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Cytokine Gene Polymorphisms in Chinese Children with Idiopathic Nephrotic Syndrome

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ABSTRACT

Background: Cytokines play a role in the progression of idiopathic-nephrotic syndrome (INS).

Objectives: To investigate the association of different cytokine genes polymorphisms with INS incidence and response to steroid therapy in Chinese children.

Methods: 182 children with INS and 100 healthy controls were enrolled in this study. Blood genomic DNAs were used to analyze20 single nucleotide polymorphisms (SNPs) in 8 cytokine genes includingIL-21, IL-18, IL-6, IFN-γ, IL-4, IL-10, IL-17F, IL-17A d by multi-PCR with next-generation sequencing.

Results: Among 182 children with INS, 89 (48.6%) were steroid-sensitive (SS), 73 (39.9%) were steroid-dependent (SD) and 21 (11.5%) were steroid-resistant (SR). In 20 SNPs, IL-4-rs2243283 exhibited a significantly different genotype distribution between INS and the healthy controls (CC is a risk genotype: 66.5% of INS VS 51% of the control; OR=1.91, p=0.012). Patients carrying AG genotype (rs2275913, IL-17A) had a significantly higher risk of steroid-dependent response (69.1% of SD VS 46.4% of SS; OR=2.58, p=0.014). Similarly, patients carrying A allele of IL-10-rs1800872 (39.0% of SD VS 26.7% of SS; OR=1.76, p=0.018) and C allele of IL-10-rs1800896 (12.3% of SD VS 3.9% of SS; OR=3.44, p=0.004) had a higher risk of steroid-dependent response. However, none of these 20 SNPs showed a significant difference between SS group and SR group.

Conclusion: Among the 20 cytokine gene SNPs, IL-4-rs2243283 might increase the susceptibility to INS in Chinese children; rs2275913 of IL-17A, rs1180972, and rs1800896 of IL-10 show association with the steroid -response in Chinese INS children.

Keywords: Cytokine, Gene, Polymorphisms, Idiopathic-nephrotic syndrome

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INTRODUCTION

Idiopathic-nephrotic syndrome (INS) is one of the most common glomerular diseases in children, with an annual global incidence rate of 16:100,000 (1). Due to structural and morphological changes in the glomerular basement membrane (GBM) of the kidney, INS is characterized by severe proteinuria, hypocholesterolemia, hypoalbuminemia, and edema (2). At present, steroid treatment remains one of the most effective therapeutic strategies for INS, and most cases of INS are alleviated within several weeks of steroids therapy (3). However, the therapeutic effect of steroids in certain INS patients is not ideal. Based on different steroid-treatment responses, INS is further divided into steroid-sensitive nephrotic syndrome (SSNS, SS), steroid-dependent nephrotic syndrome (SDNS, SD), and steroid-resistant nephrotic syndrome (SRNS, SR) (4). In steroid-resistant nephrotic syndrome, 75% of patients revealed renal histological features of focal segmental glomerulosclerosis (FSGS), frequently suffered from relapses and needed to be treated with immunosuppressive agents (5). Moreover, not only is the blind use of steroid therapy with an unknown steroid response phenotype ineffective for treatment in SR patients, but also it triggers potentially severe side effects such as cushingoid changes, hyperglycemia, abnormal bone metabolism, so on and so forth (6, 7). Therefore, early detection of the steroid-response phenotype is of great importance in the timely adjustment of medication.

Genetic characteristics have been proposed to be an important factor in the disease incidences of INS (8, 9). In addition, several gene polymorphisms and mutations have also been recognized as a relatively common etiology of SRNS in childhood (10-12). INS is an autoimmune disease whose incidence and development have been found to be associated with the imbalance of Th1/Th2 and Th17/Treg cells (13). Produced from Th-cell, Th-associated cytokines act as mediators of inflammation in INS progressions, such as TNF-α, IL-13, IL-4, and IL-10 (14). Furthermore, several studies suggested that cytokines are also involved in the responses to steroid therapy in INS patients. For instance, the expression of IL-18 is significantly correlated with SSNS (15, 16). However, the relationship between cytokine gene polymorphisms and steroid therapy responses in children with INS was rarely studied. As a result, the current study was undertaken to investigate the relationship between SNPs of cytokine IL-4, IL-17A, IL-17F, IL-6, IL-21, IL-10, and IFN-γ and steroid therapy responses in Chinese INS children.

MATERIALS AND METHODS

Study Population

In this study, we recruited 183 INS and 100 control cases from our hospital. The diagnostic criteria of INS were based on the appearance of edema, 24-h urinary protein excretion of ≥50 mg/kg, morning urinary protein/creatinine of >2 mg, hypoalbuminemia of <25 g/L, and the disease of unknown causes. Standard steroid therapy had been arranged for all INS children and based on their clinical responses to steroids, they were classified into three species: SS, SD , and SR. SS patients who were thought to have had negative urinary protein for 4 weeks after being treated with sufficient prednisone [2 mg/(kg · d) or 60 mg/(m · d)]. SR patients were defined as individuals who failed to achieve remission after 4 weeks of daily sufficient prednisone. SDs were defined as patients who relapsed within 2 weeks after two consecutive doses reduction or withdrawal (17). Exclusion criteria:(1) Patients who have been diagnosed with nephritis-NS (eg, IgA nephropathy) or suspected of secondary NS before the assignment; (2) Patients who have severe infections or opportunistic infections within 6 months before the assignment; (3) Patients who have a malignant tumor or history of malignant tumor; (4) Patients who present

deteriorated kidney function. This study was approved by the Ethics Committee of the Children's Hospital of Zhejiang University, School of Medicine (2020-IRB-057). 100 healthy controls were defined as those aged <18 years, without a history of damaged renal function.

DNA Extraction

1 mL blood sample was collected by using an ethylene diamine tetraacetic acid (EDTA) anticoagulant tube. 200µl whole blood sample was prepared for human genome DNA extraction by using Biospin genomic DNA extraction Kit (BIOER technology, #BSC06S1). DNA concentration and purity were measured by using a Nanodrop 1000c spectrophotometer (Thermo Scientific, USA). Genomic DNA was stored at -20℃ for the subsequent experiments.

SNPs Selection and Genotyping Analysis

A total of 20 SNPs sites of cytokine IL-21, IL-18, IL-6, IFN-γ, IL-4, IL-10, IL-17F, IL-17A genes were detected by using multiplex PCR and next-generation sequencing assay (18). First-round multiplex PCR was performed in a Gene Amp PCR system 9600 (Norwalk, USA) under the following conditions: 15 min. at 95 ℃; 4 cycles of 30 s at 94 ℃ 10 min. at 60 ℃ and 30 s at 72 ℃; 20 cycles of 30 s at 94 ℃, 1 min. at 60 ℃ and 30 s at 72 ℃. 1 µl first-round product served as a sample in second-round PCR under this condition: 15 min. at 95 ℃; 5 cycles of 30 s at 94 ℃, 4 min. at 60 ℃ and 30 s at 72 ℃; 10 cycles of 30 s at 94 ℃ 1 min. at 65 ℃ and 30 s at 72 ℃. Primers used for multiplex PCR are shown in Table 1. Then the second round PCR product was purified and sequenced on an X-10 platform (Illumina, USA). All sequencing data were analyzed and compared by the Illumina bcl2fastq Analysis software, the genotyping results are shown in Figure 1.

Statistical Analysis

SPSS software package (revision 17.0) was selected for Statistical analysis. All SNPs were tested for agreement with the Hardy–Weinberg equilibrium (HWE) by using a goodness-of-fit Chi-square ($\chi 2$) test. We used Student's t-test or Wilcoxon rank-sum test to compare the means of age between every two groups. Chi-square tests were applied for the

Table 1. Primers for Multi-PCR

Gene	SNP	Forward primer	Reward primer
IL-4	rs2243250	TTATGGGTAAGGACCTTATGGAC	TATTTTAACCTGGCTTCTTCCAAG
	rs2243248	ACCTTATTGTGTCCACATGAATTC	CTCCCAAAGCTCTGAGATTACAG
	rs2243283	AGGTGAACAGATTTGGGATATGAC	AATTGAACTCTTGATCTTCTGCTG
IL-6	rs2069837	CTCTGGACTCCATCAGTAAAATTG	TCAGTTTCCTTATCTCCAAAAACC
	rs2066992	GACTCAGGATTAAGTAACACACCTAAAG	GTTACATGTCTGGGAAAGAATACC
	rs1800796	CTTGAAGTAACTGCACGAAATTTG	TTAACAGGCTAGAATTTAGCGTTC
	rs2069840	TGTATACATATAGATCCAGGCAGC	CCCAGGATGAACTAATTAAACCTG
IL-10	rs3021094	AAAACAGAGGATTCAACAGTGATG	GAGAAAGAAAAGCAGAGAACAGG
	rs1800872	GTGGGCTAAATATCCTCAAAGTTC	AGCATATAAGAAGCTTTCAGCAAG
	rs1800896	AAAGTTTAAAAGATGGGGTGGAAG	CTTACCTTCTACACACACACACAC
IL-17A	rs2275913	AGTAAGAATGAAAAGAGGACATGG	GCGCTATCGTCTCTCTTTTTATAG
	rs4711998	TGAGAGTTATCATTCACCTCAGTG	GATGAGAACTAGAAAGGAGAGGAG
	rs3819025	GTCCATCTCATAGCAGGCACAAAC	CTACCAAAGCTTTCATTTCCTATCCTAC
IL-17F	rs12203736	GTAACTCAATTCCAGGACTCTTAGAAG	GCAGTTTGTCAAGACAAGGTATATGAG
	rs763780	GAATATTTTCTGTTTCCATCCGTG	CTGTTTCTTTCCAGTTGGAGAAG
IL-18	rs360718	ATGGCTGACTTTCCAAATAAAGAG	GACAGTCAGCAAGGAATTGTCTC
	rs187238	GAAATAAAGTGGCAGAGGATACG	GGAAGTCTGAAAATGAAGAGAGAC
	rs7106524	TTGAGAAAGTCTCGCTCTGTTTAG	CTTTCAGGCCAGGTGCACTAG
IL-21	rs2221903	TTTCTGAAAGCCTTTGAATGGTAC	TGATGTGCATATAAAGCCAATTCC
IFN-γ	rs2069727	CAGACAATAAAGCTGAAACTTAGAC	CACACAGAGATTTATTTCTAGCCC

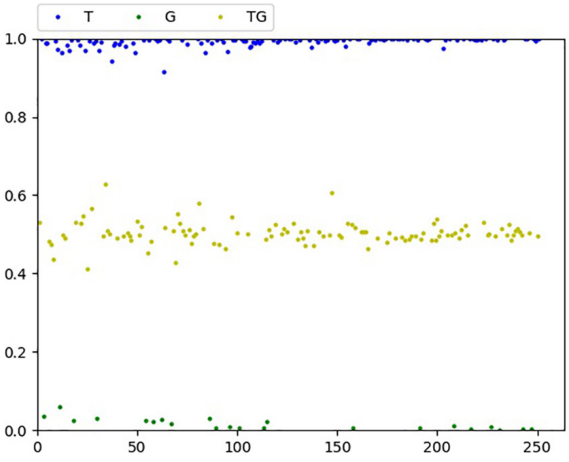

Figure 1. Genotyping results of SNP (eg. rs1800872).

differences of sex. P>0.05 was considered to have no significant difference. We used $\chi 2$ test to compare allele and genotype frequencies of SNPs between every two groups. We used the Odds Ratio (OR) and 95 % confidence interval (CI) to estimate the relative risk. P<0.05 was considered as a significant difference.

RESULTS

Patients' Characteristics

This case-control study included 183 children suffering from INS (involving 62 females and 121 males, mean age: 5.5±1.2 years) and 100 healthy children (involving 34 females and 66 males, mean age: 4.9±1.9 years). Of those children with INS, 89 (48.6%) were classified as SS, 73 (39.9%) were SD and 21 (11.5%) were SR. By age and gender, the healthy control group was matched to the INS group. No significant differences between INS and the healthy children were found (P=0.16, P=0.57 respectively).

Gene Polymorphisms in INS Patients and Healthy Children

20 SNPs genotyped results of all samples were tested for the HWE, and no deviations from the HWE were found in this study (P>0.05; 0.16-0.97). Genotype and allele frequencies of 20 SNPs in INS group and

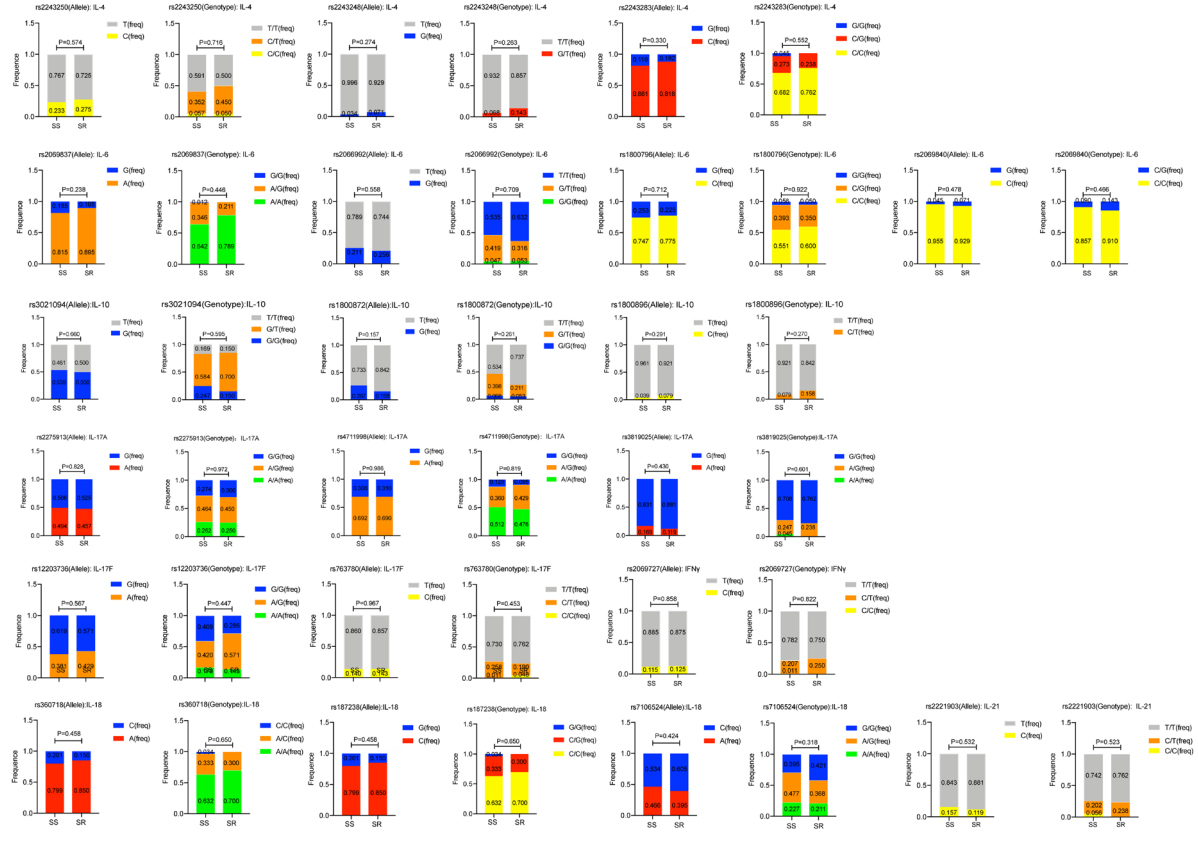

Figure 2. Cytokine gene polymorphisms in INS cases and HC (healthy control).

the control group are shown in Figure 2. In 20 SNPs, only rs2243283 of IL-4 exhibited a significantly different genotype distribution among children with INS compared with the control group (CC genotype: 66.5% of INS VS 51% of control; P=0.012). Patients with CC genotypes had an increased risk of developing INS (OR 1.91; 95 % CI 1.16-3.14). The rest of 19 SNPs, including IL-6 (rs2069837, rs2066992, rs1800796 and rs2069840), IL-10 (rs3021294, rs1800872, rs1800896), IL-17A (rs2275913, rs4711998, 3819025), IL-17F (rs12203736 and rs763780), IL-18 (rs360718, rs187238, rs7106524), IL-21(rs2221903), IFN-γ (rs2069727), as well as rs2243250 and rs2243248 of IL-4 displayed no statistically significant difference between the INS group and the healthy controls (P>0.05).

Gene Polymorphisms in SS and SD Cases

Genotype and allele frequencies of 20 SNPs in SS and SD patients are shown in Figure 3. There were no significant differences in the distribution of genotypes between SS and SD patients, including IL-4 (rs2243250, rs2243248 and rs2243283), IL-6 (rs2069837, rs2066992, rs1800796 and rs2069840), IL-10 (rs3021294), IL-17A (rs4711998, 3819025), IL-17F (rs12203736 and rs763780), IL-18 (rs360718, rs187238, rs7106524), IL-21(rs2221903) and IFN-γ (rs2069727). However, there was a significant difference in the genotypes frequencies of IL-17A SNP rs2275913 between SS and SD (AG genotype: 69.1% of SD VS 46.4% of SS; P=0.014). Patients with AG genotypes had an increased risk of developing SD (OR 2.58; 95 % CI 1.32-5.05). Similarly, we found that the rs1800872 and rs1800896 of IL-10 exhibited a significantly different genotype distribution among the children with SS compared with the SD. The allele frequencies of G allele of rs1800872 and C allele of rs1800896 were different between SD and SS (rs1800872: 39.0% of SD VS 26.7% of SS, P=0.018; rs1800896: 12.3% of SD VS 3.9% of SS, P=0.004). Patients with G allele of rs1800872 had a higher risk of developing

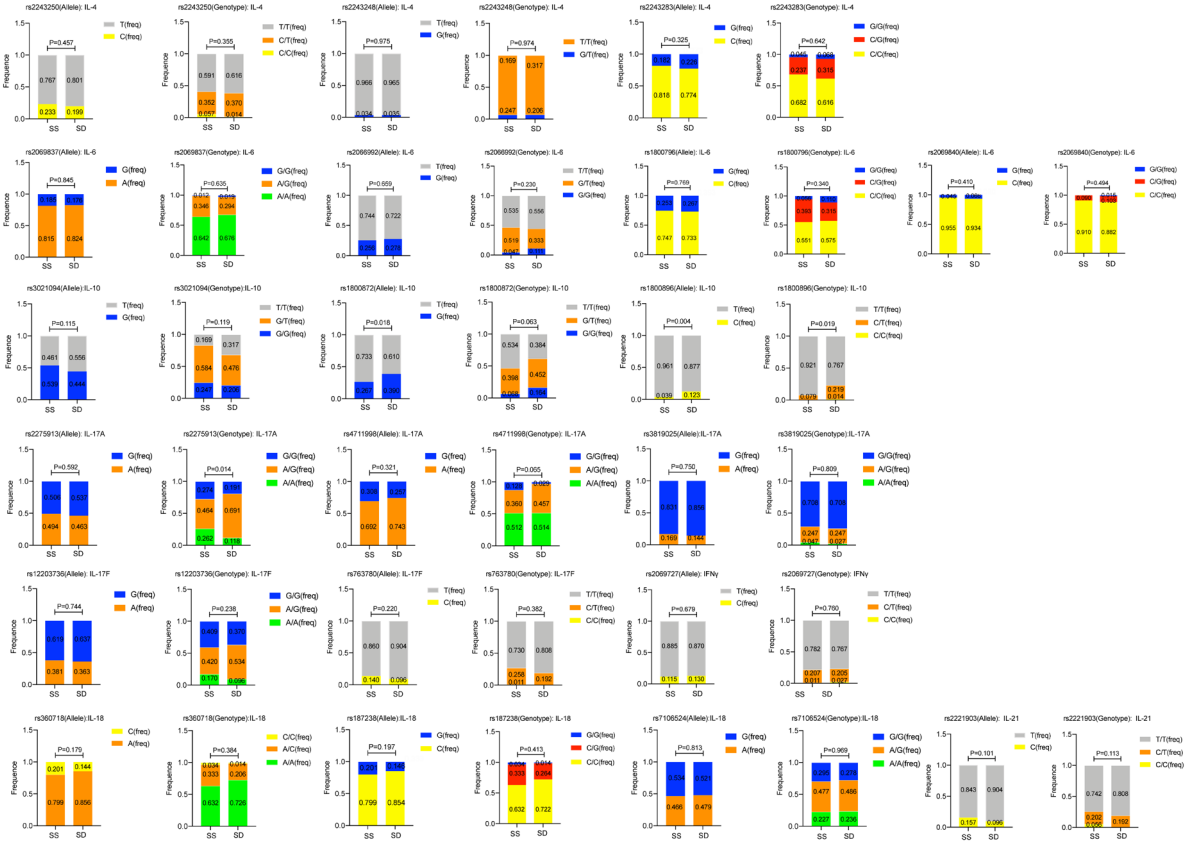

Figure 3. Cytokine gene polymorphisms in SS and SD cases.

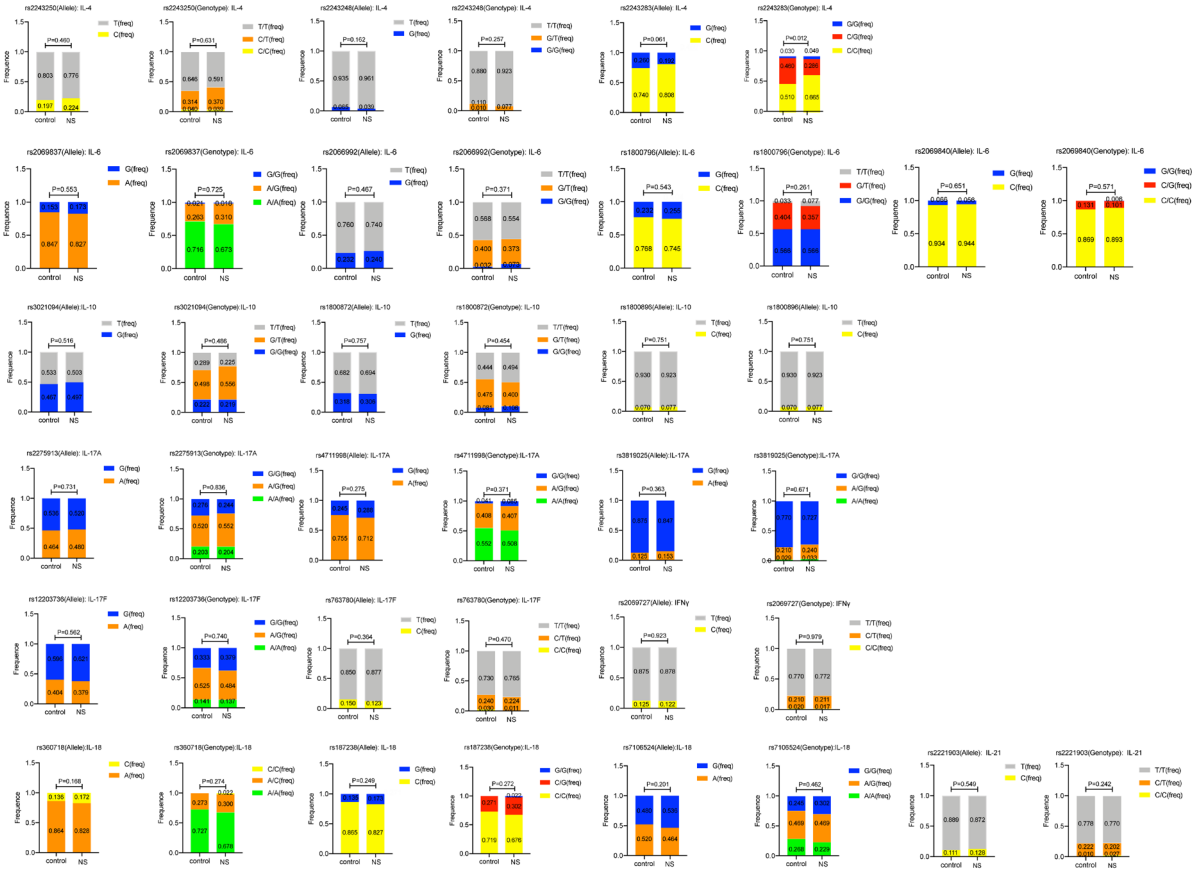

Figure 4. Cytokine gene polymorphisms in SS and SR cases.

therapy results of SD (OR 1.76; 95% CI 1.10-2.82). Also, patients with C allele or CT genotype of rs1800896 had an increased risk of developing therapy results of SD (OR 3.44; 95% CI 1.39-8.47 and OR 3.29; 95% CI 1.27-8.51, respectively).

Gene Polymorphisms in SS and SR Cases

As shown in Figure 4, genotype and allele frequencies of 20 SNPs showed no significant differences in the distribution of genotype in SS and SR patients.

DISCUSSION

INS is a glomerular disease with unclear pathogenesis, which is not uncommon in children. INS featured with podocyte injury has more common clinical characteristics including proteinuria and hypoalbuminemia, posing a serious threat to patients' health. (2). Despite the fact that the incidence of INS has not been elucidated, steroid therapy is always effective in a large proportion of INS patients. Unfortunately, a fraction of INS patients became resistant to or dependent on steroid therapy (4). Evidences suggested that immunogens and cytokines might work on INS pathogenesis and therapy (19). Furthermore, numerous studies had indicated genetic variations of cytokines which participated in individual susceptibility to INS and responsiveness to steroid therapy (20).

Previous studies revealed that the genetic variation of cytokines is related to INS pathogenesis. Dudnyk et al. found out that gene polymorphism of IL-1β (-511) can be considered as a marker in the progression of glomerulonephritis and nephrotic syndrome (21). IL-4 is a Th2 cytokine involved in the early stage of the INS (22). A significant increase of IL-4 can be observed in kidney minimal change disease (MCD) patients with frequent relapses (22). In our results, we found out that rs2243283 of IL-4 has a

relationship with INS, too, and that especially those children who contain CC genotype of IL-4 may be susceptible to INS.

The variation of cytokines is also involved in response to steroid treatment. Cortvrindt et al. indicated that IL-6-G174C and TNFα-G308A polymorphisms of cytokines have a relationship with the response to steroid therapy in INS children (23). To confirm the relationship between polymorphism of cytokines and steroid-response, we contrasted the SNPs of INS patients with different steroid responses. We found out that rs2275913 of IL-17A may be connected with SD patients. IL-17A can be produced by CD4+ T cells, natural killer (NK) cells, and other multiple cells. IL-17A has a great impact on inflammatory activation by inducing the expression of many factors, such as pro-inflammatory cytokines, matrix metalloproteases, and chemokines (19). Due to its involvement in different autoimmune and inflammatory diseases, IL-17A has been applied as a good therapeutic target to prevent the renal disease from the end stage (24). In this study, we found out that INS children with AG genotypes (rs2275913 of IL-17A) had a higher risk of developing SD. It has suggested the potential association between IL-17A gene polymorphism and steroid response.

As a cytokine secreted by Th-cells, IL-10 plays both anti-inflammatory and immunosuppressive roles. Previous studies indicated that IL-10 significantly increased in MCD patients with frequent relapses (21). However, several studies on INS children showed that SNP (rs1800896) of IL-10 exhibited no significant differences in INS children, and our current study, too, yielded the same results. (17). Nevertheless, our results suggested that the polymorphism of IL-10 is related to the steroid-response of children with nephrotic syndrome. In INS children with G allele of rs1800872, C allele of rs1800896, and CT allele of rs1800896 appeared to be at a higher risk of SD. IL-10 gene polymorphism also might be used to predict the SD patients in the proper time, and this finding might become a diagnostic indicator of INS. The frequency of 20 SNPs between the SS and SR groups did not differ significantly in this study.

CONCLUSION

In conclusion, IL-4-rs2243283 might affect the susceptibility to INS in Chinese children. The rs2275913 of IL-17A, rs1180972 and rs1800896 of IL-10 might affect steroid response in INS pediatric patients. Larger multiracial and multicenter studies will be required to obtain more conclusive data for elucidating the clinical implications of cytokine polymorphisms in INS children.

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AUTHORSHIP CRITERIA

Wei Li and Jianhua Mao designed the study, analyzed the data, and wrote the manuscript. Lin He and Haidong Fu performed the experiments, and analyzed the data. Lin Li and Yun Du performed the experiments. Zhaoyang Peng and Wenqing Xiang collected the data.

Conflicts of Interest: None declared.

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