus, alopecia and skin lesions [11], which is similar to the symptoms of patients suffering from AD. Ohmatsu et al. [34] reported that sIL-31 levels were significantly elevated in patients with cutaneous T cell lymphomas (CTCL) when compared with healthy controls. Moreover, they examined sIL-31 levels in CTCL patients with different types of skin lesions and found that sIL-31 levels were significantly correlated with disease activity. Tseng et al. [23] reported that sIL-31 levels were increased after intravenous immunoglobulin (IVIG) treatment in patients with Kawasaki disease (KD) and were significantly associated with coronary artery lesion (CAL) formation. IL-31 was suggested to be a novel risk factor for predicting KD and CAL formation. However, in our present study, we found that sIL-31 levels were significantly increased in patients with SLE compared with healthy controls ($P < 0.01$). The results of our study indirectly suggest that IL-31 may play a role in patients with SLE. These observations make IL-31 an interesting candidate gene for a role in human SLE.

Several studies have investigated the association between IL-31 polymorphisms and diseases susceptibility, but most of their researches have focus on eczema and atopic dermatitis (AD) [35–37]. Lan et al. [35] reported that the rs7977932 G allele of IL-31 gene was associated with the development of atopic eczema and nonatopic hand dermatitis in Taiwanese nursing population, while, in the study of Schulz et al. [36], they identified three main haplotypes for IL-31 gene and finally found that the haplotype containing rs7977932 G allele was associated with the development of nonatopic eczema. Sokolowska-Wojdylo et al. [37] reported that the frequency of GA genotype in

IL-31-2057 was higher in patients with AD than those in the control group and was linked to an increased risk of AD development. In our present study, we found that there were significant differences in the genotype and allele frequencies of IL-31 gene rs7977932 C/G polymorphism between the group of patients with SLE and the control group ($P < 0.05$). The rs7977932 G allele was associated with a significantly increased risk of SLE as compared with the rs7977932 C allele. Our finding suggested that IL-31 gene may play a role in the pathogenesis of SLE, and the rs7977932 C/G polymorphism may serve as novel genetic markers of susceptibility to SLE in the Chinese population.

So far, investigations on the IL-31 gene rs7977932 C/G polymorphism and its soluble level, which were associated with SLE, have not been performed. Our data demonstrated that IL-31 gene rs7977932 C/G polymorphism was associated with SLE ($P < 0.05$). Also, the level of sIL-31 was found to be elevated in SLE patients ($P < 0.01$). Moreover, genotypes carrying the IL-31 rs7977932 G variant allele (CG or GG genotype) were associated with increased IL-31 levels compared to the homozygous wild-type genotype (CC genotype) in patients with SLE ($P < 0.01$). Additionally, our results showed that sIL-31 levels were not associated with the polymorphisms of the IL-31 in healthy controls. A plausible explanation is that the sIL-31 expression is inducible and its expression is upregulated after stimulation, and such inflammatory stimulation in healthy controls should be missing. Furthermore, we found that individuals carrying the rs7977932 G allele of the IL-31 rs7977932 C/G polymorphism, which has been associated with increased sIL-31 production, were at a significantly increased risk of SLE. This finding suggests an association between IL-31 genotypes and its soluble form. We speculate that IL-31 gene rs7977932 C/G polymorphism may exert an impact on its protein metabolism and stability.

In summary, we found that the rs7977932 C/G polymorphism of IL-31 and the levels of sIL-31 were significantly associated with the risk of SLE. These results suggest that the IL-31 gene may contribute to an inherited predisposition to SLE although additional studies with larger sample sizes will be necessary to confirm our findings. Because genetic polymorphisms often vary between different ethnic groups, further studies are needed to clarify the association of the IL-31 polymorphisms with the risk of SLE in diverse ethnic populations.

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Compliance with ethical standards

Conflict of interest No competing financial interests exist.

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