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Relationship Between FKBP5 Polymorphisms at Rs1334894, Rs9394309, and Rs6912833 Loci, and Dyslipidemia in Pediatric Nephrotic Syndrome

Shuting Peng, Fang Yang*, Zhiqiang Guo, Ding Liu

Department of Pediatrics, First Affiliated Hospital of Jinan University, Guangzhou, China

Email address:

935899643@qq.com (Shuting Peng), tyf@jnu.edu.cn (Fang Yang)

*Corresponding author

Abstract: Background: This study aimed to investigate the relationship between rs1334894, rs9394309, and rs6912833 polymorphisms in *FKBP5* and hyperlipidemia in nephrotic syndrome (NS). Methods: The case group included 74 children with primary NS, while the control group included 76 healthy children. Polymerase chain reaction and gene sequencing were used to detect polymorphisms at the rs1334894, rs9394309, and rs6912833 loci of *FKBP5*, in children with NS. Clinical data of total cholesterol (CHOL), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and plasma albumin were collected. Correlations between *FKBP5* polymorphisms and serum lipid levels were analyzed during the active period of the disease. Results: A significant difference in LDL levels between the AA and TA genotypes was observed at the rs6912833 locus of *FKBP5* in the case group, but no statistical difference in CHOL, TG, and HDL levels between these genotypes was found. No statistically significant differences in LDL levels between the AA and TA genotypes, and among the steroid-sensitive, -dependent, and -resistant groups were noted. Moreover, no statistically significant differences in the CHOL, TG, HDL, and LDL levels were observed between TT and TC genotypes at the rs1334894 locus. Conclusion: The AA genotype at the rs6912833 locus of *FKBP5* may be correlated with plasma lipid levels (LDL) in PNS patients.

Keywords: Primary Nephrotic Syndrome, *FKBP5*, Dyslipidemia, Gene Polymorphism

1. Introduction

Primary Nephrotic Syndrome (PNS) is a clinical syndrome characterized by various pathophysiological changes, resulting from increased permeability of the glomerular filtration membrane to plasma proteins, leading to the loss of large amounts of plasma proteins from the urine. PNS is a common pediatric glomerular disease clinically characterized by proteinuria, hypoalbuminemia, edema, and hyperlipidemia.

Hyperlipidemia has attracted increased attention over the years, it is an important pathophysiological feature of NS. The lipid metabolism disorder in patients leads to the increase of the incidence of cardiovascular events and the aggravation of renal function damage, mainly because the increase of lipid is not only involved in the occurrence of atherosclerosis but also leads to the accumulation of glomerular lipids and aggravation of glomerular sclerosis [1-3]. Ninomiya T followed up 1,440 Japanese without CKD for 5 years, in this study they found that metabolic syndrome including high triglyceride levels and low HDL cholesterol levels is a risk factor for the development of chronic kidney disease CKD [4]. A previous study of 4,483 healthy males has suggested that dyslipidemia are associated with a risk of renal dysfunction [5]. Therefore, research on the mechanism underlying dyslipidemia is of considerable significance to prevent renal damage and delay renal failure in children.

At present, the lipid metabolism in NS is reported to be caused by the extensive loss of urinary protein and the decrease of plasma albumin [6-8]. But it's still not fully recognized. This study examined the genetics of lipid metabolism in children with NS. A previous report by Maria J [9] suggests that FKBP5 polymorphisms correlate with

lipid metabolism in type 2 diabetes. They investigated the relationship between lipid levels in diabetes and FKBP5 polymorphisms at the rs1334894, rs9394309, rs6912833 loci, revealing that polymorphisms at these loci are related to respectively high-density lipoprotein (HDL) and triglyceride (TG) levels in type 2 diabetes. This study investigated the FKBP5 polymorphism to reveal whether it regulates the lipid levels in NS by affecting the expression of FK506 binding protein 51 (FKBP51).

2. Materials and Methods

2.1. Selection and Description of Participants

2.1.1. Case Group Inclusion Criteria

The inclusion criteria were as follows [10-12]: i) Age < 18 years; ii) diagnosis of NS, 24 h urine protein $\geq$ 50 mg/(kg·d) or urine protein/creatinine ratio $\geq$ 2.0, plasma albumin $\leq$ 25 g/L; iii) exclusion criteria, secondary and congenital NS; iv) control group, 76 healthy children.

2.1.2. Classification Criteria for NS

The classification criteria were as follows [11-12]: i) steroid-sensitive NS, a sufficient dose of steroid treatment achieves complete remission four weeks after treatment initiation; ii) steroid-resistant NS, a sufficient dose of steroid treatment fails to achieve complete remission four weeks after treatment initiation; iii) steroid-dependent NS, steroid treatment cannot be discontinued due to repeated relapse (> 2 times) after reduction or discontinuation of treatment.

2.1.3. General Subject Information

The case group consisted of 74 children (53 males and 21 females) who met the PNS diagnostic criteria from December 2009 to September 2016; the age of onset was 4.53 ± 3.08 years. A total of 45, 13, and 16 patients were classified into the steroid-sensitive, -dependent, and -resistant groups, respectively. Ten cases of renal biopsy were recorded, of which four, two, one, and three showed minimal change nephropathy, membranous nephropathy, mesangial proliferative nephritis, and focal segmental glomerulosclerosis, respectively. As a control, 76 outpatients (43 males and 33 females), with healthy physical examinations and age of 4.55 ± 3.67 years, were recruited for genetic testing.

2.2. Experimental Methods

2.2.1. Blood Samples and DNA Extraction

Exactly 2 mL of venous blood was drawn from each child and shaken in vacuum blood collection tubes containing EDTA. Samples were centrifuged at 3000 rpm in a high-speed refrigerated centrifuge, at 4°C for 15 min, to separate the plasma. Next, the separated blood sample was added to an equal volume of physiological saline (1 mL) and stored at −80°C.

2.2.2. Genotype Identification Using Polymerase Chain Reaction (PCR)

Primer design and synthesis were performed by Shanghai

Shenggong Bioengineering Co., Ltd. (Shanghai, China). The following primers were used: i) rs1334894, F-CCTTCGGTCTGACCTCATCTG, R-TGACTCTGAGTGCTGAGTTGG; ii) rs9394309, F-AGGAACTGTGGTTGTTTGCTG; R-TGGCCCTGATGGATAGTGGA; iii) rs6912833, F-CTAACATTCCCATGACCATCCTT; R-AAGCAGTGGGGATTCTCTGAA. The 50μL PCR master mix consisted of the following (Takara Biotech, Dalian, China): 1 μL of both forward and reverse primers, 2 μL of DNA template (each of the three loci and the DNA template), 0.25 μL of TaKaRa Taq, 5 μL of 10× PCR buffer, 4 μL dNTP mixture, and 36.75 μL of ddH2O. The PCR reaction conditions were as follows: i) rs1334894, pre-denaturation at 94°C for 5 min, denaturation at 94°C for 30 s, annealing at 60°C for 40 s, extension at 72°C for 50 s, for 35 cycles, final extension at 72°C for 7 min; ii) rs9394309, pre-denaturation at 94°C for 5 min, denaturation at 94°C for 30 s, annealing at 59°C for 30 s, extension at 72°C for 30 s, for 35 cycles, final extension at 72°C for 7 min; iii) rs6912833, pre-denaturation at 94°C for 5 min, denaturation at 94°C for 30 s, annealing at 58°C for 40 s, extension at 72°C for 50 s, for 35 cycles, final extension at 72°C for 7 min.

2.3. Agarose Gel Electrophoresis

Exactly 1.5 g of agarose was weighed into a beaker and mixed with 100 mL of 0.5× TBE solution. The mixture was placed in a microwave oven for approximately 3 min to boil. After cooling for 1 min, 5 μL of EB substitute dye was added to the beaker. The mixture was shaken well and poured into a horizontal rubber plate. After cooling 24°C for 30 min, the gel was removed and placed in an electrophoresis tank containing 0.5× TBE solution. Exactly 5 μL of the PCR product was thoroughly mixed with 2 μL of 6× loading buffer, and loaded into the wells on the gel plate. A voltage of 145 V was applied for 15 min, and the results of the gel imaging system were observed and photographed.

2.4. Gene Sequencing

PCR products with the desired bands were sent to the Shanghai Yingjie Jieji Company (Shanghai, China) for sequencing, using the BigDyeTM Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher).

2.5. Clinical Indicators

Cholesterol (CHOL), triglycerides (TG), HDL, low-density lipoprotein (LDL) and plasma albumin were collected from the case group.

2.6. Statistics

SPSS 17.0 statistical software was used to analyze the experimental data. An independent-sample t-test with a completely random design was used to compare differences in blood lipid and plasma albumin levels among different groups. Correlations between plasma albumin and blood lipid levels in the case group were analyzed using linear regression.

The distributions of rs1334894, rs9394309 and rs6912833 loci, in the case and control groups, as well as among children with different hormonal effects, were analyzed using Fisher's exact test. Differences were considered statistically significant at P<0.05.

3. Results

3.1. The PCR Amplicon

It is shown in Figures 1-3 that the PCR amplicon of 399bp for the rs6912833 locus; The PCR amplicon of 366bp for the rs1334894 locus; The PCR amplicon of 300bp for the rs9394309 locus.
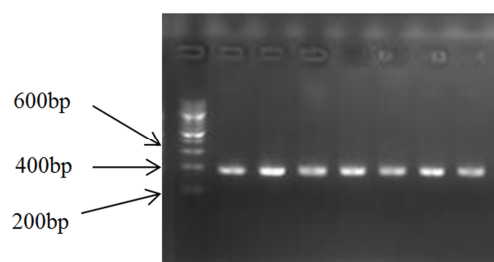

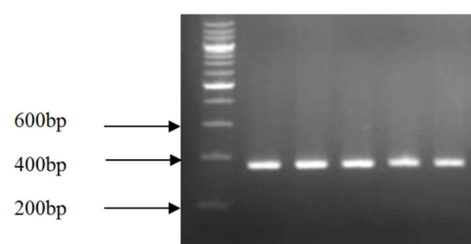**Figure 1.** *Amplified fragment measuring 399 bp in length.*

Figure 2. *Amplified fragment measuring 366 bp in length.*
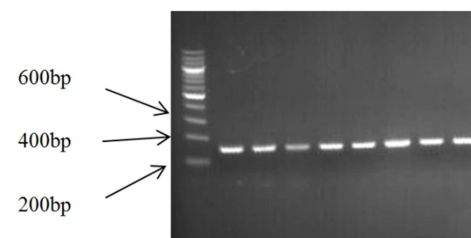

Figure 3. *Amplified fragment measuring 300 bp in length.*

3.2. Statistics and Analysis of Data

3.2.1. The Basic Characteristics

The analysis of the basic characteristics of the case group and the control group are presented in Table 1. Age and gender distribution in the study sample were similar in the case group and control group (P > 0.05).

Table 1. *Age and gender distribution in the study samples.*

	N	Case group	N	Control group	p
Age (years)	74	4.53 ± 3.08	76	4.55 ± 3.67	0.961
Gender (male/female)	74	53/21	76	43/33	0.055

3.2.2. Frequencies of the Genotypes at the rs1334894, rs9394309, rs6912833 Locus

The frequencies of the GG, AA, and GA genotypes at the rs1334894 locus in the case groups, were 86.5%, 12.2% and 1.3%; in the control groups, were 86.8%, 13.2%, and 0%, respectively. The frequencies of the TT, CC, and TC genotypes at the rs9394309 locus in the case groups were 55.4%, 4.1% and 40.5%; in the control groups, were 61.8%, 4.0% and 34.2%, respectively. The frequencies of the AA, TA,

and TT genotypes at the rs6912833 locus in the case groups were 54.1%, 41.9% and 4%; in the control groups, were 60.5%, 35.5% and 4%, respectively. No significant differences in the distributions of the GG, AA, and GA genotypes at the rs1334894 locus; the TT, CC, and TC genotypes at the rs9394309 locus; and the AA, TA, and TT genotypes at the rs6912833 locus of FKBP5 were observed between the case and control groups (P > 0.05; Table 2).

Table 2. *Analysis of FKBP5 polymorphisms between the case and control groups.*

	Case group (n=74)			Control group (n=76)			P
rs1334894							
Genotype	GG	GA	AA	GG	GA	AA	0.90
Number	64	9	1	66	10	0	
rs9394309							
Genotype	TT	TC	CC	TT	TC	CC	0.81
Number	41	30	3	47	26	3	
rs6912833							
Genotype	AA	AT	TT	AA	AT	TT	0.81
Number	40	31	3	46	27	3	

3.2.3. Relationships Between FKBP5 Polymorphisms and Blood Lipids

As the number of cases of the TT, CC, and AA genotypes at

the rs9394309, rs1334894, and rs6912833 loci, respectively, were deficient (i.e., three, one, and three cases, respectively), comparing variances with a completely random design was not possible. Differences in blood lipid levels among these

three genotypes were identified, and accordingly, these three genotypes were excluded from the statistical analyses.

No significant differences in CHOL, TG, HDL, and LDL levels were observed between the GG and GA genotypes at the rs1334894 locus (all P>0.05). Furthermore, no significant differences in CHOL, TG, HDL, and LDL levels were observed between the TT and TC genotypes at the rs9394309 locus (all P>0.05). In the case group, differences in LDL levels between the AA and TA genotypes, at the rs6912833 locus of FKBP5, were statistically significant (P<0.05), with AA showing higher levels of LDL than TA. No significant differences in CHOL, TG, and HDL levels were observed between these two genotypes (both P > 0.05; Table 3).

Table 3. *Analysis of relationships between FKBP5 polymorphisms and blood lipids in nephrotic syndrome.*

	Genotype	CHOL (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
rs1334894	GG (n = 64)	10.40 ± 3.75	3.39 ± 2.47	1.82 ± 0.67	4.92 ± 2.55
	AG (n = 9)	9.78 ± 1.88	3.53 ± 1.36	1.79 ± 0.49	4.47 ± 2.69
	T	0.49	0.17	0.13	0.50
	P	0.63	0.87	0.90	0.62
rs9394309	CT (n = 41)	9.67 ± 2.73	2.93 ± 1.66	1.87 ± 0.79	4.26 ± 2.17
	TT (n = 30)	10.75 ± 3.93	3.85 ± 2.72	1.76 ± 0.53	5.35 ± 2.77
	T	1.29	1.75	-0.686	1.80
	P	0.20	0.08	0.49	0.08
rs6912833	AA (n = 40)	10.82 ± 3.96	3.68 ± 2.53	1.75 ± 0.53	5.43 ± 2.75
	TA (n = 31)	9.62 ±2.70	3.18 ± 2.13	1.87 ± 0.78	4.18 ± 2.17
	T	1.45	0.88	0.77	2.09
	P	0.15	0.38	0.45	0.04

3.2.4. Analysis of FKBP5 Polymorphisms at rs6912833 Locus in Different Steroid Effect Groups

The albumin levels in children with NS, harboring AA or AT genotype at the rs6912833 locus, were 18.39±7.8 g/L and 17.43±6.7 g/L, respectively. No significant difference in albumin levels between the case and control groups was found (t = 0.55, P = 0.59 > 0.05).

Table 4. *Distribution of AA, TT, and AT genotypes at the rs6912833 locus of children with NS, with different hormonal effects.*

Group	Genotype			Sum
	AA	TT	AT	n
Steroid-sensitive	27	1	17	45
Steroid-dependent	6	1	6	13
Steroid-resistant	7	1	8	16
Control group	46	3	27	76

Annotation: P = 0.61

For the case group at the rs6912833 locus, the AA, TA, and TT genotypes in the steroid-sensitive group totaled 27, 17, and one, respectively; the AA, TA, and TT genotypes in the steroid-dependent group totaled six, six, and one, respectively; the AA, TA, and TT genotypes in the steroid-resistant group totaled seven, eight and one, respectively. In the control group, the AA, TA, and TT genotypes were observed in 46, 27, and three cases, respectively. No significant difference in the genotypes at the rs6912833 locus was observed among the steroid-sensitive, -dependent, -resistant, and control groups (P > 0.05; Table 4).

Blood lipid levels in children with AA and AT genotypes at the rs6912833 locus in the steroid-sensitive, -dependent and -resistant groups all showed P > 0.05. For the case group, at the rs6912833 locus, the AA and AT genotypes in the steroid-sensitive group totaled 27 and 17, respectively; the AA and AT genotypes in the steroid-dependent group totaled 6 each, and the AA and AT genotypes in the steroid-resistant group totaled 7 and 8, respectively. No significant differences in lipid levels between the AA and AT genotypes, at the rs6912833 locus of the three groups, were observed (P > 0.05; Table 5).

Table 5. *Blood lipids in the AA and AT genotypes at the rs6912833 locus in different steroid effect groups.*

(mmol/L)	Steroid-sensitive		Steroid-dependent		Steroid-resistant	
	AA (n=27)	AT (n=17)	AA (n=6)	AT (n=6)	AA (n=7)	AT (n=8)
CHOL	10.1 ± 3.6	8.6 ± 2.4	10.4 ± 1.3	11.8 ± 2.5	14.1 ± 5.1	10.1 ± 2.4
TG	3.8 ± 2.6	2.7 ± 1.1	2.1 ± 1.2	2.5 ± 1.1	4.5 ± 2.4	4.6 ± 3.5
HDL	1.8 ± 0.6	1.7 ± 0.5	1.6 ± 0.3	2.5 ± 1.3	1.6 ± 0.5	1.7 ± 0.7
LDL	5.0 ± 2.7	3.6 ± 2.0	6.1 ± 2.8	5.4 ± 1.8	6.5 ± 2.5	4.5 ± 2.5

4. Discussion

In the present study, rs1334894, rs9394309, and rs6912833 polymorphisms in the FKBP5 were compared between case and control groups, and no statistically significant differences in genotype distribution at the three loci were identified. These polymorphisms have not been previously correlated with NS pathogenesis, which, at present, remains unclear. The leading causes of NS are considered as follows: Changes in the structure or charge of the glomerular capillary wall, damage to the filtration membrane caused by immune complex deposition, and immune dysfunction, especially T lymphocyte abnormalities.

Maria J [9] assessed whether polymorphisms in FKBP5 might contribute to the susceptibility to develop type 2

diabetes or other diabetes-related phenotypes by analyzing data from publically available genome-wide association study databases. They found that rs6912833 polymorphisms are associated with triglyceride levels. Our study also compared CHOL, TG, HDL, and LDL levels of different genotypes at the three loci, in the case group. Our results demonstrated that LDL levels in children with PNS, carrying the AA genotype at rs6912833, were higher than those in children carrying the AT genotype.

The common dyslipidemias in NS are hypercholesterolemia, high levels of LDL-c and very low-density lipoprotein-cholesterol (VLDL-C). Hypercholesterolemia in NS is primarily due to impaired clearance and catabolism of LDL and its principal apoprotein, apoB100 [13-14]. Therefore, we think that this is the likely reason why the polymorphism at site 6912833 was associated with LDL, but not with TG. According to Tobey TA 's study [15], TG levels are increased in the context of insulin resistance. Triglycerides induce central leptin and insulin receptor resistance, decreasing satiety and cognition [16]. Also Yann C Klimentidis showed that TG-associated SNPs with TG levels are related to level of insulin resistance [17]. so the polymorphisms in FKBP5 could be related to the susceptibility to develop insulin resistance and dyslipidemia in type 2 diabetes; however, we investigated the polymorphism of FKBP5 to reveal whether it regulates the lipid levels in NS by affecting the expression of FKBP51.

FKBP51, encoded by FKBP5, was first discovered by J. Siiekierka [18]. It contains 457 amino acids, with one TPR (TPR1, TPR2, and TPR3) and two FKBD (FK1 and FK2) domains [19], and is highly expressed in many human tissues, including the kidney, liver, muscle, and heart. Research into FKBP51 and fat metabolism is gradually increasing, with many studies reporting FKBP51 involvement in both fat synthesis and metabolism. Furthermore, it has been identified as an essential regulator of preadipocyte differentiation and transformation into mature adipocytes. Toneatto J [20] showed that low expression of FKBP51 promotes fat formation, while high expression of FKBP51 prevents fat formation. Another study found that high expression of FKBP51 in the hypothalamus of mice inhibits the action of the glucocorticoid receptor (GR) and promotes the increase of fat production, leading to obesity in the absence of increased food intake [21]. Stechschulte's [22] study also revealed that the formation of fat requires the participation of FKBP51, FKBP51 as a fat cell differentiation marker in the process of adipocyte differentiation into mature fat cells. They also reported that high expression of FKBP51 was induced in 3T3-L1 cells, and the 3T3-L1 cells missing FKBP51, the accumulation of lipid is lower, and lack of FKBP51 causes almost no accumulation of lipid in mice. Domestic research by Man Zhang suggested that mice with FKBP51 knockout resist obesity induced by high fat. There was less accumulation of lipid droplets in the liver of the mice. In addition, FKBP51 knockout causes impaired fat differentiation in MEF cells [23].

The N-terminal FK1 of the FKBP51 protein has peptidylprolyl cis-trans isomerase activity; it is an immunophilin that participates in the formation of GR complexes with the co-chaperone, Hsp90 [24-25]. FKBP51 can retain GR in the cytoplasm by regulating its function through the TPR domain and co-chaperone Hsp90 [26], thereby inhibiting its transcriptional activity and eventually inactivating the protein. After glucocorticoid binds to the complex, the structure of the complex changes and its binding affinity for FKBP51 decreases, to be replaced by the high binding affinity for FKBP52. Westberry [27] showed that FKBP51 overexpression affects the binding of hormone receptors, reduces the binding rate of hormones, and leads to GR insensitivity. FKBP51 has been reported as an essential regulator of GRα and PPAR-γ, which controls the cellular physiological process of lipid metabolism in adipocytes [22]. The FKBP51 protein regulates lipid synthesis by regulating the Akt-p38 pathway and activating PPAR-γ, while inhibiting GRα [28-29]. As a chaperone or scaffold protein of the Akt-specific phosphatase, PHLPP, KBP51 promotes dephosphorylation of Akt, downregulates Akt signaling pathway, and inhibits the activation of p38 kinase [30-32]. p38-MAPK enhances the phosphorylation of GR at S220 and S234, inhibits the phosphorylation of PPAR-γ in S112 [33], and regulates GRα and PPAR-γ. Therefore, it is thought that the AA genotype, at rs6912833 of FKBP5, affects the sensitivity of GR to GC by regulating FKBP51 expression, and thus, it affects LDL levels in children with NS, especially those with steroid-resistant NS.

In this study, the distributions of AA, TT, and TA genotypes at the rs6912833 locus of FKBP5 were compared in children with PNS, with different steroid effects; no differences in the distributions of these genotypes were found. Blood lipid levels in children carrying the AA or TA genotype at this locus with different steroid effects were also compared. No significant differences in the levels of CHOL, TG, HDL, and LDL between the AA and TA genotypes were observed among the steroid-sensitive, -dependent, or -resistant groups. Thus, we could not confirm whether the AA genotype at rs6912833 affected the sensitivity of GR to GC through the regulation of FKBP51 expression, thereby affecting LDL levels in children with NS. Aouadi [28, 29] showed that FKBP51 is mainly involved in lipid regulation by affecting nuclear receptors PPAR-γ and GRα. Van Wijk [34] found that PPAR-γ agonists can increase LDL levels. Whether rs6912833 in FKBP5 regulates PPAR-γ through FKBP51, to affect dyslipidemia in NS, requires further study. At the same time, we also need to expand the sample size.

5. Conclusion

This study examined the genetics of lipid metabolism in children with NS. A previous report [9] suggests that FKBP5 polymorphisms correlate with lipid metabolism. Our research confirms that The AA genotype at the rs6912833 locus of FKBP5 may be correlated with plasma lipid levels (LDL) in PNS patients. In our study, the specific mechanism is still unclear, and we need to collect more cases and improve

follow-up experiments.

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