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*Original Article*

# Association between interleukin-10 gene polymorphism and development of IgA nephropathy in a Chinese population

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**Abstract:** We carried out a study to investigate the association between three promoter SNPs (-592G/A, -819T/C and -1082A/C) of Interleukin-10 (*IL-10*) and development of IgA nephropathy. A hospital-based case-control design was taken in this study. The present study consisted of 184 patients with IgA nephropathy and 237 healthy controls. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay was applied to assess *IL-10* -592G/A, -819T/C and -1082A/C gene polymorphisms. By Chi-square test, we observed a significant difference in terms of genotype distributions of *IL-10* -1082A/C between patients with IgA nephropathy and control subjects ($\chi^2$=12.81, P=0.002). Using unconditional logistic regression analysis, the CC genotype of *IL-10* -1082A/C was found to have 3.69 folds risk of IgA nephropathy when compared with the AA genotype (adjusted OR=3.69, 95% CI=1.62-8.81) (P<0.001). Also, we found that the C allele of *IL-10* -1082A/C was associated with an increased risk of IgA nephropathy risk when compared with the A allele, and the adjusted OR (95%) were 1.65 (1.21-2.25) (P=0.001). In our study, we firstly reported a significant relationship between *IL-10* -1082A/C genetic variation and IgA nephropathy in a Chinese population.

**Keywords:** IL-10, polymorphism, IgA nephropathy

## Introduction

IgA nephropathy is one of the most common primary glomerulonephritis worldwide, which has the features of predominant IgA deposition in the glomerular mesangial area [1, 2]. The pathogenesis mechanism of IgA nephropathy is not well understood, and it is reported that the development of IgA nephropathy involves both genetic and environmental factors, such as Henoch-Schonlein purpura nephritis, hypertension, infection, seronegative spondylarthritis, tumor, leprosy, liver disease, and family IgA nephropathy [3-7]. However, individuals who are exposed to the similar factors would not develop the IgA nephropathy, which suggested that many genetic factors would also play an important role in the development of this disease. Current studies have reported that genetic risk factors contribute to the development of IgA nephropathy, such as TNFSF13, FDX1, miR-146a, transforming growth factor-β1 gene-509C/T, MTMR3 and angiotensinogen gene M235T [8-12]. Thus, it is necessary to identify novel molecular targets involved in the pathogenesis of IgA nephropathy.

Interleukin-10 (*IL-10*) is an immunoregulatory cytokine produced by Th2 cells, regulatory T cells, and monocytes/macrophages. The gene encoding for IL-10 is located on chromosome 1 (1q31-1q32). *IL-10* is an anti-inflammatory cytokine that may inhibit the synthesis of cytokines such as *IL-6*, *IL-1β*, *IL-1α*, and tumor necrosis factor-α in activated macrophage and interferon γ by T cells [13]. Previous study has reported that expression level of *IL-10* could influence the pathogenesis and clinical manifestations of IgA nephropathy [14, 15]. Currently, few studies have reported the association between interleukin-10 genetic polymorphisms and risk of IgA nephropathy, and no study reported their association in Chinese population [16-19]. Therefore, we carried out a study to investigate

**Table 1.** Primers, restriction enzyme and digested fragment of *IL-10* -592G/A, -819T/C and -1082A/C

| *IL-10* gene polymorphisms | Primers | Restriction enzyme | Length of digested fragment |
|---|---|---|---|
| -592G/A | 5'-CTACTAAGGCCTCTCCGGGAG-3' | *Rsa*I | 314 bp |
| | 5'-ACTACTAAGGCTTCTTGAGGAA-3' | | |
| -819T/C | 5'-TCATTCTATGTGCTCCTGATGG-3' | *Ssp*I | 315 bp |
| | 5'-TCCGGGAAGTGGGTAAGAGT-3' | | |
| -1082A/C | 5'-TCATTCTATGTGCTCCTGATGG-3' | *Bsl*I | 315 bp |
| | 5'-TCCGGGAAGTGGGTAAGAGT-3' | | |

the association between three promoter SNPs (-592G/A, -819T/C and -1082A/C) of *IL-10* and development of IgA nephropathy.

## Materials and methods

### *Subjects*

A hospital-based case-control design was taken in this study. The present study consisted of 184 patients with IgA nephropathy and 237 healthy controls. All patients with IgA nephropathy were consecutively recruited from the First affiliated hospital of Baotou Medical College between February 2012 and October 2014, and they were genetically unrelated Han Chinese individuals. Patients who were newly diagnosed with histopathologically confirmed IgA nephropathy by renal biopsy, and the diagnosis criteria were based on the criteria from the World Health Organization. The exclusion criteria for patients with IgA nephropathy were those with chronic and acute infection diseases, diabetes and systemic lupus erythematosus.

Healthy control subjects (237 cases) were randomly selected from individuals who visited clinics and receiving physical examination at our hospital during the same period of time. Control subjects were confirmed to be free of IgA nephropathy, renal diseases, diabetes, systemic lupus erythematosus and infection diseases.

Information in terms of demographic and clinical characteristics of the study subjects were collected from medical records, such as age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum immunoglobulin A (sIgA), serum creatinine (Scr) and blood urea nitrogen (BUN). The study was carried out with permission from the Institutional Review Board of the First affiliated hospital of Baotou Medical College. Written informed consents were obtained from all patients with IgA nephropathy and control subjects. Performance of study procedures was followed the standards of the Declaration of Helsinki.

### *DNA extraction and SNP genotyping*

Five mL peripheral blood sample was obtained from each patient and control subject, and the blood samples were kept at -20°C until using. DNA was extracted from the peripheral blood samples using the TIANamp blood DNA kit (Tiangen Biotech, Beijing, China). Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay was applied to assess *IL-10* -592G/A, -819T/C and -1082A/C gene polymorphisms. The primers, restriction enzyme and product size were shown in **Table 1**. The PCR reaction was performed in 25 μl of reaction mixture containing 1× PCR buffer, 1.5 mM $MgCl_2$, with 0.5 μM of both primer, 200 μM of each dNTP's, 100 μg/ml bovine serum albumin (BSA) and 1 U Taq polymerase (DNAzyme II DNA Polymerase, Thermo Scientific) and approximately 300 ng DNA. The PCR conditions included an initial melting step of 94°C for 5 min and followed by 30 cycles of 94°C for 45 s, variable annealing temperature for 30 s and 72°C for 45 s for all the four polymorphic sites. The resulted fragments were electrophoresized on 2% agarose gel stained with ethidium bromide to determine the genotypes of the subjects for the three polymorphic sites. The reproducibility of the genotyping results was very important and was checked by repeating it for 10 % random samples without knowing the status of sample of being a case or a control.

**Table 2.** Characteristics of patients with IgA nephropathy and control subjects

| Variables | Patients N=184 | % | Controls N=237 | % | $\chi^2$ or *t* test | *P* value |
|---|---|---|---|---|---|---|
| Age, years | 37.70±10.32 | | 36.72±11.07 | | 0.93 | 0.18 |
| Gender | | | | | | |
| Female | 75 | 40.76 | 106 | 44.73 | | |
| Male | 109 | 59.24 | 131 | 55.27 | 0.66 | 0.42 |
| SBP, mmHg | 124.08±11.45 | | 120.25±10.33 | | 3.60 | <0.001 |
| DBP, mmHg | 76.01±13.63 | | 74.73±10.25 | | 1.10 | 0.14 |
| sIgA, g/L | 2.96±1.31 | | 2.26±1.17 | | 5.78 | <0.001 |
| Scr, μmol/L | 111.98±49.46 | | 86.83±16.43 | | 7.33 | <0.001 |
| BUN, mmol/L | 6.56±3.35 | | 4.55±1.20 | | 8.56 | <0.001 |

**Table 3.** Genotype distributions of *IL-10* -592G/A, -819T/C and -1082A/C between the study groups

| SNPs | Patients N=184 | % | Controls N=237 | % | $\chi^2$ test | *P* value | *P* for HWE | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Patients | Control |
| -592G/A | | | | | | | | |
| GG | 71 | 38.59 | 107 | 45.15 | | | | |
| GA | 88 | 47.83 | 105 | 44.30 | | | | |
| AA | 25 | 13.59 | 25 | 10.55 | 2.14 | 0.34 | 0.78 | 0.92 |
| -819T/C | | | | | | | | |
| TT | 67 | 36.41 | 100 | 42.19 | | | | |
| TC | 86 | 46.74 | 103 | 43.46 | | | | |
| CC | 31 | 16.85 | 34 | 14.35 | 1.54 | 0.46 | 0.70 | 0.37 |
| -1082A/C | | | | | | | | |
| AA | 75 | 40.76 | 127 | 53.59 | | | | |
| AC | 85 | 46.20 | 99 | 41.77 | | | | |
| CC | 24 | 13.04 | 11 | 4.64 | 12.81 | 0.002 | 0.99 | 0.13 |

The product sizes after enzyme digestion were 314 bp for C allele of *IL-10* -592G/A, and were 134 bp and 180 bp for A allele. The product sizes were 315 bp for C allele of *IL-10* -819T/C, and were 24 bp and 291 bp for T allele. The product sizes were 314 bp for C allele of *IL-10* -1082A/C, and were 134 bp and 180 bp for A allele.

*Statistical analysis*

Means of quantitative variables were compared between groups using Student *t*-test after log transformation to obtain normal distribution, while distributions of categorical variables were compared by Pearson $\chi^2$-test. Chi-square ($\chi^2$)-test with one degree of freedom was used to evaluate the departure from Hardy-Weinberg equilibrium (HWE) in controls and compare the difference between cases/controls or subgroups of categorical variables. The association between *IL-10* -592G/A, -819T/C and -1082A/C gene polymorphisms and risk of IgA nephropathy were analyzed using unconditional logistic regression analysis, and the results were expressed using Odds Ratio (ORs) and their 95% confidence interval. The results were adjusted for confounding factors, such as sex and age. All tests were two-sided with a significant level of *P*-value <0.05. All statistical analyses were conducted using the IBM SPSS Statistics, version 16.0 (IBM Cor-poration, Armonk, NY, USA).

## Results

The demographic characteristics of patients with IgA nephropathy and control subjects were shown in **Table 2**. The patients with IgA nephropathy were comparable with control subjects with respect to age (*t*=0.93, P=0.18), gender ($\chi^2$=0.66, P=0.42) and DBP (*t*=1.10, P=0.14). By $\chi^2$ or *t* tests, significant differences were observed between patients with IgA nephropathy and control subjects in terms of SBP (*t*=3.60, P<0.001), sIgA (*t*=5.78, P< 0.001), Scr (*t*=7.33, P<0.001) and BUN (*t*= 8.56, P<0.001).

By Chi-square test, we observed a significant difference in terms of genotype distributions of *IL-10* -1082A/C between patients with IgA nephropathy and control subjects ($\chi^2$=12.81, P=0.002) (**Table 3**). We did not find significant differences with respect to genotype distributions of *IL-10* -592G/A ($\chi^2$=2.14, P=0.34) and -819T/C ($\chi^2$=1.54, P=0.45) between the two study groups. Using Chi-square-test with one degree of freedom, we observed that the genotype frequencies of the three study SNPs were

**Table 4.** Relationship between *IL-10* -592G/A, -819T/C and -1082A/C genetic polymorphism and IgA nephropathy risk

| SNPs | Patients N=184 | % | Controls N=237 | % | OR (95% CI)[1] | *P* value |
|---|---|---|---|---|---|---|
| -592G/A | | | | | | |
| GG | 71 | 38.59 | 107 | 45.15 | 1.0 (Ref.) | - |
| GA | 88 | 47.83 | 105 | 44.30 | 1.26 (0.82-1.95) | 0.27 |
| AA | 25 | 13.59 | 25 | 10.55 | 1.51 (0.76-2.97) | 0.20 |
| Allele | | | | | | |
| G | 230 | 62.50 | 319 | 67.30 | 1.0 (Ref.) | - |
| A | 138 | 37.50 | 155 | 32.70 | 1.23 (0.92-1.66) | 0.15 |
| -819T/C | | | | | | |
| TT | 67 | 36.41 | 100 | 42.19 | 1.0 (Ref.) | - |
| TC | 86 | 46.74 | 102 | 43.46 | 1.26 (0.81-1.96) | 0.28 |
| CC | 31 | 16.85 | 34 | 14.35 | 1.36 (0.73-2.52) | 0.29 |
| Allele | | | | | | |
| T | 220 | 59.78 | 303 | 63.92 | 1.0 (Ref.) | - |
| C | 148 | 40.22 | 171 | 36.08 | 1.19 (0.89-1.59) | 0.20 |
| -1082A/C | | | | | | |
| AA | 75 | 40.76 | 127 | 53.59 | 1.0 (Ref.) | - |
| AC | 85 | 46.20 | 99 | 41.77 | 1.45 (0.95-2.23) | 0.07 |
| CC | 24 | 13.04 | 11 | 4.64 | 3.69 (1.62-8.81) | <0.001 |
| Allele | | | | | | |
| A | 235 | 63.86 | 353 | 74.47 | 1.0 (Ref.) | - |
| C | 133 | 36.14 | 121 | 25.53 | 1.65 (1.21-2.25) | 0.001 |

[1]Adjusted for age, sex, sIgA, Scr and BUN.

not departure from Hardy-Weinberg equilibrium in patients (*P* values for HWE were 0.78, 0.70 and 0.99 for *IL-10* -592G/A, -819T/C and -1082A/C, respectively) and controls (*P* values for HWE were 0.92, 0.34 and 0.13 for *IL-10* -592G/A, -819T/C and -1082A/C, respectively).

Using unconditional logistic regression analysis, the CC genotype of *IL-10* -1082A/C was found to have 3.69 folds risk of IgA nephropathy when compared with the AA genotype (adjusted OR=3.69, 95% CI=1.62-8.81) (P< 0.001) (**Table 4**). Also, we found that the C allele of *IL-10* -1082A/C was associated with an increased risk of IgA nephropathy risk when compared with the A allele, and the adjusted OR (95%) were 1.65 (1.21-2.25) (P=0.001). However, the *IL-10* -592G/A and -819T/C genetic polymorphisms were found to have no relationship with the development of IgA nephropathy. Further, we also evaluated the interaction between *IL-10* -1082A/C genetic polymorphisms and clinical and demographic characteristics in the risk of IgA nephropathy, but no significant interaction was found between them (P for interaction <0.05).

## Discussion

Polymorphisms, which play an important role in the regulation the expression of protein, can contribute to the differences between individuals in the susceptibility to a disease and its severity. The human IL10 gene is located on chromosome 1q31-1q32 and composed of five exons and four introns [20]. In the *IL-10* gene promoter region, the alleles of -1082G, -819C, and -592C for three common single nucleotide polymorphisms (SNPs) have been associated with increased production of *IL-10*, and thus influence the expression and function of protein [20-23]. In this study, we evaluated the relationship between *IL-10* -592G/A, -819T/C and -1082A/C and development of IgA nephropathy, and we observed that the CC genotype and C allele of *IL-10* -1082A/C gene was correlated with an increased risk of this diseases in a Chinese population.

Previous studies have reported that the genetic polymorphism of *IL-10* gene is association with production of this gene [24-26]. Turner et al. conducted a experimental study and demonstrated that the genetic polymorphisms of *IL-10* gene promoter are associated with *IL-10* protein production in vitro [24]. Crawley et al. reported that the ATA haplotype of *IL-10* was correlated with lower transcriptional activity than the GCC haplotype, and the ATA/ATA genotype was associated with lower *IL-10* production compared to other genotypes [25]. Another experimental study have reported that the ATA haplotypes in the promoter region (-592G/A and -819T/C) of the *IL-10* gene were associated with low *IL-10* production [26]. Previous experimental studies have indicated that the *IL-10* expression could contribute to the natural course of human glomerulonephritides [27-29].

Several studies reported the relationship between *IL-10* genetic polymorphism and development of nephropathy, but the results are inconclusive [16, 17, 19, 29, 30]. Bantis et al. conducted a study with 103 patients with IgA nephropathy and 206 controls in a German population, and reported that *IL-10* -1082A/C genetic polymorphism was associated with an increased recurrent of IgA nephropathy [19]. Bantis et al. suggested that *IL-10* -1082A/C genetic variation plays a critical role in the progression of IgA nephropathy and focal segmental glomerulosclerosis [16]. Chin et al. conducted a study in a Korean population, and indicated that *IL-10* -1082A/C polymorphism contributed to the susceptibility to IgA nephropathy [17]. Coppo et al. demonstrated that polymorphisms of *IL-10* were correlated with protein from early recurrence of IgA nephropathy [30]. Lim et al. also conducted study in a Korean population, and suggested that *IL-10* genetic polymorphisms are involved in the processes of inflammation and immunological injury in IgA nephropathy [29]. The above mentioned studies indicated that *IL-10* -1082A/C genetic polymorphism contributed to the susceptibility to IgA nephropathy.

Three limitations should be considered in our study. First, selection bias may be present, as all patients and control subjects were recruited from one hospital. However, genotype distributions of *IL-10* -1082A/G, -819T/C, and -592A/C were in line with HWE, and similar with MAF in dbSNP, suggesting that the samples in our study were good representations of the general population. Second, other cytokine genes which may have interacted with the IL-10 gene were not included in our statistical analysis.

In our study, we firstly reported a significant relationship between *IL-10* -1082A/C genetic variation and IgA nephropathy in a Chinese population. Further studies with larger sample sizes may serve to fully elucidate the impact of these polymorphisms on the risk of IgA nephropathy.

## Disclosure of conflict of interest

None.

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