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NPHS1 Gene Mutations in Children with Focal Segmental Glomerulosclerosis

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Abstract

Objective: To summarize the clinical data of NPHSI gene mutation in a case of a child with focal segmental glomerulosclerosis (FSGS), to improve the understanding of NPHS1 mutation phenotype, to study the relationship between NPHSI gene mutation and FSGS.

Method: Medical history, laboratory examination results and family history of a child with FSGS were collected. Exon detection (NGS) was applied to perform a full-exon high-throughout sequencing on the child and her parents. Meanwhile, bioinformatics analysis was carried out. Sanger sequencing was used to verify the results of high-throughout sequencing, and relevant literature review was conducted.

Result: The proband: female, 7 years old, onset on her age of six, developed nephrotic syndrome, result did not turn to be negative when Glucocorticoid uroprotein was applied, renal pathology indicates FSGS. Family survey revealed that the father suffered nephrotic syndrome with a pathological diagnosis of membranous nephropathy. Sequencing found that the missense mutations of NPHS1 gene c.803G>A(carried by her father),c.1339G>A and c. 1802G>C (carried by her mother)were found in the child. The c.1339G>A, c.1802G>C, which were predicted by Mutationtaster software as harmful mutations, and c.803G>A mutation as polymorphism. The c.1339G>A and c. 1802G>C, which have to be proven as a pathogenic mutation carried by mother on NPHS1, while c.803G>A have not been reported at present.

Conclusion: NPHS1 mutation can cause nephritic syndrome with FSGS in children. Mutation c.803G>A is probably the newly discovered and further enrich the NPHS1 gene spectrum.

Keywords: Focal segmental glomerulosclerosis; NPHS1 gene mutation; Child

Case Presentation

Female child,7 years old, was admitted to our hospital on July 4th, 2017 in the name of "*nephrotic syndrome*" due to "*a continuously progressing facial edema 2 days ago ,and low urine output for half day*."

Double eyelid swelling was present 2 days ago with no obvious causes. No fever, cough, vomiting, diarrhea, or rash was observed. No special treatment was given. Edema aggravated half a day ago, with reduced urine output. There was foam and no color change observed in urine. No convulsion was observed. Urinalysis in former hospital showed protein 3+, no urine red cell, and normal blood routine test results. The patient was admitted to our hospital for further diagnosis and treatment. The urine routine reexamination indicated protein 4+, BLD 1+, urine red cell negative. Then she was received by in the name of "*nephritic syndrome*".

The child has a healthy medical history, first only and mature born, with neither birth injury nor history of asphyxia, and grew and developed in line with peers. The father of the child has an unclear history of kidney disease and the mother remained healthy.

Physical examination

Blood pressure was 93/58 mmHg; weight was 19.5 kg; general normal physical condition. Facial region and both eyelids experienced edema; abdomen was in flat; shifting dullness turned to be negative; no edema on both lower limbs; cardiopulmonary examination did not reveal obvious change.

Laboratory examination

Biochemistry analysis: albumin 15.7 g/L, total cholesterol 6.85 mmol/L, blood urea nitrogen 14.64 mmol/L, creatinine 65.6 μmol/L; antinuclear antibody was negative; ENA pattern was negative; complement C30.76 g/L; antistreptolysin test was negative; no obvious abnormal was observed in ultrasound clinics. Enough methylprednisolone pulse treatment was given and repeated urinalysis

reexamination did not turn negative. Renal biopsy was done on July 25th, 2017, Immunofluorescence reveals : IgG: -, IgA: -, IgM: - , C3: -, C1q: - , κchain: - , λchain: -. Pathological diagnosis: mild proliferative glomerular mesangial lesion including podocyte lesions. Electron microscopy results: diffuse effacement of podocyte foot processes. No electron dense deposition. Combined with the pathological findings of the child, the child was considered to be apical FSGS (Figure 1).

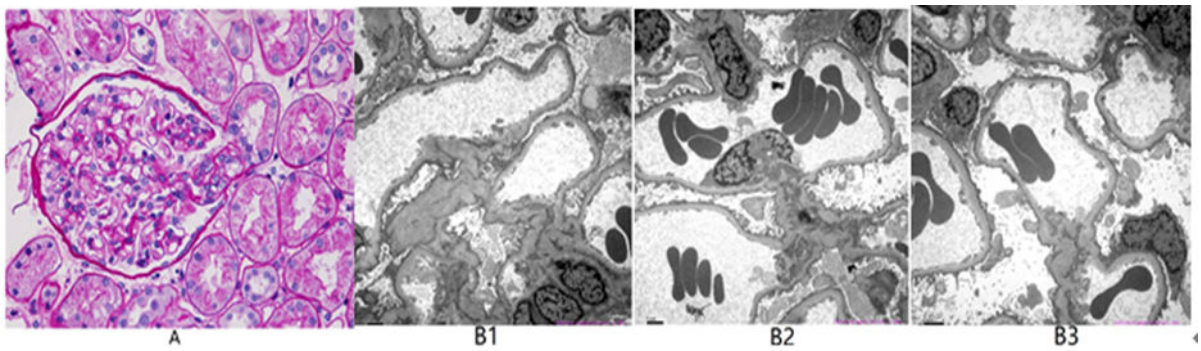

Figure 1: Histological changes of kidney (**A**: HE staining,X400Apical type FSGS; **B1-B3**: Electron microscopy).

Prednisolone was given 2 mg/(kg.d) for 4 weeks after the child was admitted to our hospital. Since urinary protein could not be relieved, the amount of prednisolone given was decreased gradually. The child was treated with tacrolimus and received 2 courses of methylprednisolone pulse therapy according to the renal puncture results.

Periodic renal function monitoring of the child was carried out to indicate her renal function. Due to "*upper respiratory tract infection*", the patient was hospitalized again on April 27th, 2018. On April 30th, renal function monitoring showed urea nitrogen 22.09 mmol/L, creatinine 302.3 μmol/L, and potassium 6.29 mmol/L. After mutiple reviews, renal function was suggested to be insufficient. After treatment, renal function returned to normal. The patient is still in follow-up.

The father of the child was diagnosed with nephritic syndrome 1.3 years before the onset of the child, with normal renal function and membranous nephropathy indicated by renal biopsy. The child's mother and grandparents showed normal results in multiple urine tests, but the grandparents have not taken a genetic test.

Since the child's father was found to have nephrotic syndrome, family whole exon sequencing was performed on the child and her parents after the consent of the parents and the medical ethics committee. 2 mL of the child and her parents' venous blood was taken and blended respectively in EDTA anticoagulation tube for single gene high-throughput sequencing, which revealed a NPHS1 missense mutation c.803G>A, c.1339G>A, c.1802G>C in the child, mutation c. 803G>A carried by her father and c.1339G>A, c.1802G>C mutations carried by her mother. C.803G>A (P.R268Q)has not been reported in the HGMD Professional Edition database. C.1339G>A(P.E447K)has been reported to be associated with congenital nephrotic syndrome, Finnish type, and c.1802G>C (P.G601A) has been reported to be associated with steroid-resistant nephrotic syndrome, in the HGMD Professional Edition database. The c.1339G>A, c.1802G>C, which were predicted by Mutationtaster software as harmful mutations, and c.803G>A mutation as polymorphism . The mutations mentioned above occurred at a very low frequency in the population. The c. 803G>A mutation in gnomAD database has a frequency of 0.0198 in the East Asian population. No literature has reported this mutation. The overall pathogenicity of the mutation is Variant Uncertain Significance (VUS). http://gnomad.broad institute.org/about.The inheritance mode of NPHS1 gene is autosomal recessive. Combined with the clinical manifestations and histological changes of the kidney, c.803G>A mutation is probably as a newly discovered mutation in East Asian children (Figure 2 and Table 1).

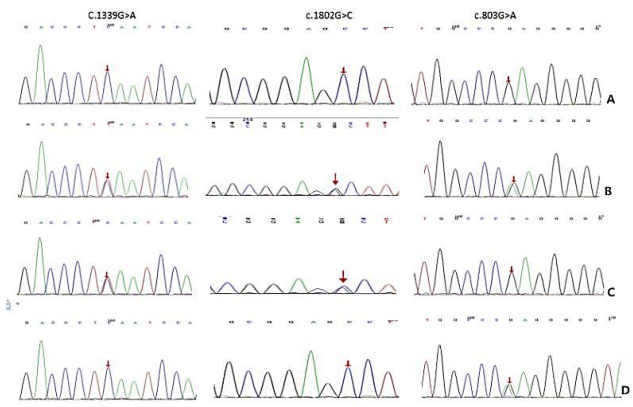

Figure 2: NPHS1 mutations in the family (Notes A: nomal; B: patient;C: the mother of patient;D: the father of patient; arrows indicated mutations).

NPHS1 (NM_004646)					
Chromosome location	**Exon**	**Nucleotide change**	**Effect on protein**	**Source of variation**	
				Father	**Mother**
chr19-36340175	7	c.803G>A	p.R268Q	Het	No Variation
chr19-36339044	11	c.1339G>A	p.E447K	No Variation	Het

chr19-36336398	14	c.1802G>C	p.G601A	No Variation	Het

Table 1: Characteristics of NPHS1 mutation gene.

Note: The mutations of c.803G>A, c.1339G>A, c.1802G>C in NPHS1 gene were found. The c.803G>A resulted in the mutation of amino acid 268 from arginine to glutamine. The c.1339G>A resulted in the mutation of amino acid 447 from glutamic acid to lysine. The c. 1802G>C resulted in the mutation of 601 amino acid from glycine to alanine. The c.1339G>A mutation has been reported to be associated with congenital nephrotic syndrome, Finnish type, The c.1802G>C mutation has been reported to be associated with steroid-resistant nephrotic syndrome, and c.803G>A mutation has not been reported in the past, which is a newly discovered mutation. (Reference database HGMD).

Literature retrieval and review

"*Focal segmental glomerulosclerosis AND (NPHS1 OR gene)*" was used as the keyword or subject words to retrieve relevant literature from the CNKI (China National Knowledge Infrastructure), Wanfang, VIP and China Biology Medicine disc; *"[(focal segmental glomerulosclerosis) OR (FSGS)] AND (NPHS1 OR gene)*" was used as the search strategy to search on PubMed and EBSCO database. The deadline was set to be July 31st, 2018, and literature that has not been sequenced by NPHS1, guidelines, traditional reviews and literature about animal experiments were all excluded. One paper of Chinese database met the inclusion criteria. A total of 23 relevant papers were found in English database, of which 10 papers met the criteria. Within these papers, a total of 22 cases of NPHS1 homozygous mutation or composite heterozygous mutation and 2 cases of NPHS1 polymorphism were found, with 4 cases were adults, 16 cases were children and 2 cases were of unknown age. Among these cases, 11 cases progressed to ESRD. The clinical characteristics of totally 23 cases including the one described in this paper are shown in Table 2.

Number	Country	Age	Gender	Renal Biopsy	Biopsy	ESRD	Nucleotide Change	Effect on Protein	Exon Intron	Reference
1	China	11	F	NS	FSGS	Yes	c.1339 G>A	p.E447K	Exon: 1	17
2	China	2.7	M	NS	FSGS	Yes	1c.1339 G>A	p.E447K	Exon: 1	17
3	American	0.25	M	CNS	FSGS	Yes	c.1223 G>A	P.	Exon: 0	18
4	American	37	F	NS	FSGS	Unknown	c.2928G>T	p.A9T6S	Exon: 22	16
5	Saudi Arabia	1.5	Unknown	NS	FSGS	Unknown	c.2215G>A	P.A739T	Unknown	19
6	Spain	0.25	M	CNS	FSGS	Yes	c.2143G>C	p.G7:SR	Exon: 6	20
7	Spain	0.25	M	CNS	FSGS	No	c.1538T>C	p.1513P	Exon: 2	20
8	Spain	6	F	SRNS	FSGS	No	c.1099 C>T; c. 361 GIA	P.R367C; p.F. 121K	Exon: 0	20
9	Spain	1	M	SRNS	FSGS	No	c.1099 C>T; c. 361 GIA	P.R367C; p.F. 121K	Unknown	20
10	Spain	7	F	SRNS	FSGS	No	c.1329G>A; c. 2928G>T	p.R160Q; p.R 97W	Exon: 1.22	20
11	Spain	0.67	F	SRNS	FSGS	No	c.791C>G; c. 2006C>T	p.P264R; p.P67W	Exon: 7.15	20
12	Spain	27	F	SRNS	FSGS	No	c.2475C>A; c. 2928G>T	p.R97W; p.R827X	Exon: 22.18	20
13	Spain	11	F	SRNS	FSGS	Yes	c.1610C>T; c. 1223 G>A	p.T537M; p.R409Q	Exon: 2.10	20
14	Spain	27	M	SRNS	FSGS	Yes	c.563A>T	p.N1881	Exon: 5	20
15	Spain	29	F	SRNS	FSGS	Yes	c.291C>G	p.P264R	Exon: 7	20
16	Unknown	0.5	M	SRNS	FSGS	Yes	c.379G>A; c. 2928G>T	p.R460Q; p.R9W	Exon: 11.22	8
17	Unknown	3.8	M	SRNS	FSGS	No	c.48C>G; c. 2928G>T	p.Y156X; p.R9MS	Exon: 1	8

18	Unknown	3.1	M	SRNS	FSGS	Yes	c.51delC>; c. 2928G>T	p.17126175X: p.R9W	Exon: 1	8
19	China	*5	M	SRNS	FSGS	Yes	1358A>G	p.Q153R	Exon: 1	21
20	Italy	Unknown	Unknown	SRNS	FSGS	No	c.563A>T	p.N1881	Unknown	22
21	China	Unknown			FSGS	Unknown	c.G928>A	p.D310N	Unknown	23
22	Unknown	Unknown	Unknown	Unknown	FSGS	Unknown	c.1802G>C	p.G601 A	Exon: 4	25
23	China	6	F	SRNS	FSGS	Yes	c.503G>A		Exon: 1	

Table 2: Mutations of NPHS1 in FSGS patients (F: Female; FSGS: Focal Segmental Glomerulosclerosis; M: Male; ESRD: End-Stage Renal Disease; Y: Year; NS: Nephrotic Syndrome; CNS: Congenital Nephrotic Syndrome; SRNS: Steroid-Resistant Nephrotic Syndrome).

Discussion

Among patients having nephrotic syndrome(NS)with childhood onset, 80% patients are sensitive to steroids and have histological featured of slightly changed NS. 10% to 20% of children with PNS are resistant to hormone, namely, steroid- resistant nephrotic syndrome (SRNS). About 63%-73% of patients having SRNS with childhood onset usually have focal segmental glomerulosclerosis (FSGS) and its renal histologic features [1,2]. FSGS is a serious chronic progressive glomerular disease in children. Rich first described in 1957 that the main pathological changes was complex sclerosing lesion in a focal and segmental distribution in some glomerular (<50%) and part of capillary loops, and clinical manifestation was mainly characteristics by proteinuria, hematuria, nephrotic syndrome, high blood pressure and resistance to steroids. These together are main reasons for end-stage renal disease (ESRD) with childhood onset. According to pathogenesis, the mechanism can be divided in to primary (or idiopathic) and secondary FSGS; from the perspective of heredity, FSGS are usually divided into familial FSGS and sporadic FSGS. With studies on etiology and pathogenesis of FSGS, a large amount of data has indicated an essential role genetic factors played in the pathogenesis of FSGS, and about 10% of FSGS have familial aggregation (hereditary FSGS). Such feature is different from other glomerular disease.

Up to now, more than 20 gene mutations have been found to possibly cause the attack of SRNS, and the pathological changes are mainly FSGS [3-6]. The mutations mainly include NPHS1, NPHS2, PLCε1, ACTN4, TRPC6, PTPRO, CD2AP, APOL1, INF2, MYO1E, WT1, LAMB2, MYH9, COQ2, COQ6, DPSS2, ITBG4, CD151, SMARCAL1, SCARB2, LMX1B, ZMPSTE24, PMM2, ALG1, LMNA, MTTL1 and so on [3-7]. Among them, NPHS1, NPHS2, WT1 and LAMB2 are common pathogenic genes for SRNS or FSGS in children. Among less-than-one-age children with NS, 2/3 of the cases are caused by mutations in NPHS1, NPHS2, WT1 and LAMB2. Carolin et al. [7] reported that the most common pathogenic gene for congenital NS was NPHS1, and mutation in NPHS2 was the most common genetic mutation in individuals with SRNS onset in the age of 1 to 18 years old (SRNS caused by recessive genes (NPHS1, LAMB2 and PLCE1) are manifested in early childhood, while mutations in dominant genes INF2 and TRPC6 are more common in early adulthood.

In 2000, Abhay Vats et al. discovered NPHS1 gene in a member of a North American familial FSGS family,located at 19q13 .The NPHS1 gene is 26 kb long, contains 29 exons and encodes nephrin protein. Nephrin is synthesized by secretion of podocyte, mainly expressed as podocytes and is an important component of hiatal membrane [8]. Nephrin plays an important role in maintaining the mesangial structure of podocyte. The mouse model without nephrin expression quickly developed proteinuria and disappearance of the foot process. The foot process of animals injected with anti nephrin antibodies will also disappear. NPHS1 was identified as the most common type of pathogenic gene of congenital NS (CNS) and Finnish CNS [9]. Recently, NPHS1 mutation has been reported to be found in SRNS that occurred in childhood and adulthood [10]. A large number of gene mutation modes have been reported, including deletion, insertion, nonsense mutation, missense mutation and splie site mutation, etc. [4,11-13]. A patient can exhibit significant clinical manifestations only if NPHS1 homozygous mutation cause an absence of gene function.

The mutation of NPHS1 gene results in the change of protein function or structure. Podocytes damage the glomerular filtration barrier and cause proteinuria by affecting the cytoskeleton structure, signal transduction, cell homeostasis and so on. This also suggests that podocytes play a key role in the development of FSGS.

In this study, the patient developed the disease at the age of 6, with clinical manifestations of "*severe proteinuria, high edema, hyperlipidemia and hypoproteinemia*". After 8 weeks of treatment with prednisolone, the urinary protein did not turn negative. And the effect of treatment with tacrolimus was poor. Such phenomena, combining with renal pathology, was consistent with diagnosis of FSGS. According to the pathological classification criteria of FSGS, it can be divided into non-special type, portal type, cell type, apical type and collapse type. The apical FSGS manifested segmental sclerosis or cell proliferation at the glomerular urinary pole. Balloon adhesion was observed and tubulointerstitial lesions were mild. Combined with the pathological findings of the child, the child was considered to be apical FSGS (Figure 1A).

The patient had her first onset in childhood, with the disease rapidly progressed to ESRD. High-throughput sequencing of this child and her parents revealed that the child had NPHS1 heterozygotic missense mutation c.803G>A, c.1339G>A, c.1802G>C, among which c.803G>A mutation was from the child's father and c.1339G>A and c.1802G>C were from the child's mother. c.1802G>C mutation is not a pholymorphic site, and its occurrence frequency is extremely low in the population. The HGMD premium database has been reported related to SRNS. C.1339G>A mutation has been reported by the database to be relevant to CNS. The single base mutation was analyzed by protein function prediction software Phast Cons, SIFT, PolyPhen2 and Mutationtaster. The mutation c.1339G>A was located in exon 11 of NPHS1 chr19-36339044, resulting in the change of amino acid p.E447K; the mutation c.1802G>C was located in exon 14 of NPHS1

chr19-36336398, resulting in the change of amino acid p.G601 A. The two variants are all pathogenic. The mutation c.803G>A was located in exon 7 of NPHS1 chr19-36340175, which resulted in the change of amino acid p.R268Q, and the mutation was polymorphic.The transcripts of c.1339G>A, c.1802G>C and c.803G>A mutations were NM_001009944. Considering the clinical manifestations of the child, the C. 803G>A mutation originated from the father of the child may be a new mutation of FSGS related pathogenic site.

From the literature analysis, the pathogenicity mutation of FSGS found in Caucasian population and African-American population has not been well duplicated in Chinese FSGS patients.

The father of the child was diagnosed with nephrotic syndrome 1.3 years before the onset of the child. Renal puncture was performed and indicated membranous nephropathy. Whole exon sequencing showed the presence of heterozygous mutation of PKD1 gene c.10102 G>A, c. 3931G>A, c.6704C>T. The PKD1 gene is located at 16p13.3, with a total span of about 56 kb. It consists of 46 exons. The length of transcripted RNA is 14135 bp, and it encodes polycystin 1 (PC1) composed of 4302 amino acids. The mutation of PKD1 gene results in structural abnormalities of PC1 protein, leading to polycystic kidney disease. Some studies have confirmed that [14], the insertion of 8 bases in the intron region of the PKD1 gene in the patient caused the shift of the coding region of the protein, resulting in the early termination of the translation of polycystic protein 1 and the formation of a truncated protein consisting of only 2995 amino acids. Truncated proteins, due to their absence of transmembrane and intracellular regions, affect signal transduction and intracellular localization, thus losing their normal functions, leading to abnormal proliferation and secretion of renal epithelial cells, leading to the occurrence of polycystic kidney disease.

C.10102G>A (p.D3368N) and c.3931G>A (p.A1311T) are missense mutations. The mutation occurs very rarely in the population , has been reported to be associated with Polycystic kidney disease in HGMD Professional Edition database. C.6704C>T (p.S2235L) is a missense mutation. The mutation is not a polymorphic site and occurs very low in the population. It has not been reported in the HGMD Professional Edition database. Autosomal dominant polycystic kidney disease (ADPKD) is a late-onset multisystem disorder characterized by the clinical presentation of cyst of double kidney and other organs such as liver, pancreatic gland, seminal vesicle and arachnoid. The clinical manifestations of a patient include: high blood pressure, pain and insufficient renal function. 85% of ADPKD are caused by mutations in PKD1and 15% of ADPKD are caused by mutations in PKD2. ADPKD is an autosomal dominant disease. About 95% of patients with ADPKD have their parents also experience ADPKD; while the other 5% cases were caused by newly occurred mutations. Based on the clinical manifestation and auxiliary examination results of patients' fathers, it is not currently supported that mutations in PKD1 lead to onset of ADPKD.

According to this literature review, 69.6% of the patients (16/23) had childhood or prechildhood onset, and there was no significant difference in male / female ratio (10:9). There are obvious regional and ethnic differences in the incidence of the disease, among which the incidence of Europeans (56.5%, 13/23) is higher than that of Asians (21.7%, 5/23). 55% (11/20) of patients with FSGS resulted by mutation in NPHS1 showed insufficient renal function. With the extension of follow-up time, renal damage might still be found in other patients, which also confirmed that FSGS was the main causation of the end-stage renal disease (ESRD). Up to now, a total of 3 cases of FSGS caused by NPHS1 mutation have been reported in China, all of which have progressed to ESRD (Table 2). The child reported in this paper also exhibited renal insufficiency. The distribution of mutations in genes related to FSGS varies according to the age of onset. Studies [13] indicated that, among children with the age of 0 to 3 months, all of the 5 patients (100%) carried mutations in NPHS1 (n=3) and NPHS2 (n=2). Among patients at the age of 4 months to five-year-old, 2 of the total 9 patients (22%) exhibited mutations in NPHS1 (n=1) and WT1 (n=1). No pathogenic mutations were found in all of the 3 patients aged 6 to 12. However, from this literature review, we can see that NPHS1 mutation could be found in children of all ages with FSGS. Among the children aged 6 to 12, 7 of them exhibited mutation of NPHS1, which was inconsistent with previous reports and could be related to racial differences as well as genetic heterogeneity.

According to large international multi-center studies, the top 5 genes with the highest detection rate in congenital (with onset in 3 months) and infantile (with onset from 3 months to 3-year-old) SRNS are NPHS1, NPHS2, WT1, LAMB2 and PLCE1. The detection rates of NPHS2, WT1, and SMARCAL1 are the highest in child-type SRNS (with onset from 1 to 12-year-old) [13]. For FSGS in adults, in 2015, Gast et al. [15] screened 39 candidate genes for 81 adults with FSGS, and the result showed that COL4A 3-5 was the most common mutation in adults with FSGS. Therefor, determining a patient's genetic pattern and his/her onset age through family investigation will be helpful to select candidate genes. Through this literature review, it was found that among the 19 patients with FSGS with known age, 11 were children aged 6-14 and adults, suggesting that mutations on different gene loci on one gene can lead to different age of onset [16].

Children with congenital NS (CNS) caused by the homozygous or combined heterozygous mutation of NPHS1 developed to ESRD 2 to 3 years after onset [17], and developed to ESRD in an average of 8.7 years, the time that a child with NS progressed to ESRD can be predicted if the NPHS1 is detected [10-11,17-24]. Santin S, et al's research indicated that, compared with patients with NPHS2 mutations, patients with mutations in NPHS1 would proceed to ESRD more rapidly. None of these mutation carriers had recurrence after kidney transplantation. However, there are also reports stating that, for child-type SRNS caused by NPHS1 mutation, the recurrence rate of urinary protein after renal transplantation is 28.5%. In this study, the patient developed renal insufficiency at the 9th month after the onset of the disease with rapid progression and a poor prognosis.

Conclusion

To sum up, renal biopsy should be performed as soon as there is clinical manifestation of hormone or immunosuppressive drug resistance or frequently-recurrent nephrotic syndrome to clarify the pathological type. Once the diagnosis of FSGS is confirmed, gene detection should be carried out as soon as possible, which is conducive to the identification of clinical pathogens, guidance of treatment and prognosis. Our study found that mutations in NPHS1 can lead to child-type FSGS. The new discovery, c.803G>A mutation, further enriches NPHS1 gene spectrum and provides guidance for clinical work. The mutation c.803G>A may be different genetic variation in Chinese FSGS patients, and the mutation of this gene locus may be the pathogenic mutation of Chinese Han population in FSGS patients. From retrieved literatures, there is no in vitro study of the new mutation site. Next, we will carry out cell or animal experiments to verify the function of the mutation site and clarify its biological significance.

Conflict of Interest

The authors declare no conflicts of interest.

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