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Association of *GTF2I* gene polymorphisms with renal involvement of systemic lupus erythematosus in a Chinese population

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Abstract

The purposes of the study was to validate the relationship between General transcription factor II-I (GTF2I) genetic variants and kidney involvements of systemic lupus erythematosus (SLE) patients in a Chinese Han population.

Samples from 400 SLE patients and 400 age- and sex-matched healthy controls were collected and genotyped by improved multiplex ligation detection reaction technique. The relationship between gene polymorphism of rs117026326, rs73366469, and susceptibility, progression of SLE were analyzed.

The present study provided evidence that rs117026326 and rs73366469 were both associated with SLE susceptibility (both C vs T: $P < .001$). The analysis of dominant, recessive disease model provided us with further validation ($P < .001$). Both gene polymorphisms are associated with a triad of disease manifestations among SLE patients. Patients carrying genotype TT of rs117026326 had lower 24-hour urinary total protein (24 hours UTP, g/24 hours), 24-hour urinary protein level (g/L·24 hours), lower frequency of the proteinuria and lupus nephritis (LN). Patients carrying genotype TT at rs73366469 had higher 24-hour urinary protein level, higher frequency of the proteinuria, LN and positive anti-dsDNA than those with other genotypes.

This study identified the involvement of *GTF2I* gene polymorphisms in development of SLE, particularly in renal involvement.

Abbreviations: 24 h UTP = 24-hour urinary total protein, CI = confidence interval, CYS-C = cystatin-C, GTF2I = general transcription factor II-I, HC = healthy controls, HWE = Hardy–Weinberg Equilibrium, LN = lupus nephritis, OR = odds ratio, pSS = primary Sjögren syndrome, SLE = systemic lupus erythematosus, SNPs = single nucleotide polymorphisms.

Keywords: autoantibody, renal involvement, single nucleotide polymorphisms, systemic lupus erythematosus

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypic, heterogeneous autoimmune disorder characterized by the presence of pathogenic autoantibodies which can affect multiple organs and systems.[1] Although the underlying mechanism of SLE remains uncertain,[2] genetic factors seem rather effective at its occurrence. Recent Genome-Wide Association studies (GWAS) revealed that some of single nucleotide polymorphisms (SNPs) in *GTF2I* gene were related to multiple autoimmune diseases,[3–5] including primary Sjögren syndrome (pSS), rheumatoid arthritis, and SLE. However, as 1 of main clinical challenges of SLE, the genetic background of lupus nephritis (LN) has not been completely clarified. LN occurs in 15% - 55% of SLE patients, and patients from Asia have a higher prevalence than others and always present with a more severe disease.[6] Whether *GTF2I* polymorphisms are associated with clinical indexes and disease manifestations among SLE patients is still uncertain, so we performed this case-control study on polymorphism rs117026326 and rs73366469, and explored the correlation of these locus to susceptibility to SLE and renal involvement in the present study.

2. Materials and methods

2.1. Patients

This study was approved by the Ethics Committee of West China Hospital, having gained the ethic approval. Total of 800 individual participates including 400 SLE cases and 400 age- and gender-matched healthy controls (HC) were recruited from the West China Hospital. Informed consents for using their results were obtained from all the study participants and any form of registration that may identify a patient were excluded from the content of the paper.

All the SLE patients in the study were hospitalized patients, fulfilling the American College of Rheumatology 1997 classification criteria. Patients with drug-induced SLE were excluded.

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Total of 400 healthy individuals randomly selected from the Health Examination Center were enrolled as HC. Their physical examinations and blood tests were all within normal range. None of these healthy individuals had infectious diseases, autoimmune disorders or family history of autoimmune diseases.

2.2. Clinical and laboratory evaluation

The clinical and laboratory data of the patients including proteinuria, rash, pericarditis, pleuritis, arthritis, the serum level of anti-dsDNA, anti-Sm, anti-RNP, IL-1β, IL-4, IL-6, urea, creatinine, CYS-C, uric acid, 24 hours UTP (g/24 hours) and 24-hour urinary protein level (g/L·24 hour) were recorded. Anti-dsDNA, anti-Sm, and anti-RNP were detected in all the 400 SLE patients. Anti-dsDNA was determined through indirect immunofluorescence, while anti-Sm and anti-RNP were estimated through line immunoassays (Euroimmun, Germany). 143 of SLE patients were selected randomly for cytokine testing. IL-1β, IL-4 and IL-6 were quantitatively detected using R&D Human Inflammation Assays.

All these tests were performed strictly in accordance with the relevant guidelines and regulations. Blood samples for assessing these indexes were detected at the same time.

2.3. GTF2I polymorphisms genotyping and linkage disequilibrium evaluation

All the samples were genotyped for rs117026326 and rs73366469 using improved multiplex ligation detection reaction (iMLDR) (Genesky Biotechnologies Inc, China). Polymerase chain reaction was performed at 95°C for 2 minutes followed by 11 cycles of denaturation (94°C, 20 seconds), annealing (65°C–0.5°C/cycle 40 seconds) and 24 cycles of 94°C 20 seconds, 59°C 30 seconds, 72°C 1 minutes 30 seconds, plus 1 cycle of 72°C for 2 minutes. During detection, some of samples were randomly selected for direct sequencing to confirm the results genotyped using iMLDR. The Haploview software version 4.2 was applied to perform linkage disequilibrium (LD) evaluation for combination of SNPs by calculating the pairwise r^2 coeffcient.

2.4. Statistical analysis

Hardy–Weinberg equilibrium (HWE) was performed for the polymorphisms by the 2-sided Chi-Squared (χ^2) test. Median and interquartile, mean ± SD or number and percentage were used to describe variables. Student *t* test or Mann–Whitney *U* test for quantitative variables were used to compare demographic and clinical data between patients and controls as appropriate. Chi-Square (χ^2) test or Fisher exact test were applied to analyze differences in allelic and genotypic frequencies. If allele x is the major allele of the SNP, y is the minor allele, recessive model is known as xx + xy vs yy, dominant model as xx vs xy + yy, co-dominant model as xx vs xy vs yy. The association between genetic polymorphisms and LN, proteinuria was evaluated using the logistic regression model, calculated odds ratios (ORs) and 95% confidence intervals (CIs).

The statistical analyses were applied by using the Statistical Package for the Social Sciences (SPSS) software (version 19.0). Statistical power was calculated using "Power and Sample Size Calculation" software. A two-sided *P* value less than .05 was considered as statistically significant.

Table 1

Demographic and clinical features of the study participants.

Characteristics	SLE	HC	*P* value
Number of cases	400	400	
Age, mean ± SD (years)	36.33 ± 12.99	37.21 ± 12.16	.323
Female (%)/male (%)	89.75/ 10.25	86.25/13.75	.128
SLEDAI, mean ± SD	15.51 ± 7.54		
Disease duration, median (interquartile range) (months)	36.0 (5.25–84.00)		
IL-4, mean ± SD (pg/ml)	12.67 ± 32.40		
IL-6, mean ± SD (pg/ml)	13.17 ± 26.94		
C3, mean ± SD (g/L)	0.51 ± 0.22		
C4, mean ± SD (g/L)	0.11 ± 0.06		

HC = healthy controls, LN = lupus nephritis, SLE = systemic lupus erythematosus.

3. Results

3.1. The main characteristics of the study population

The demographic and clinical characteristics of all the included subjects were illustrated in Table 1. The age ($P = .323$) and sex ($P = .128$) of SLE patients and controls were adequately matched. The average age of SLE patients and healthy controls were 36.33 ± 12.99 and 37.21 ± 12.16 years old, and the gender ratio (Female/male) were 359/41 and 345/55, respectively. Among all the SLE patients, the median disease duration is 36 months, the average SLEDAI score is 15.51 ± 7.54 and the average level of IL-4, IL-6, C3, C4 in SLE patients were 12.67 ± 32.40 pg/ml, 13.17 ± 26.94 pg/ml, 0.51 ± 0.22 g/L, 0.11 ± 0.06 g/L, respectively (Table 1).

3.2. Polymorphisms association with SLE susceptibility

Cohorts showed no significant deviation from HWE for genotyped SNPs (all $P > .05$). When comparing allele frequency of rs117026326 and rs73366469 between SLE patients and HC, significant differences were indicated (both $P < .001$, statistical power = 1.000) with rs117026326 *T* allele correlated to an increased risk of SLE and rs73366469 *T* allele correlated to a decreased risk of SLE (Table 2). The odds ratio and 95% confidence interval ((OR) 95% CI) were 3.265 (2.452–4.348) and 0.420 (0.325–0.543), respectively. When comparing genotype frequency, we observed that *TT* and *CT* genotype at rs117026326 and rs73366469 were associated with SLE susceptibility (*TT* at rs117026326: OR (95% CI) = 10.190 (3.526–29.449); *CT* at rs117026326: OR (95%CI) = 3.172 (2.269–4.435); *TT* at rs73366469: OR (95%CI) = 0.147 (0.064–0.336); *CT* at rs73366469: OR (95%CI) = 0.312 (0.133–0.731), all $P < .05$). These results were also supported by further disease model analysis (rs117026326: Dominant model: OR (95% CI) = 3.568 (2.581–4.932); Recessive model: OR (95% CI) = 7.452 (2.589–21.447); rs73366469: Dominant model: OR (95% CI) = 0.186 (0.081–0.423); Recessive model: OR (95% CI) = 0.407 (0.302–0.550), All $P < .001$).

3.3. Polymorphisms association with clinical characteristics of SLE patients

SLE is a heterogeneous autoimmune disease. Patients with SLE always have variations in disease severity and clinical involvement. Thus, we tried to examine the effect of gene polymorphisms on clinical parameters and phenotypes among SLE patients,

Table 2

Genotype and allele frequencies of SNPs within GTF2IRD1-GTF2I region in SLE patients and controls.

			SLE		HC			
SNP	**Model**	**Genotype/Allele**	**N**	**%**	**N**	**%**	**OR (95%CI)**	***P* value**
rs117026326	Dominant	TT+CT	174	43.5	71	17.8	3.568 (2.581–4.932)	<.001
		CC	226	56.5	329	82.2	1.000 (ref)	
	Recessive	TT	28	7.0	4	1.0	7.452 (2.589–21.447)	<.001
		CT+CC	372	93.0	396	99.0	1.000 (ref)	
	Co-dominate	TT	28	7.0	4*	1.0	10.190 (3.526–29.449)	<.001
		CT	146	36.5	67	16.8	3.172 (2.269–4.435)	<.001
		CC	226	56.5	329	82.2	1.000 (ref)	
	Allele	T	202	25.25	75	9.37	3.265 (2.452–4.348)	<.001
		C	598	74.75	725	90.63	1.000 (ref)	
rs73366469	Dominant	TT+CT	365	91.2	393	98.2	0.186 (0.081–0.423)	<.001
		CC	35	8.8	7	1.8	1.000 (ref)	
	Recessive	TT	220	55.0	300	75.0	0.407 (0.302–0.550)	<.001
		CT+CC	180	45.0	100	25.0	1.000 (ref)	
	Co-dominate	TT	220	55.0	300†	75.0	0.147 (0.064–0.336)	<.001
		CT	145	36.2	93	23.2	0.312 (0.133–0.731)	.005
		CC	35	8.8	7	1.8	1.000 (ref)	
	Allele	T	585	73.13	693	86.63	0.420 (0.325–0.543)	<.001
		C	215	26.87	107	13.37	1.000 (ref)	

* $P_{HWE}=0.78$.
† $P_{HWE}=0.95$.

Table 3

Association between polymorphisms with clinical features in SLE patients.

	rs117026326					rs73366469				
	Genotype frequency (n (%))					Genotype frequency (n (%))				
Clinical characteristics	**CC**	**CT**	**TT**	χ^2	***P***	**CC**	**CT**	**TT**	χ^2	***P***
Clinical manifestations										
proteinuria	202 (89.38)	119 (81.51)	19 (67.86)	10.64	<.001*	24 (68.57)	118 (81.38)	198 (90.00)	13.21	.001**
LN	150 (66.37)	92 (63.01%)	12 (42.86)	5.96	.051	16 (45.71)	92 (63.45)	146 (66.36)	5.55	.062
Rash	88 (38.94)	63 (43.15)	8 (28.57)	2.22	.328	11 (31.43)	65 (44.83)	83 (37.73)	2.94	.229
Pericarditis	69 (30.53)	49 (33.56)	7 (25.00)	0.92	.629	11 (31.43)	49 (33.79)	65 (29.55)	0.735	.693
Pleuritis	73 (32.30)	45 (30.82)	7 (25.00)	0.63	.727	10 (28.57)	45 (31.03)	70 (31.82)	0.15	.926
Arthritis	57 (25.22)	38 (26.03)	8 (28.57)	0.15	.925	10 (28.57)	36 (24.83)	57 (25.91)	0.21	.899
lupus encephalopathy	25 (11.06)	18 (12.33)	3 (10.71)	0.15	.924	3 (8.57)	18 (12.41)	25 (11.36)	0.418	.811
Expression of auto-antibodies										
anti-dsDNA pos	185 (81.86)	109 (74.66)	24 (85.71)	3.535	.171	31 (88.57)	105 (72.41)	182 (82.73)	7.64	.022†
anti-RNP pos	145 (64.16)	87 (59.59)	14 (50.00)	2.46	.292	17 (48.57)	89 (61.38)	140 (63.64)	2.90	.235
anti-Sm pos	101 (44.69)	64 (43.84)	10 (35.71)	0.81	.665	12 (34.29)	67 (46.21)	96 (43.64)	1.63	.442
Clinical indexes (median, interquartile range)										
24-hour urinary total protein (g/24h)	1.0 (0.3–3.9)	0.4 (0.2–2.0)	0.3 (0.2–0.8)	–	.005‡	0.3 (0.2–1.6)	0.5 (0.3–2.3)	0.9 (0.3–3.6)	–	.046§
24-hour urinary protein level (g/L·24h)	0.6 (0.2–2.2)	0.3 (0.1–1.2)	0.2 (0.1–0.4)	–	.002‖	0.2 (0.1–0.7)	0.3 (0.1–1.4)	0.5 (0.2–2.1)	–	.030¶
Urea (mmol/L)	5.8 (4.2–8.4)	6.0 (4.5–8.0)	5.2 (4.2–6.9)	–	.447	5.4 (4.1–7.2)	5.9 (4.5–8.1)	5.7 (4.3–8.4)	–	.770
creatinine (umol/L)	61.3 (49.8–78.0)	60.5 (49.0–75.0)	60.0 (49.0–69.3)	–	.754	60 (49.0–72.0)	60 (49.0–73.5)	61.45 (50.0–77.8)	–	.772
CYS-C (mg/L)	1.2 (1.0–1.7)	1.2 (1.0–1.5)	1.1 (0.9–1.4)	–	.363	1.06 (0.9–1.7)	1.19 (1.0–1.5)	1.205 (1.0–1.7)	–	.338
uric acid (umol/L)	320.0 (256.0–402.3)	322.0 (260.0–382.5)	315.5 (270.8–374.5)	–	.848	317 (269.0–383.0)	325 (262.5–393.5)	316.5 (255.3–399.5)	–	.967
IL-1β (pg/ml)	3.15 (1.87–5.62)	4.39 (2.51–8.02)	3.15 (1.71–4.70)	–	.292	3.15 (2.19–4.855)	3.15 (2.51–8.02)	3.15 (1.87–5.62)	–	.46
IL-4 (pg/ml)	4.57 (4.57–4.57)	4.57 (4.57–13.46)	4.57 (4.57–15.15)	–	.35	4.57 (4.57–13.46)	4.57 (4.57–13.46)	4.57 (4.57–4.57)	–	.33
IL-6 (pg/ml)	3.51 (2.30–8.29)	4.41 (2.08–8.21)	4.72 (3.06–9.59)	–	.75	4.72 (2.75–7.45)	4.41 (2.00–8.67)	3.51 (2.30–8.29)	–	.82

* $P=.004$ genotype CC vs genotype TT.
** $P=.002$ genotype CC vs genotype TT.
† $P=.019$ genotype TT vs genotype CT, $P=.046$ genotype CC vs genotype CT.
‡ $P=.005$ genotype CC vs genotype CT, $P=.032$ genotype CC vs genotype TT.
§ $P=.048$ genotype CT vs genotype TT.
‖ $P=.002$ genotype CC vs genotype CT, $P=.025$ genotype CC vs genotype TT.
¶ $P=.041$ genotype CC vs genotype TT, $P=.043$ genotype CT vs genotype TT.

Table 4

Association between polymorphisms with LN in SLE patients performed on recessive model.

SNP	Model	genotype	SLE with LN		SLE without LN		*P* value
			N	(%)	N	(%)	
rs117026326	Recessive	TT	12	(42.85)	16	(57.14)	.019
		CC+CT	242	(65.05)	130	(34.95)	
rs73366469	Recessive	TT	146	(65.77)	76	(34.23)	.001
		CC+CT	108	(50.23)	107	(49.77)	

summarized in Table 3. The results suggested that there was association between these polymorphisms and renal involvement in SLE patients.

Although there was no significant association between the polymorphisms and levels of urea, creatinine, cystatin-C (CYS-C), uric acid, IL-4, IL-6, IL-1β in SLE patients, we found that the 24 hours UTP and 24-hour urinary protein level had significant difference in SLE patients with different genotypes of rs117026326 ($P=.005$, $P=.030$, respectively) or rs73366469 ($P=.046$, $P=.002$, respectively). SLE cases with CC genotype at rs117026326 had higher 24 hours UTP and 24-hour urinary protein level than patients with other genotypes, while cases with TT genotype at rs73366469 had significant increased 24 hours UTP and 24-hour urinary protein level than patients with other genotypes.

What's more, the frequency of proteinuria had significant difference in SLE patients with different genotypes of rs117026326 or rs73366469 ($\chi^2=10.64$, $P<.001$; $\chi^2=13.21$, $P=.001$, respectively). When detailed analysis was performed on co-dominant model, results revealed that cases with TT genotype at rs117026326 (67.86%) had decreased frequency of the proteinuria than patients with CC genotype (89.38%) ($P=.004$), while cases with TT genotype at rs73366469 (90.00%) had significant increased frequency of the proteinuria than patients with CC genotype (68.57%) ($P=.002$). Furthermore, there was a strong trend towards significance when comparing the frequency of LN in patients with different genotypes of rs117026326 or rs73366469 ($P=.051$, .062, respectively). We also observed that the positive frequency of anti-dsDNA in patients with TT genotype at rs73366469 (82.73%) was significantly higher than those with CT genotype (72.41%) ($\chi^2=5.532$, $P=.019$).

Further analysis performed on recessive model indicted that patients with genotype TT at rs117026326 (42.85%) had significantly lower prevalence of LN than those with other genotypes (65.05%) ($P=.019$), while patients with genotype TT at rs73366469 (65.77%) had significantly higher prevalence of LN than patients with other genotypes (50.23%) ($P=.001$) (Table 4).

3.4. Linkage analysis

We constructed the LD analysis of rs117026326 and rs73366469. The result showed that they were in strong linkage disequilibrium with $r^2=0.71$ (Fig. 1).

4. Discussion

In this case-control study, we focused on the influence of *GTF2I* gene polymorphisms on susceptibility and clinical characteristics of SLE in a Chinese Han population. We described, for the first time, an interesting relationship between rs117026326, rs73366469 and kidney involvement of SLE patients. Results suggested that there was a highly significant association between rs117026326 and proteinuria, while rs73366469 was associated with proteinuria as well as expression of anti-dsDNA. Moreover,

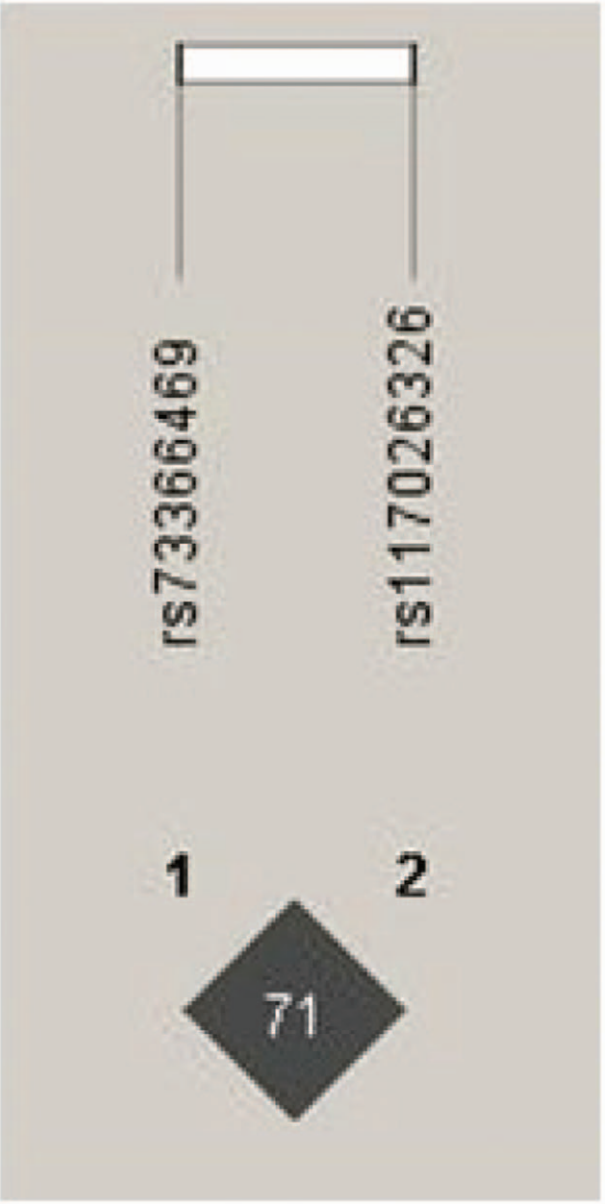

Figure 1. Linkage disequilibrium for rs117026326 and rs73366469 in *GTF2I* gene. The LD status is expounded by the r^2 value. There was strong LD between two SNPs ($r^2=0.71$).

the association between two SNPs and the frequency of LN was also observed on recessive model.

GTF2I gene is clustered on chromosome 7 within a 1.8 Mb region. It can encode the transcription factor IIi (TFII-I) family, involving in regulation of growth factor signaling, immune cell signaling, and cell proliferation.[7] As a signal-induced transcription, TFII-I can not only regulate transcription,[8] signal transduction and development of bone, neural tissue,[9] but also participate in the process of immune regulation. It can act as a cellular regulator of transcription from the promoter of cytomegalovirus, and its transcriptional regulation can be induced by immune signaling of lymphocytes. The activity of TFII-I is significantly related to expression of β-globin gene in erythroid cells.[10] Previous study indicated that *GTF2I* gene can contribute to regulation of immunoglobulin heavy chain transcription in B lymphocytes.[11] All these recent studies emphasized the validity and immune relevance of this gene.

Recent GWAS study identified susceptibility locus in GTF2I for pSS.[5] Given the close clinical relationship and similar pathophysiological features between pSS and SLE, and given the fact that *GTF2I* gene is one of genetic susceptibility factors of SLE, *GTF2I* gene may play an essential role in SLE. rs117026326 is located in intron of *GTF2I* gene on chromosome 7q11.23 and was recently identified as a risk gene loci for pSS,[12] RA[13] and SLE.[14,15] rs73366469 is located within conserved enhancers, overlaps transcription start sites for *GTF2I* gene. It was also one of autoimmune susceptibility loci for RA[13] and SLE.[15] Our study indicated that rs117026326 and rs73366469 were candidate risk factors for SLE in a Chinese Han population, which further confirmed previously reported associations. What is more, differences exist in linkage disequilibrium in different populations. When only enrolling in West Chinese population, associations between rs73366469 and rs117026326 were consistently replicated, but the r^2 in our study was higher than those in Kim and Sun, et al's study with Asian ancestry.[13,15]

Although there was no correlation between rs117026326 genotypes and GTF2I expression,[13] our study showed that the GTF2I polymorphisms are correlative with clinical parameters and phenotypes of SLE. As one of the most known devastating kidney-threatening manifestation of SLE patients,[16,17] LN affects about 40% to 70% of SLE patients and Asian, African populations have relatively higher incidence.[18] Some genes have been shown to possess the potential of predisposing susceptible population to LN.[19,20] Proteinuria can indicate potential kidney disorders, suggestive for the presence of LN.[21] With regard to autoimmune antibodies, anti-dsDNA as one of nephrotoxic autoantibodies can directly involve in renal pathology of SLE[22,23] and increased incidence of LN,[24] of which one of the reasons is immune complex with anti-dsDNA can lead to renal inflammation if deposited in kidney,[25] and may result in activation of complement, reactive oxygen species and some cytokines which are also causative factors of LN.[26] Moreover, positive anti-Sm, anti-RNP[27–29] and biomarkers for inflammation such as interleukin[30–32] are also associated with renal involvement. Both IL-4 and IL-6 play important roles in kidney injury, IL-4 has function in polarization of macrophages to M2 phenotype, essential for recovery from acute kidney injury,[33] while IL-6 is one of markers of chronic kidney damage. In addition, upregulation of IL-1β caused by TLR7 stimulation can lead to development of LN.[34] In order to investigate relationship between GTF2I polymorphisms and kidney injury, we measured the frequency of proteinuria, LN, serum levels of clinical indexes which are related to kidney including urea, creatinine, CYS-C, uric acid, IL-4, IL-6, IL-1β and positivity of anti-dsDNA, anti-Sm, and anti-RNP. The result of our study showed that GTF2I polymorphisms were related to severity of kidney impairment of SLE.

Last year, an international group developed a new classification criteria for SLE patients. The criteria was based on a scoring system for clinical and laboratory domains. A positive antinuclear antibody (ANA) at a titer 1:80 or greater by immunofluorescence (IFA) is used as the entry criterion. The data in our study took years to collect, so we did not change the inclusion criteria in order to keep condition of enrolled patients in accordance with each other. All the SLE patients we enrolled have positive ANA, and the HC are from Health Examination Center of our hospital, so the diagnosis will not change by newer criteria and the result will hold true.

Ultimately, this is the first study carried out in Chinese SLE patients which is tempting to suppose that GTF2I polymorphisms were possibly useful predictors for kidney impairment in SLE patients. The present study suggested that 24 hours UTP, 24-hour urinary protein level, frequency of the proteinuria and prevalence of LN were significantly lower in cases with rs117026326 TT genotype, while patients with rs73366469 TT genotype had higher 24-hour urinary protein level, frequency of the proteinuria, prevalence of LN, and positive frequency of anti-dsDNA.

Author contributions

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