CASE REPORT

Isolated steroid-resistant nephrotic syndrome in a Chinese child carrying a de novo mutation in WT1 gene: a case report and literature review

Yiyang Li1†, Chuan Tian1†, Yajun Wang2, Guoda Ma2 and Riling Chen2*

Abstract

Background: Isolated steroid-resistant nephrotic syndrome (ISRNS) is caused by mutations in the Wilms’ tumor-1 (WT1) gene, which encodes glomerular podocytes and podocyte slit diaphragm [1–3]. The WT1 gene mutation is found in 6% to 7% of patients with ISRNS younger than 18 years of age and in 10% to 12% of female patients [4, 5]. The age of onset ranges from birth to adolescence [1–3]. It responds poorly to immunosuppressants and has no extrarenal manifestations, such as Wilms’ tumor or urogenital malformations [1]. The main types of renal pathology are diffuse mesangial sclerosis (DMS) and focal segmental glomerulosclerosis (FSGS) [3, 6]. It is progressively worsening and progresses to end-stage renal disease (ESRD) 0.1 to 11 years after the onset of disease [3, 7]. We report a case of an 11-year-old female child with ISRNS caused by de novo mutation in the WT1 gene, presenting a new type of pathology. We also systematically review previous reports of ISRNS in Chinese children.

Case presentation: A 8-year-old Chinese patient who had steroid-resistant nephrotic syndrome, responded poorly to immunosuppressant, and had no extrarenal manifestations. The patient had a female phenotype and karyotype of 46, XX. A new type of renal pathology, proliferative sclerosing glomerulonephritis (PSG), and a de novo missense mutation in WT1 gene, c.748C > T (p.R250W), which have not yet been reported, were identified. She was diagnosed with ISRNS. The patient progressed to end-stage renal disease at the age of 10 years, underwent dialysis and kidney transplant. Renal function and urine protein were normal during 4-year follow-up.

Conclusions: WT1 gene testing should be performed to guide treatment for patients with steroid-resistant nephrotic syndrome, especially for isolated cases and female patients.

Keywords: Isolated Steroid-resistant Nephrotic syndrome, WT1 gene

Background

Isolated steroid-resistant nephrotic syndrome (ISRNS) is caused by mutations in the Wilms’ tumor-1 (WT1) gene (OMIM 607102), which encodes glomerular podocytes and podocyte slit diaphragm [1–3]. The WT1 gene mutation is found in 6% to 7% of patients with ISRNS younger than 18 years of age and in 10% to 12% of female patients [4, 5]. The age of onset ranges from birth to adolescence [1–3]. It responds poorly to immunosuppressants and has no extrarenal manifestations, such as Wilms’ tumor or urogenital malformations [1]. The main types of renal pathology are diffuse mesangial sclerosis (DMS) and focal segmental glomerulosclerosis (FSGS) [3, 6]. It is progressively worsening and progresses to end-stage renal disease (ESRD) 0.1 to 11 years after the onset of disease [3, 7]. We report a case of an 11-year-old female child with ISRNS caused by de novo mutation in the WT1 gene, presenting a new type of pathology. We also systematically review previous reports of ISRNS in Chinese children and summarize experience and progress in its diagnosis and treatment.

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Case presentation

The patient was female, and experienced foamy urine and symmetrical edema of lower limbs at the age of 8 years. Physical examination: 26 kg, blood pressure 130/100 mmHg (90–110/60-75 mmHg), moon-shaped face, buffalo back, hairy upper arms, no obvious swelling of eyelids or lower limbs, no palpable mass in the abdomen, and normal external genitalia. There were no abnormalities in visual, hearing, and intelligence tests.

Urinalysis showed urine protein 3+ (226 mg/kg.d). Blood chemistry revealed albumin 28.7 g/L (38-54 g/L), urea nitrogen 10.48 mmol/L (2.48–8.07 mmol/L), creatinine 161.3 μmol/L (34.0–80.0μmol/L), cholesterol 13 mmol/L (3.1–5.7 mmol/L), glomerular filtration rate (GFR) 38.79 ml/min*1.73 m^2 (> 90 ml/min*1.73 m^2); mild anemia, normal complement C3 levels, negative anti-streptolysin O, negative hepatitis B virus antigen; and no abnormalities in autoantibodies (antinuclear antibodies, anti-dsDNA), T cell subsets, immunoglobulins, and erythrocyte sedimentation rate. Color ultrasound and computed tomography (CT) of the genitourinary system showed no tumors or developmental abnormalities. The renal pathology suggested proliferative sclerosing glomerulonephritis (PSG) (Fig. 1).

The patient had no history of tumor, hepatitis, allergic purpura, medication taken without renal impairment. Birth history was uneventful. There was no consanguinity and birth history was uneventful. There was no family renal disease.

The diagnosis was nephritic syndrome, chronic renal failure (stage III), renal hypertension, and renal anemia. The patient was treated with initial 2 mg/kg.d oral prednisone. Urine protein remained positive during the treatment for more than 3 months, fluctuating between 2+ and 3+. After the type of pathology was identified, 25 mg/kg.d of oral mycophenolate mofetil (MPA) was also prescribed, combined with benazepril and erythropoietin to manage her hypertension and anemia, respectively, and dietary intervention was also carried out. A follow-up evaluation 6 months later showed morning urine protein remaining 3+ and a reduction in 24-h urine protein (42 mg/kg.d). Blood chemistry suggested hypercholesterolemia, azotemia, and normal albumin levels. Patient didn’t achieve remission. GFR was 37.36 ml/min*1.73 m^2, indicating no significant progress in chronic renal failure. Hence, MPA was changed to cyclophosphamide (CTX), which was administered every 2 weeks for a total of five treatment cycles to make a cumulative dose of 104 mg/kg, but no remission was achieved.

She progressed to ESRD at the age of 10 years and underwent hemodialysis for 9 months. Kidney transplantation was performed at the age of 10 years and 9 months. The patient was followed up regularly. The renal function and urine protein were normal during 4 years of follow-up.

Karyotype and genetic testing

In order to confirm the diagnosis, a blood sample was collected from the patient after informed consent was obtained from her parents. Chromosome karyotype was 46, XX (Fig. 2). Hereditary nephrotic syndrome-related genes were sequenced. (Table 1) After suspected pathogenic variants were detected, peripheral blood was collected from the patient’s parents and younger brother for pedigree verification by Sanger sequencing. It was found that the proband had a heterozygous mutation in exon 9 of the WT1 gene on chromosome chr11:32,413,566, that is, c.748C > T. Specifically, nucleotide 748 in the coding region was changed from cytosine to thymine, which
caused amino acid 250 to be changed from arginine to tryptophan, that is, p.R250W, which was a missense mutation. The transcript was NM_001198551. This mutation is not present in the 1000 Genomes Project or Exome Aggregation Consortium database. Pathogenic variants of this mutation, which have the same amino acid change, are registered in the Human Gene Mutation Database (HGMD) (ID CM107177 and ID CM910411). However, there is no report about the heterozygous mutation c.748C>T causing ISRNS. This is a new mutation site. This mutation is not a polymorphic locus and occurs at an extremely low frequency. Mutation Taster predicts that this mutation can change the splice site. PhyloP and PhastCons Nucleotide conservation scores were 2.917 and 1, respectively. The sequence of amino acid at the missense mutation site was aligned with homologous sequences of other species. The results are shown in Table 2. The amino acid at this site of WT1 is highly conserved among human, chimpanzee, rhesus, mouse, chook, Fugu rubripes, zebra fish, fruit fly, nematode, and African melon toad. This variant was classified as a pathogenic variant in HGMD, ClinVar, and Mutation Taster.

The pedigree analysis showed that no mutation at this site was found in the proband's parents or younger brother with a normal clinical phenotype. This mutation was co-segregated with the disease in the family (Fig. 3). According to the 2015 American College of Medical Genetics and Genomics (ACMG) guideline, this variant is a pathogenic variant (PS1+PS2+PS4+PM1+PM2+PM5+PP1+PP3).

**Discussion**

The WT1 gene is located on chromosome 11p13 and contains 10 exons. WT1 is a zinc finger-like transcription factor. The amino terminus is rich in proline and glutamic acid, is encoded by exons 1 to 6, and can activate transcription. The carboxyl terminus contains 4 zinc finger domains that can bind to DNA, each consisting of 2 cysteines and 2 histidines, and are encoded by exons 7 to 10, respectively [3, 4, 8]. The two subtypes, WT1+KTS and WT1-KTS, produced by the insertion of a tripeptide amino acid fragment composed of lysine-threonine-serine (KTS) encoded by exon 9 between the 3rd and 4th zinc fingers have clear functions [3, 4, 8]. WT1+KTS plays an important role in maintaining the normal function of podocytes. WT1-KTS is essential for the development of embryonic

**Table 1** Analytical genes associated with hereditary nephrotic syndrome list

| Number | Symbol   | Number | Symbol   | Number | Symbol   | Number | Symbol   | Number | Symbol   |
|--------|----------|--------|----------|--------|----------|--------|----------|--------|----------|
| 1      | ACTN4    | 16     | THSD7A   | 31     | PLA2R1   | 46     | CRB2     | 61     | LAMB3    |
| 2      | ADCK3    | 17     | TRPC6    | 32     | PLC1     | 47     | CUBN     | 62     | CD2AP    |
| 3      | ADCK4    | 18     | TSC2     | 33     | PMM2     | 48     | DGKE     | 63     | KANK1    |
| 4      | ALG1     | 19     | UMOD     | 34     | PTPRO    | 49     | EMP2     | 64     | KANK2    |
| 5      | ANLN     | 20     | WDR73    | 35     | SCARB2   | 50     | NPHP1    | 65     | KANK4    |
| 6      | APOA1    | 21     | WT1      | 36     | MVH9     | 51     | CFH      | 66     | LAMA3    |
| 7      | APOE     | 22     | XPOS     | 37     | GLA      | 52     | COL4A3   | 67     | LAMB2    |
| 8      | APOL1    | 23     | LYZ      | 38     | INF2     | 53     | COL4A4   | 68     | MME      |
| 9      | ARHGAP24 | 24     | ARHG1A   | 39     | NPHS1    | 54     | COL4A5   | 69     | ZMPSTE24 |
| 10     | COQ6     | 25     | B2M      | 40     | NPHS2    | 55     | COQ2     | 70     | LAMC2    |
| 11     | MYO1E    | 26     | CD151    | 41     | NUP107   | 56     | MEFV     | 71     | LMX1B    |
| 12     | NEIL1    | 27     | PAX2     | 42     | NUP205   | 57     | FAT1     | 72     | COL4A6   |
| 13     | NEK8     | 28     | PDSS1    | 43     | NUP93    | 58     | FGA      | 73     | ITGA3    |
| 14     | SCL35A2  | 29     | PDSS2    | 44     | SLC17A5  | 59     | FLG      | 74     | ITGB4    |
| 15     | SMARCAL1 | 30     | PEX1     | 45     | COQ9     | 60     | FN1      |        |          |
An appropriate WT1+KTS/-KTS ratio (the normal ratio is close to 2:1) is indispensable for the normal development of the kidney and urogenital system [3, 4, 8].

In this study, the heterozygous mutation in exon 9 of the WT1 gene, c.748C>T, resulted in the mutation of amino acid 250 from arginine to tryptophan. On the one hand, the WT1 gene mutation produces an allele that only expresses the -KTS subtype, resulting in an abnormal WT1+KTS/-KTS ratio, which can lead to abnormal kidney development [8]. On the other hand, as a nuclear transcription factor, WT1 can bind to the promoters and enhancers of 18 podocyte disease-related mutant genes, such as Nphs1, Nphs2, Actn4, and CD2AP [8, 9]. Mutations in exon 9 affect the binding of the zinc finger domains to DNA and affect the recognition and binding of WT1 to target genes, thereby affecting target kidney and gonads.

### Table 2: Homology comparison of WT1 amino acid sites corresponding to missense mutations

| Species                     | Amino Acid Site | Amino Acid | DNA Change |
|-----------------------------|----------------|------------|------------|
| Human (Homo sapiens)        | 250            | FQCKTCQRKFS | R          |
| Chimpanzee (Ptroglodytes)   | 325            | TCQRKFS     | R          |
| Rhesus (Mmulatta)           | 462            | TCQRKFS     | R          |
| Mouse (Mmusculus)           | 462            | TCQRKFS     | R          |
| Chook (Gallus)              | 362            | CKTCQRKFS   | R          |
| Fugu rubripes (Trubripes)   | 361            | CETCQRRFA   | R          |
| zebra fish (Dmelenogaster)  | 364            | YTCKVCGQVFS | R          |
| Fruit fly (Dmelenogaster)   | 665            | YTCKVCGQVFS | R          |
| Nematode (Celegans)         | 165            | FQCKTCQRKFS | R          |
| African melon toad (Xtropicalis) | 368  | FQCKTCQRKFS | R          |

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**Fig. 3** Sequences of the WT1 gene mutation of the proband and her younger brother and parents. T1 (II2) proband; T2 (II1) proband’s younger brother; F (I1) proband’s father; M (I2) proband’s mother.
| References | gender | The onset age(year/age) | Age of ESRD (Onset(year) | Mutations Region | Mutations type | Sequence Changes | Protein Changes | Renal Pathology | Therapy | treatment response | Renal outcome |
|------------|--------|-------------------------|--------------------------|------------------|---------------|----------------|----------------|----------------|---------|-------------------|--------------|
| 1 | This report | female | 8 | 10 | Exon 9 | Missense mutation | c.748C > T | p.R250W | PSG | MP → P + MMF → CTX → HD → KT | Resistant | ESRD |
| 2 | Li J, Ding L, et al. [12] | female | 0.3 | 3 | Exon 9 | Splice mutation | c/559+5G > A | p.D319N | FSGS | GC → C-A | Resistant | ESRD |
| 3 | | female | 1 | 1.3 | Exon 9 | Splice mutation | c/559+5G > A | p.D319N | — | GC → CTX | Resistant | ESRD |
| 4 | Liangzhong sun et al. [2] | female | 0.5 | 0.5 | Exon 8 | Missense mutation | c.1097G > A | p.R366H | DMS | — | — | — |
| 5 | | female | — | — | Exon 8 | Missense mutation | c.1097G > A | p.R366H | — | — | — | — |
| 6 | | female | 0.1 | 0.1 | Exon 9 | Missense mutation | c.1180C > T | p.R394W | FSGS | P → PK06 | Complete remission | Normal |
| 7 | | female | — | 9 | Exon 9 | Missense mutation | c.1180C > T | p.R394W | DMS | — | — | — |
| 8 | Yue Z, et al. [4] | female | 0.4 | 0.4 | Intron 9 | Splice mutation | c.1228+4C > T | — | — | — | — | ESRD |
| 9 | | female | 9 | — | Intron 9 | Splice mutation | c.1228+4C > T | — | — | — | — | ESRD |
| 10 | | female | 1 | 6.8 | Intron 9 | Splice mutation | c.1228+4C > T | — | — | — | — | ESRD |
| 11 | | female | 5 | — | Exon 9 | Missense mutation | c.1180C > T | p.R394W | FSGS | P → PK06 | — | — | Normal |
| 12 | | female | 0 | 0.2 | Exon 9 | Missense mutation | c.1180C > T | p.R394W | DMS | — | — | — | ESRD |
| 13 | | female | 0.5 | 0.5 | Exon 8 | Missense mutation | c.1097G > A | p.R366H | DMS | — | — | — | ESRD |
| 14 | Yang Yonghui et al. [11] | female | 2 | — | Exon 9 | Missense mutation | c.1180C > T | p.R394W | DMS | — | — | — | ESRD |
| 15 | | female | 8.1 | — | Exon 9 | Missense mutation | c.1051A > G | p.D319N | — | — | — | — | Normal |
| 16 | | female | 6.3 | 6.3 | Exon 9 | Missense mutation | c.1051A > G | p.D319N | — | — | — | — | Resistant |
| 17 | | male | 6.3 | 6.3 | Exon 9 | Missense mutation | c.1051A > G | p.K331E | — | — | — | — | Resistant |

Cyclosporine A, CTX Cyclophosphamide, DMS Diffuse Mesangial Sclerosis, ESRD End-stage Renal Disease, PK06 Tacrolimus, FSGS Focal Segmental Glomerular Sclerosis, GC Glucocorticoid, HD Hemodialysis, PSG Proliferative Sclerosing Glomerulonephritis, KT Kidney Transplantation, MCD Minimal Change Disease, MMF Mycophenolate Mofetil, MP Methylprednisolone, NC Not Clear, P Prednisone
were female and only 1 was male, suggesting that this dis-
cases of ISRNS were retrieved. Among them, 15 patients
not been reported before.
that cyclosporine (CsA) effectively reduced urine pro-
podocyte actin cytoskeleton [1, 12, 14, 15]. However,
of hereditary nephrotic syndrome caused by WT1 gene
mutations, and therefore, calcineurin inhibitors
protein in hereditary nephrotic syndrome caused by WT1
plete response in patients [2]. It has also been reported
recurrence rate [13]. Sun et al. reported that 3 chil-
treatment is kidney transplantation, because of the low
protect kidney function, and delay disease progression.
immunosuppressants with caution [1, 4, 12]. At pre-
Identified "steroid-resistant" nephrotic syndrome as
A literature search was conducted in China National
"WT1 gene", "Chinese", "children", "isol-
ated", "steroid-resistant", and "nephrotic syndrome" as
As shown in Table 3, a total of 16 cases of ISRNS were retrieved. Among them, 15 patients were female and only 1 was male, suggesting that this disease is more likely to occur in female children. The average age of onset was 3.4 years. The earliest onset was at birth. It progressed to ESRD in an average of 1.1 years, and even started with acute renal failure. Regarding the type of pathology, there were 5 cases of DMS, 4 cases of FSGS, 1 case of MCD. The type of pathology, PSG, described in this paper has not been reported before. The WT1 gene mutations that cause ISRNS are mainly heterozygous missense mutations in exons 8 and 9 and splicing mutations in intron 9. The most common mutation is c.1180C > T. The mutation site described in this paper has not been reported before.
ISRNS is resistant to glucocorticoids and responds poorly to most immunosuppressants. Hence, it is recom-
method to use glucocorticoids and to use immunosuppressants with caution [1, 4, 12]. At pre-
, the treatment is mainly to reduce proteinuria, protect kidney function, and delay disease progression.
progression. It can quickly progress to ESRD. In this case, the best treatment is kidney transplantation, because of the low recurrence rate [13]. Sun et al. reported that 3 children with FSGS were treated with tacrolimus (FK506), which induced partial response in 1 patient and complete response in patients [2]. It has also been reported that cyclosporine (CsA) effectively reduced urine protein in hereditary nephrotic syndrome caused by WT1 gene mutations, and therefore, calcineurin inhibitors (FK506 and CsA) have a certain effect in the treatment of hereditary nephrotic syndrome caused by WT1 gene mutations, which may be achieved by stabilizing the podocyte actin cytoskeleton [1, 12, 14, 15]. However, the efficacy needs to be further confirmed by a multi-
In conclusion, WT1 gene testing should be performed to guide treatment for patients with steroid-resistant nephrotic syndrome, especially for isolated cases and female patients.

In addition to causing ISRNS, WT1 gene mutations can also result in Denys-Drash syndrome (DDS), Fras-
nerve, and other urological malformations, gonadal tumors, Wilms' tumor, and other manifestations [1, 3, 16]. DDS, FS, and WAGRS are easier to identify due to extrarenal manifestations. Therefore, for children with a female phenotype and ISRNS with DMS or FSGS, detailed physical and imaging examinations (e.g., B-ultrasound and CT) of the genitourinary system should be performed to exclude genitourinary malformations, tumors, and other lesions, and chromosome karyotype and WT1 gene mutation analysis should be performed to identify patients with ISRNS [16] to avoid unnecessary treatment with steroids and other immunosuppressants. Children with ISRNS caused by WT1 gene mutations progress to ESRD 0.1 to 11 years after the onset, which is not only about 10 years faster than those without gene mutations, but also than faster those with hereditary nephrotic syndrome caused by mutations in other genes (e.g., NPHS2, NPHS1, PTPRO, and LAMB1) [17]. Therefore, WT1 mutation analysis is also helpful for prognosis evaluation. Although most of the WT1 gene mutations were new [2, 4, 7], there are also reports of mothers passing the mutated gene to their children [7, 10, 18]. Therefore, WT1 mutation analysis can be used in genetic counseling and prenatal genetic diagnosis for families at high risk of WT1 mutations.

The clinical manifestations of the patient reported in this study were ISRNS, with the new renal pathology type, PSG and de novo mutation in the WT1 gene, c.748C > T. Pelletier et al. reported that mutations at this site could cause DDS [19]. Therefore, it is necessary to follow up this patient to detect possible gonadal tumors and Wilms' tumors, etc.

**Abbreviations**

ISRNS: Isolated Steroid-resistant Nephrotic Syndrome; WT1: Wilms' tumor-1 gene; PSG: Proliferative Sclerosis Glomerulonephritis; DMS: Diffuse Mesangial Sclerosis; FSGS: Focal Segmental Glomerulosclerosis; ESRD: End-stage Renal Disease; GFR: Glomerular Filtration Rate; CT: Computed Tomography; PSG: Proliferative Sclerosis Glomerulonephritis; MPA: Mycophenolate; CTX: Cyclophosphamide; HGMD: Human Gene Mutation Database; ACMG: American College of Medical Genetics and Genomics; FK506: Tacrolimus; CsA: Cyclosporine; DDS: Denys-Drash syndrome; FS: Frasier syndrome; GC: Glucocorticoid; HD: Hemodialysis; FS: Frasier syndrome; GC: Glucocorticoid; HD: Hemodialysis; KT: Kidney transplantation; MCD: Minimal change disease; MMF: Mycophenolate Mofetil; MP: Methylprednisolone; P: Prednisone.

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Authors' contributions
YYL, CT cared for the patient and designed the project and wrote the manuscript. GDM collected clinical information. YJW helped with the analysis. RLC approved the proposal and revised the manuscript. All authors have read and accepted the manuscript.

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Availability of data and materials
The datasets generated and analysed during the current study are available in the https://www.uniprot.org/uniprot/P19544 repository.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by Affiliated Hospital of Guangdong Medical University. The patients provided their written informed consent to participate in this study.

Consent for publication
Written informed consent to publish was obtained from the patient's parents.

Competing interest
The authors declare no competing interests.

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References
1. Hongwen Z, Wang F, Ding J. Research progress of cyclosporine A in the treatment of hereditary nephrotic syndrome caused by WT1 gene mutation. Chin J Pract Pediatr. 2011;26(1):862–4.
2. Sun LZ, Wang HY, Li M, et al. Clinical and pathological features and mutational types of WT1 mutation-associated nephropathy. Zhonghua Er Ke Za Zhi. 2018;56(10):769–74.
3. Jingjing W, Liyan Ye, Huayu Zi. Kidney disease and WT1 gene. Chin J Pract Pediatr. 2009;47(3):233–7.
4. Yue Z, Wang H, Lin H, et al. WT1 mutation-associated nephropathy: a single-center experience. Clin Nephrol. 2017;87(05):245–54.
5. Lijun W, Jianguo Li. Research progress on molecular genetic mechanism of corticosteroid resistant nephrotic syndrome in children. Chin Matern Child Health. 2018;33(11):10621–5.
6. Ahn YH, Park EJ, Kang HG, et al. Genotype-phenotype analysis of pediatric patients with WT1 glomerulopathy. Pediatr Nephrol. 2017;32(1):81–9.
7. Mustafa A, Ozaltin F, Hinkes BG, et al. Mutations in the Wilms’Tumor 1 gene cause isolated steroid resistant nephrotic syndrome and occur in exons 8 and 9. Pediatr Res. 2006;59(2):325.
8. Hasting ND. Wilms’tumor 1 (WT1) in development, homeostasis and disease. Development. 2017;144(16):2862–72.
9. Gellermann J, Stefanidis CJ, Mitsios A, et al. Successful treatment of steroid-resistant nephrotic syndrome associated with WT1 mutations. Pediatr Nephrol. 2010;25(7):1285–9.
10. Yang Yonghui. Analysis of WT1 gene mutation in Chinese children with corticosteroid resistant nephrotic syndrome. Graduate Thesis of Fujian Medical University, 2012.
11. Li J, Ding J, Zhao D, et al. WT1 gene mutations in Chinese children with early onset nephrotic syndrome. Pediatr Res. 2010;68(2):155.
12. Malakasioti G, Iancu D, Tullus K. Calcineurin inhibitors in nephrotic syndrome secondary to podocyte gene mutations: a systematic review. Pediatr Nephrol. 2021;36(6):1353-1364.
13. Santin S, Bullich G, Tazon-Vega E, et al. Clinical utility of genetic testing in children and adults with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2011;6(5):1139–48.
14. Kemper MJ, Lemke A. Treatment of genetic forms of nephrotic syndrome. Front Pediatr. 2018;6:72.
15. Wasilewska AM, Kuroczycka-Santiutycz E, Zoch-Zwierz W. Effect of cyclosporin A on proteinuria in the course of glomerulopathy associated with WT1 mutations. Eur J Pediatr. 2010;170(3):389–91.
16. Lehnhardt A, Karnatz C, Ahlenstiel-Grunow T, et al. Clinical and molecular characterization of patients with heterozygous mutations in Wilms tumor suppressor gene 1. Clin J Am Soc Nephrol. 2015;10(5):825–31.
17. Bérody S, Heidet L, Gribouval O, et al. Treatment and outcome of congenital nephrotic syndrome. Nephrol Dial Transplant. 2019;34(3):458–67.
18. Denamur R, Bouquet N, Mougenot B, et al. Mother-to-child transmitted WT1 splice-site mutation is an early risk factor for childhood nephrotic syndrome. Nephrol Dial Transplant. 1999;10(1):2219.
19. Pelletier J, Bruening W, Kashan CE, Mauer SM, Manvel JC, Stiegel JE, Houghton DC, Junien C, Habib R, Fouser L, et al. Germline mutations in the Wilms’tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. Cell. 1991;67(2):437–47.