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ORIGINAL ARTICLE

Correlation between Polymorphisms of the Superoxide Dismutase Gene and Idiopathic Nephrotic Syndrome in Chinese Children

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ABSTRACT

Background: **Genetic mutations are closely linked to childhood idiopathic nephrotic syndrome (INS). This study aimed to explore the associations between superoxide dismutase (SOD) gene polymorphisms and susceptibility to INS, as well as response to steroid therapy, in Chinese children.**
Methods: **Five single nucleotide polymorphisms (SNPs; rs4816407, rs1041740, rs4880, rs2758346, and rs3798215) in the *SOD1* and *SOD2* genes were genotyped using multiplex PCR combined with next-generation sequencing in 183 pediatric patients with INS and 100 healthy controls.**
Results: **The genotypic distributions of the tested *SOD* SNPs did not differ significantly between the INS group and healthy controls. Patients carrying the CC genotype of *SOD1* rs1041740 exhibited a significantly higher risk of steroid-dependent (SD) nephrotic syndrome than those with steroid-sensitive (SS) nephrotic syndrome ($p = 0.002$, OR = 2.247, 95% CI = [1.191 - 4.239]). However, no significant differences in these five SNPs were observed between the SS and steroid-resistant (SR) subgroups (all $p > 0.05$).**
Conclusions: **Our findings indicate that *SOD* gene polymorphisms are not associated with susceptibility to INS in Chinese children. Notably, *SOD1* rs1041740 variants may increase the risk of steroid dependence in this pediatric population.**
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KEYWORDS

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INTRODUCTION

Idiopathic nephrotic syndrome (INS), characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia, is one of the most common glomerular diseases in children [1,2]. Statistics show that the global prevalence of INS is approximately 16 cases per 100,000 children under 16 years of age [3], while in China, the average annual number of new cases ranges from 28,000 to 56,000 [4]. To date, corticosteroids remain the first-line treatment for INS. Clinically, INS is classified into three subtypes based on patient response to corticosteroid therapy: steroid-sensitive nephrotic syndrome (SSNS), steroid-resistant nephrotic syndrome (SRNS), and steroid-dependent nephrotic syndrome (SDNS) [5-7]. SSNS accounts for approximately 80% to 90% of children over one year of age, whereas the remaining 10 - 20% are nonresponsive and classified as SRNS [8]. SRNS is often associated with focal segmental glomerulosclerosis (FSGS) on histology and is regarded as one of the most common causes of progression to end-stage renal disease (ESRD) [9]. A subset of SSNS children who experience relapse within 2 weeks after two consecutive dose reductions or steroid withdrawal are defined as having SDNS [10]. Although most children with INS respond well to steroid therapy, a considerable number suffer from frequent relapses, develop steroid dependence, or later become steroid-resistant. This necessitates repeated treatment or alternative therapeutic strategies, leading to a prolonged disease course [6,11]. Most patients who are initially steroid-sensitive experience disease relapse and require repeated steroid treatment. Long-term and repeated use of corticosteroids may lead to numerous serious adverse effects, including hyperglycemia, cushingoid changes, abnormal bone metabolism, elevated blood pressure, skin atrophy, adrenal suppression, and behavioral alterations [12]. Therefore, early differentiation of steroid efficacy and accurate prediction and evaluation of therapeutic outcomes in INS treatment are particularly crucial.

The exact etiology of INS remains elusive; however, its pathogenic mechanisms are thought to be associated with cellular oxidative stress, inflammatory responses, and immune dysregulation [13]. Reactive oxygen species (ROS) are continuously generated during glomerular filtration and tubular reabsorption. The cascade of excessive ROS production and subsequent lipid peroxidation directly induces cellular damage, which is recognized as one of the key pathogenic mechanisms underlying progressive renal injury [14,15]. Superoxide dismutase (SOD) is a core component of the body's antioxidant system and a critical regulator of oxidative stress, serving as the first line of defense against ROS. As a scavenger of superoxide anions (O_2^-), particularly through its mitochondrial manganese-dependent isoform (*SOD2*), which primarily functions to eliminate excessive intracellular O_2^-, this process also modulates hydrogen peroxide (H_2O_2) production, thereby maintaining the balance between oxidative stress and antioxidant capacity [16]. Previous studies have implicated *SOD2* in membranous nephropathy [17].

In addition, genetic mutations are closely implicated in the incidence of INS and the response to steroid therapy [18]. In children with INS, genetic defects may exist in the structural proteins that form the glomerular filtration barrier in the kidney. Currently, the most common genetic factors include *WT1*, *NPHS1*, *NPHS2*, *LAMB2*, and *PLCE1* [19]. Previous studies have suggested that mutations in key podocyte genes, such as *NPHS2*, *LAMB2*, or angiotensin-converting enzyme (*ACE*), are associated with SRNS [19,20]. To date, there are no reports on the associations between *SOD1* and *SOD2* polymorphisms and childhood nephrotic syndrome. Therefore, the present study was conducted to explore the relationships between *SOD* gene single nucleotide polymorphisms (SNPs) and susceptibility to INS as well as the response to steroid treatment in Chinese children, aiming to evaluate the population-specific predictive effect of *SOD* genetic variations on INS.

MATERIALS AND METHODS

Study population

In this study, a total of 183 INS cases and 100 control subjects were recruited from the Children's Hospital, Zhejiang University School of Medicine. The diagnosis of INS was confirmed in accordance with the following criteria: 1) 24-hour urinary protein excretion of ≥ 50 mg/kg, morning urinary protein/creatinine ratio of > 2 mg; 2) hypoalbuminemia with serum albumin < 25 g/L; 3) presence of edema; and 4) unknown etiology. The exclusion criteria were as follows: 1) patients diagnosed with nephritis-related NS (e.g. IgA nephropathy) or suspected of secondary NS prior to enrollment, 2) patients with severe infections or opportunistic infections within 6 months before enrollment, 3) patients with malignant tumors or a history of malignant tumors, and 4) patients with deteriorated renal function.

All nephrotic patients received standard steroid therapy and were classified into three subgroups, namely, the steroid-sensitive (SS), steroid-dependent (SD), and steroid-resistant (SR) groups, based on their clinical response to steroids. SSNS was defined as patients who achieved negative urinary protein (remission) within 4 weeks of receiving adequate prednisone (PDN) at a dose of 2 mg/kg/d or 60 mg/m²/d. SRNS was characterized by failure to achieve remission after 4 weeks of daily adequate PDN administration. SDNS was identified as children who experienced relapse within 2 weeks after two consecutive dose reductions or steroid withdrawal [21-23]. During the same period, 100 healthy controls were selected from children undergoing routine physical examinations at a hospital health check center, all of whom had no history of inflammation, systemic diseases, or autoimmune disorders. All participants were ethnic Han Chinese.

Genomic DNA extraction

Ethylenediaminetetraacetic acid (EDTA) anticoagulant-treated blood was collected from each child. Genomic DNA was extracted from 200 μL of whole blood using a Biospin Genomic DNA Purification Kit (BIOER Technology, #BSC06S1) in strict accordance with the manufacturer's instructions. The purity and concentration of the extracted DNA were measured using a NanoDrop 1000c spectrophotometer (Thermo Scientific, USA). DNA integrity was evaluated by 1.0% agarose gel electrophoresis. Samples that met the predefined quality requirements were stored at -20℃ until genotype assessment and then transferred to -80℃ for long-term preservation after analysis.

Detection of SNPs

Subsequently, the genomic DNA was subjected to multiplex polymerase chain reaction (PCR) for target DNA enrichment, and genotyping of the 5 SNPs, including *SOD1*-rs4816407 (NC_000021.9:g.31667716A>C), *SOD1*-rs1041740 (NC_000021.9:g.31667849C>T), *SOD2*-rs4880 (NC_000006.12:g.159692840A>C), *SOD2*-rs2758346 (NC_000006.12:g.159694389C>T), and *SOD2*-rs3798215 (NC_000006.12:g.159683806T>C), was performed via next-generation sequencing on a high-throughput genotyping platform X-10, Illumina (Illumina Inc., San Diego, CA, USA) with Bridge PCR products [24,25]. All quality controls were strictly implemented. Each sample was required to have a call rate > 95% across all markers, duplicate samples to assess concordance, requiring > 99% agreement; no-template controls (NTCs) and positive controls in each run. The primers used for multiplex PCR are listed in Table 1. It is worth noting that the *SOD1*-rs4816407 and *SOD1*-rs1041740 loci were using the same primers due to their close proximity and were subsequently confirmed by sequencing.

Statistical analysis

Statistical analyses were performed using SPSS software (version 22.0). The goodness-of-fit chi-squared (χ^2) test was used to examine the Hardy-Weinberg equilibrium (HWE) for each SNP. The χ^2 test was also applied to compare the allele and genotype frequencies of the SNPs between the two groups to identify significant differences and conduct Bonferroni correction simultaneously. Linkage disequilibrium analysis for the two *SOD1* SNPs (rs4816407 and rs1041740) and the three *SOD2* SNPs (rs4880, rs2758346, and rs3798215) used SHEsis [26]. The unconditional logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence intervals (CIs) between the different groups for estimating the effect sizes. An adjusted p-value < 0.05 was considered statistically significant, and all values were rounded to three decimal places.

RESULTS

Patient characteristics

In this study, a total of 183 INS children were recruited, including 121 males and 62 females (mean age of 4.5 ± 3.6 years). Another 100 healthy children, consisting of 66 males and 34 females (mean age of 3.2 ± 2.6 years), were included as controls. The control group had no history of steroid treatment and was matched to the case group by age and gender. There was no significant difference between INS patients and healthy controls in terms of age or sex ($p > 0.050$). Among the INS cases, 89 (48.634%) children had SS, 73 (39.890%) had confirmed SD, and 21 (11.475%) had SR.

Gene polymorphisms in INS patients and healthy controls

The genotype and allele frequencies of *SOD1* and *SOD2* in INS patients and controls are shown in Figure 1. No significant differences were observed in the distribution of these alleles or genotypes between the initial INS patients and healthy controls, including those of *SOD1* (rs4816407, p = 0.940 and 0.808, OR = 1.013, 95% CI = [0.705 - 1.458]; rs1041740, p = 0.222 and 0.051, OR = 1.273, 95% CI = [0.880 - 1.844]) and *SOD2* (rs4880, p = 0.459 and 0.265, OR = 1.210, 95% CI = [0.719 - 2.036]; rs2758346, p = 0.460 and 0.255, OR = 1.217, 95% CI = [0.718 - 2.063]; rs3798215, p = 0.421 and 0.660, OR = 1.113, 95% CI = [0.769 - 1.613]).

Gene polymorphisms in SS and SD patients

To confirm the association with standard steroid therapy response, the genotype and allele frequencies of *SOD1* and *SOD2* in SS patients and SD patients are shown in Figure 2. No significant differences were observed in the distribution of these haplotypes between initial SS and SD patients, including *SOD1*-rs4816407 (alleles: p = 0.196, OR = 1.595, 95% CI = [0.982 - 2.589]; genotypes: p = 0.407), *SOD2*-rs4880 (alleles: p = 0.541, OR = 1.124, 95% CI = [0.552 - 2.287]; genotypes: p = 0.814), *SOD2*-rs2758346 (alleles: p = 0.464, OR = 1.219, 95% CI = [0.559 - 2.657]; genotypes: p = 0.740), and *SOD2*-rs3798215 (alleles: p = 0.160, OR = 1.424, 95% CI = [0.868 - 2.336]; genotypes: p = 0.062). However, we found that the SNP frequency distributions of rs1041740 (*SOD1*) differed significantly between INS children with SD and those with SS. Specifically, INS patients carrying the CC genotype of rs1041740 had a greater risk of developing SD (54.2% of those with SD vs. 34.5% of those with SS, p = 0.002, OR = 2.247, 95% CI = [1.191 - 4.239]).

Gene polymorphisms in SS and SR patients

The genotype and allele frequencies of *SOD1* and *SOD2* in SS and SR groups among INS patients are shown in Figure 3. No significant differences were observed in the distribution of these haplotypes (rs4816407, rs1041740, rs4880, rs2758346, and rs3798215) between the SS and SR groups.

Table 1. Primers for multi-PCR.

Gene	SNP	Forward primer	Reverse primer
SOD1	rs4816407	CACTTGTTAAACAGAACATTTTGTTAAG	GTGACTACTGAATGTTAATGCCCTC
	rs1041740	CACTTGTTAAACAGAACATTTTGTTAAG	GTGACTACTGAATGTTAATGCCCTC
SOD2	rs4880	TCCTGGTACTTCTCCTCGG	GCTGTGCTTTCTCGTCTTC
	rs2758346	AAAGAATATGATGGAAGGTAGCAG	TAGCCCTAGTTACATTCTTCTGAC
	rs3798215	CTGGGACTCACTTACAAATATCAG	CCTGACATTGGAATACTCTTGATC

Table 2. Pairwise linkage disequilibrium (LD) among five SNPs.

SNP	rs4816407	rs1041740	rs4880	rs2758346	rs3798215
rs4816407	rs4816407	1.000	0.229	0.230	0.057
rs1041740	0.501	rs1041740	0.266	0.287	0.047
rs4880	0.006	0.017	rs4880	1.000	0.660
rs2758346	0.006	0.020	1.000	rs2758346	0.651
rs3798215	0.003	0.001	0.046	0.045	rs3798

Upper triangle: D' values, lower triangle: r^2 values, diagonal: SNP names. Values are rounded to three decimal places.

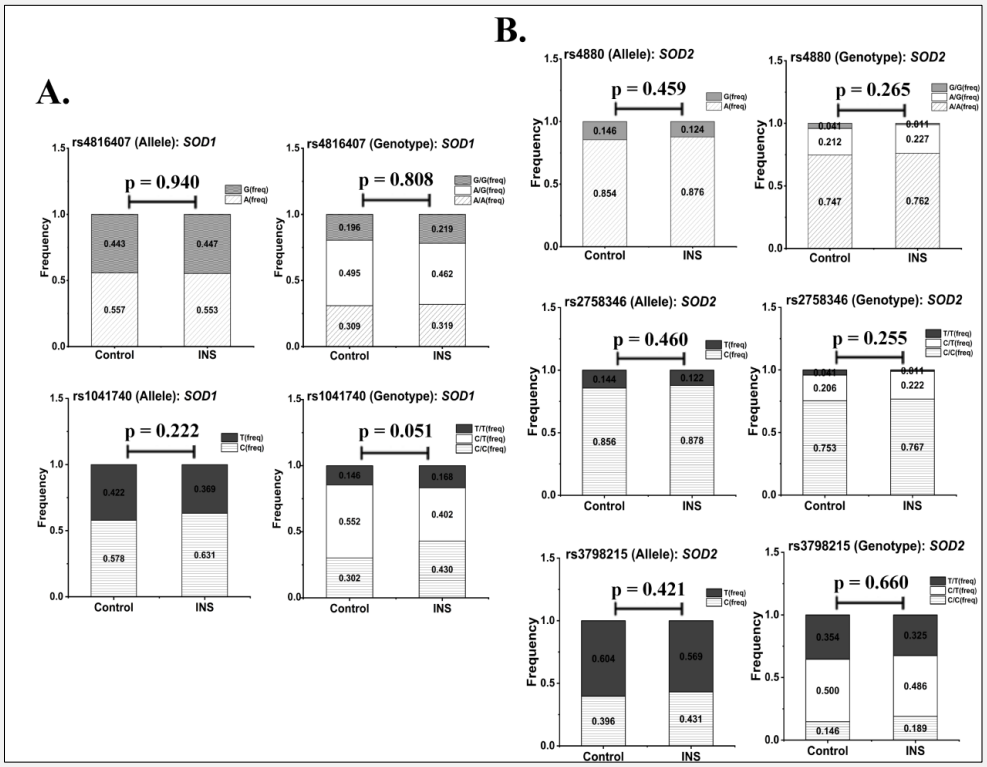

Figure 1. The genotype and allele frequencies of *SOD1* (A) and *SOD 2* (B) in idiopathic nephrotic syndrome (INS) patients and healthy controls.

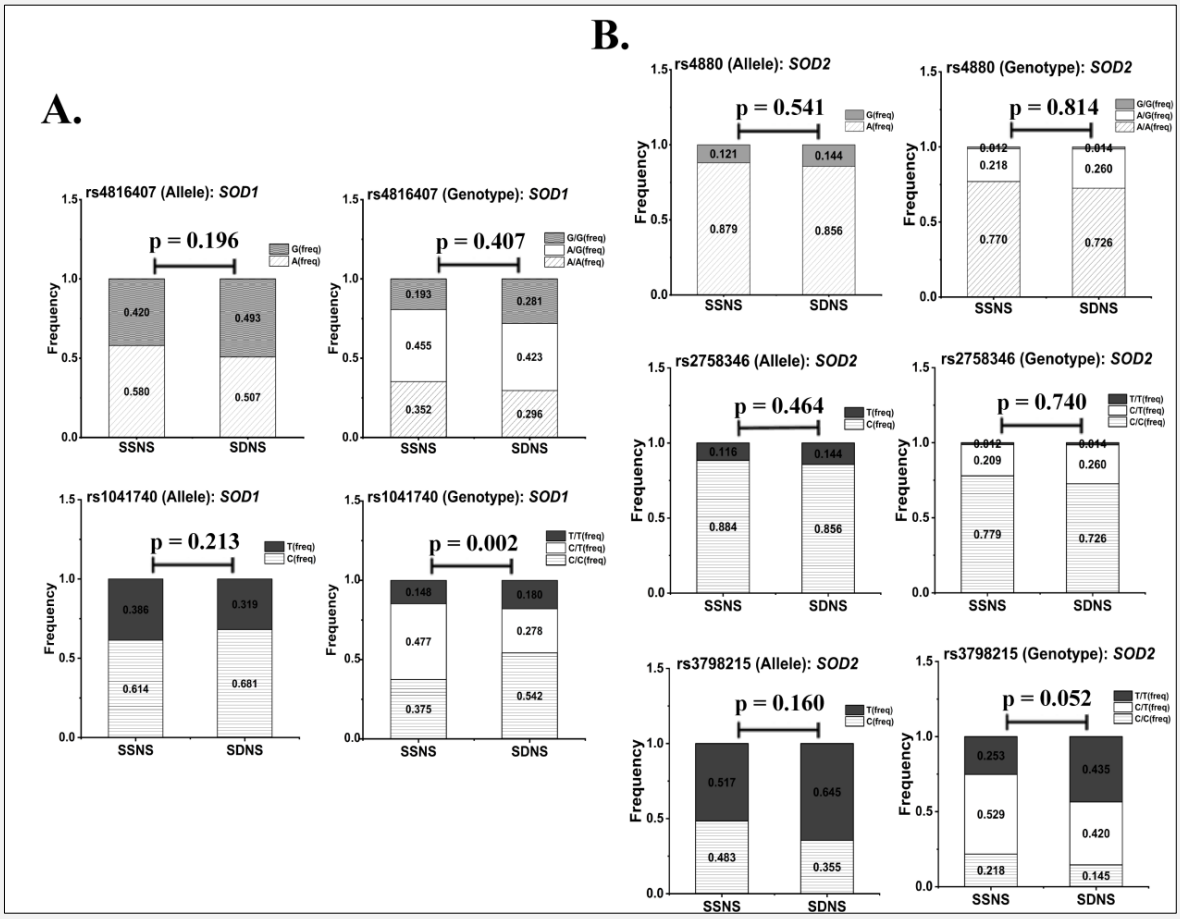

Figure 2. The genotype and allele frequencies of *SOD1* (A) and *SOD2* (B) in steroid-sensitive nephrotic syndrome (SSNS) and steroid-dependent nephrotic syndrome (SDNS).

Linkage disequilibrium analysis for the five SNPs in SOD1 and SOD2

Linkage disequilibrium (LD) analysis was performed among the five SNPs (rs4816407, rs1041740, rs4880, rs2758346, and rs3798215) using the D' and r^2 statistic, which are presented in Table 2. Strong LD (D' = 1.000) was observed between rs4816407 and rs1041740, as well as between rs4880 and rs2758346. Moderate LD was detected between rs4880 and rs3798215 (D' = 0.660) and between rs2758346 and rs3798215 (D' = 0.650). In contrast, weak or negligible LD was found among the remaining SNP pairs. However, only rs4880 and rs2758346 showed perfect correlation (r^2 = 1.000). A moderate correlation (r^2 = 0.501) was observed between rs4816407 and rs1041740. All other pairwise $r^2 \leq$ 0.046, indicating very weak or no allelic association. The perfect LD between rs4880 and rs2758346 (D' = r^2 = 1) suggests these two markers are either the same variant or are in completely linked genomic regions.

DISCUSSION

Oxidative stress (OS) refers to a state of imbalance between oxidation and antioxidation in the body, which tends to cause oxidative damage, increasing the secretion of proteases and the production of many oxidative intermediates and associated reactive oxygen species (ROS) [27]. When ROS and antioxidants are imbalanced, the body destroys mesangial cells by altering lipid metabolism, which is often observed in patients with nephrotic syndrome and glomerulonephritis [28]. *SOD* is an antioxidant metalloenzyme against ROS that plays an important role in maintaining the balance of oxidation and antioxidation in the body and is closely related to the occurrence and development of many diseases. Owing to the different metal cofactors in *SOD*, the superoxide dismutase family mainly consists of three members: *CuZn-SOD* (*SOD1)*, *Mn-SOD* (*SOD2*), and *EC-SOD* (*SOD3*) [17]. Sawant et al. reported that

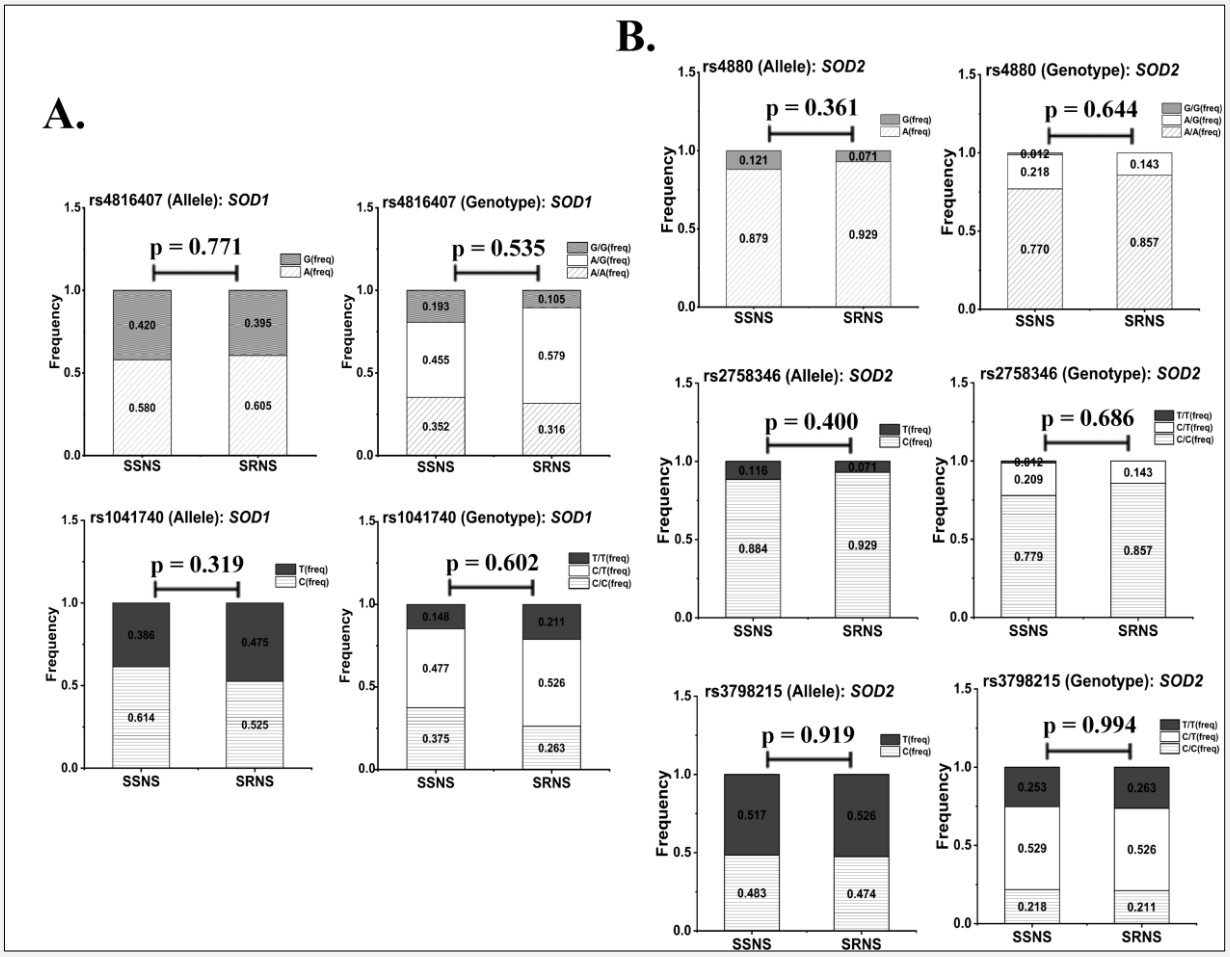

Figure 3. The genotype and allele frequencies of *SOD1* (A) and *SOD2* (B) in steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS).

SOD levels were obviously decreased in INS children [29]. INS can be caused by genetic defects in the kidney, and several genes, including *NPHS1*, *NPHS2*, *WT1*, *PLCE1,* and *LAMB2*, have been studied [19,20]. Genetic mutation is also closely related to the steroid response of INS. With the development of whole-exon sequencing (WES) technology, 10% - 30% of children with SRNS are now diagnosed with single-gene diseases [21]. *NPHS1*, *NPHS2,* and *WT1* mutations were the most common pathogenic genes in European SRNS patients, accounting for 42%, 16%, and 13%, respectively [30]. Panduru reported that a polymorphism in the *SOD1* gene was related to advanced stages of diabetic nephropathy in patients with type 1 diabetes [31]. In our study, no significant differences in the genotype or allele frequencies of *SOD1* and *SOD2* polymorphisms (rs4816407, rs1041740, rs4880, rs2758346, and rs3798215) were found between the control and INS groups with respect to INS incidence ($p > 0.05$). In further research, we will include more SNPs for the study of idiopathic nephrotic syndrome.

SOD is also involved in the response to INS steroid treatment, and a previous study reported that lower *SOD* levels were found in SSNS children [32]. To confirm whether the variations in *SOD1* and *SOD2* were involved in the response to steroid treatment, we first compared the SS and SD groups. Notably, we found that the rs1041740 polymorphism of *SOD1* had prominent effects on the risk of SD. INS patients carrying the CC genotype of rs1041740 had a greater risk of developing SD. Mohammedi et al. reported that the T allele of rs1041740 was associated with the incidence of incipient and advanced diabetic nephropathy [33]. Rs1041740 is also related to chronic kidney disease

(CKD) incidence [34]. In this study, we did not find any significant difference in the frequency of the 5 SNPs between the SS group and the SR group, implying that *SOD* polymorphisms might not confer the risk of SRNS. Nevertheless, this may be due to the small sample size of the SR group (n = 21). Further research is urgently needed to increase the sample size of SR patients.

This study also evaluated linkage disequilibrium patterns among five SNPs (rs4816407, rs1041740, rs4880, rs2758346, rs3798215) using two complementary metrics: D', which reflects historical recombination, and r^2, which measures the practical predictability between alleles. The perfect LD between rs4880 and rs2758346 ($D' = r^2 = 1$) suggests these two markers are either the same variant or are in completely linked genomic regions. They are statistically redundant and only one needs to be included in downstream analyses. What is worth mentioning is that although rs4816407 and rs1041740 share the same primer and exhibited complete linkage disequilibrium (D' = 1.000), their r^2 value was only 0.501, reflecting divergent minor allele frequencies. This pattern indicates that while no recombination has occurred between these loci, their alleles are not highly correlated, limiting their utility as mutual proxies in association analyses.

However, several limitations of this study should be acknowledged. First, the study was conducted at a single center, and all samples were recruited from the Children's Hospital, Zhejiang University School of Medicine, which may limit the generalizability of our findings to other populations or healthcare settings. Second, a major limitation is the small size of the SR group (n = 21). Our post-hoc power analysis shows that only genetic effects with OR ≥ 3.4 - 5.1 could be reliably detected. Smaller effects may have been missed. Thus, independent replication in larger cohorts is essential to validate our observations. Third, we did not include an independent replication cohort, therefore, the reported associations should be considered exploratory and require validation in external datasets. Fourth, although we attempted to adjust for relevant clinical covariates, potential confounding by treatment heterogeneity cannot be completely excluded, including differences in medication, dosage, or duration of therapy among participants. In the future, we will increase the sample size, conduct multi-center and multi-ethnic clinical studies, and conduct in-depth replication experiments and functional validations to make the results more convincing.

CONCLUSION

In conclusion, our data suggest that genetic variations in the *SOD* gene family are unlikely to confer susceptibility to the development of INS in Chinese children. However, specific SNPs, *SOD1* rs1041740, may be associated with an increased risk of a steroid-dependent response in pediatric INS patients. This study reveals the potential value of *SOD* gene-specific SNP dependence on child INS steroids. In the future, larger multiracial and multicenter studies are needed to elucidate the clinical implications of *SOD* polymorphisms in INS children. Prospective work should also be carried out to explore how *SOD* gene-related alterations affect expression levels and protein function.

Declaration of Generative AI in Scientific Writing

The authors declare that no generative artificial intelligence (AI) tools or software were used in any part of the preparation, writing, revision, or editing of this manuscript.

Ethical Approval Statement

The Medical Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine approved the study (2020-IRB-057).

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Data Availability Statement

The raw genotype and clinical data generated and analyzed in this study are not publicly available due to ethical restrictions and patient privacy protection. However, de-identified datasets are available from the corresponding author upon reasonable request and with institutional approval.

Declaration of Interest:

The authors declare that they have no conflicts of interest to report regarding the present study.

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