A novel FOXP3 mutation in a Chinese child with IPEX-associated membranous nephropathy

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Abstract

Background: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a monogenic immunodeficiency disease caused by forkhead box protein3 (FOXP3) mutation. The kidney is commonly involved in IPEX syndrome, but there were few studies focusing on renal involvement.

Methods: Whole-exome sequencing was used to identify the novel FOXP3 mutation. We collected clinical manifestations, kidney pathology, and gene function of the proband. All the previously published studies with IPEX-associated renal involvement were reviewed.

Results: We report a late-onset Chinese child with IPEX-associated membranous nephropathy (MN). Type 1 diabetes mellitus and nephrotic-range proteinuria are the main clinical manifestations. Whole-exome sequencing shows a novel c.766A > G mutation in the FOXP3 gene. The literature review indicates that renal manifestations include proteinuria, microscopic hematuria, and renal insufficiency. MN is the most common pathological type in children with IPEX, followed by tubulointerstitial nephritis, interstitial nephritis, minimal change nephrotic syndrome, and membranoproliferative glomerulonephritis.

Conclusion: In summary, we report a novel FOXP3 mutation (c.766A > G) with MN stage II in IPEX. In a literature review, MN is the most common pathological type in children with IPEX and proteinuria is the most prevalent clinical feature. IPEX should be considered in the differential diagnosis of MN patients with related endocrine diseases and immune disorders.

KEYWORDS
FOXP3, IPEX syndrome, membranous nephropathy
1 | INTRODUCTION

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome (OMIM 304790) was first reported by Powel (Powell et al., 1982) in a large kindred. Eight male infants of this big family had persistent diarrhea, eczema, endocrinopathy, such as diabetes mellitus or thyroid autoimmunity. Most of them died in their early life. The subsequent studies proved that IPEX is caused by forkhead box protein3 (FOXP3) gene mutation (Bennett et al., 2001; Chatila et al., 2000). FOXP3 gene is located in the X-chromosome at Xp11.23-Xq13.3. The gene structure of FOXP3 contains a proline-rich (PRR) amino-terminal domain, also known as repressor domains, central zinc finger (ZF) and leucine zipper (LZ) domains, and DNA-binding forkhead (FKH) domain (Bacchetta et al., 2018).

Existing studies have shown that the most common FOXP3 mutation in IPEX patients is located in the forkhead domain, followed by the leucine zipper domain and the inhibitory domain (Park et al., 2020). FOXP3 plays an important role in the development of CD4+ CD25+ regulatory T (Treg) cells, which is critical in the stability of peripheral immunologic tolerance (Fontenot et al., 2003; Marson et al., 2007). The mutation of the FOXP3 gene affects the function of T-reg cells and causes a series of autoimmune diseases. Up to now, typical IPEX is characterized by clinical features including early-onset gastrointestinal disease, type 1 diabetes mellitus (T1DM), hypothyroidism, and dermatitis. A systematic review showed that the clinical manifestations of IPEX included intestinal diseases, eczema, endocrine diseases, hematological abnormalities, infection diseases, and renal involvement, of which the morbidity of renal involvement was 16.4% (32/195) (Park et al., 2020). While, previous studies were mostly limited to the clinical phenotype of renal lesions, and there were few studies on renal pathological changes. Moreover, the mechanism of renal injury is still unclear.

Here, we report an MN patient with novel FOXP3 mutation and explore the potential mechanism of renal injury. On the other hand, we summarize the renal pathological type in children with IPEX to analyze the association of genotype and phenotype in renal lesions.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

Ethical approval for this study was gained through the Institutional Review Board, Children’s Hospital of Chongqing Medical University (2020–220). Informed consent was obtained from the patient’s parents.

2.2 | Subjects

The patient from a Chinese family participated in the present study. After signing informed consent, specimens of this family were collected in the Department of Nephrology, Children’s Hospital of Chongqing Medical University, Chongqing, China. Clinical history collection, treatment, and follow-up of this case were in the same hospital.

2.3 | Renal biopsy

Light microscopy: Paraffin-embedded renal sections were used in light microscopy. Staining methods included hematoxylin and eosin (HE), periodic acid–Schiff (PAS), periodic acid–silver methenamine (PASM), and Masson trichrome. The definition of change in renal biopsy refers to Heptinstall’s Pathology of the Kidney by J. Charles Jennette (John, 2015).

Immunohistological staining: Kept in 2–8°C, frozen sections were used in immunohistological staining. The frozen sections were cut into a thickness of about 2 mm. After being fixed in acetone for 10 min, phosphate buffer saline (PBS) was used to protect the complete structure in vitro. Staining for CD3, CD38, IgG, and IgG4 were performed in immunohistochimical. Staining for IgA, IgM, IgG, IgG subclasses (IgG1, 2, 3, 4), C1q, C3, and C4d was performed in immunofluorescence. In a total of five levels, immunofluorescence staining intensity was scoring from “−” to “+++” (−: negative, ±: suspicious positive, +: weak staining, ++: moderate staining, +++: strong staining).

Electron microscope: The renal specimens from patients were fixed in 2.5% glutaraldehyde and 1% osmium tetroxide (both solvents were PBS). The next measurement was blocked by PBS, dehydrated using graded ethanol and acetone, embedded in Epon 812, and cured by heat. Cut into about 50 nm, sections were stained with both uranyl acetate and lead citrate. Finally, a JEM-1400 PLUS electron microscope was used to observe results. The diagnosis and staging of MN were referred to standards by Ehrenreich et al. (1976).

2.4 | Genetic analysis

Genomic DNA was extracted from peripheral blood using the Solpure Blood DNA kit (Magen) according to the manufacturer’s instructions. The genomic DNA of the three patients was then fragmented by Q800R Sonicator (Qsonica) to generate 300–500bp insert fragments. The paired-end libraries were prepared following
Illumina library preparation protocol. Custom-designed NimbleGen SeqCap probes (Roche NimbleGen, Madison, Wis) were used for in-solution hybridization to enrich target sequences. Enriched DNA samples were indexed and sequenced on a NextSeq500 sequencer (Illumina, San Diego, Calif) with 100–150 cycles of single-end reads, according to the manufacturer’s protocols. Primary data came in fastq form after image analysis and base calling were conducted using the Illumina Pipeline. The data were filtered to generate “clean reads” by removing adapters and low-quality reads (Q20). Sequencing reads were mapped to the reference human genome version hg19 (2009–02 release, http://genome.ucsc.edu/). Nucleotide changes observed in aligned reads were called and reviewed by using NextGENE software (SoftGenetics, State College, Pa). Besides the detection of deleterious mutations and novel single nucleotide variants, a coverage-based algorithm developed in-house, eCNVscan, was used to detect large exonic deletions and duplications. The normalized coverage depth of each exon of a test sample is compared with the mean coverage of the same exon in the reference file, to detect copy number variants (CNVs).

2.5 Reference sequence of FOXP3 gene: NCBI reference sequence: NM_014009

Sequence variants were annotated using population and literature databases including 1000 Genomes, dbSNP, GnomAD, Clinvar, HGMD, and OMIM. PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and PROVEAN (http://provean.jcvi.org/index.php) were used to analyze the structure of the protein, predict the conservation domain, function domain, and perform the multiple sequence alignment. Variants interpretation were manipulated according to the American College of Medical Genetics (ACMG) guidelines (Ehrenreich et al., 1976).

2.6 Flow cytometry

Peripheral blood was collected from the patient and his pedigree. Peripheral blood mononuclear cells (PBMCs) were separated by density gradient centrifugation. At 4°C, 0.125 μg CD4 (IgG1, FITC, clone RPA-T4), and CD25 (IgG1, PE, clone BC96) monoclonal antibodies in 100 μl PBMCs were incubated for 30 min. After fixation and permeabilization, under conditions of 4°C and without light, 0.5 μg anti-human FOXP3 (IgG2x, PE-CY5, clone PCH101) was added to specimens. PBMCs were washed and re-centrifuged in the next step. Finally, we examined the expressions of CD4, CD25, and FOXP3 by a flow cytometer (FACSCalibur; Becton Dickinson, Mountain View, CA, USA). FLOWJO software (Tree Star, Ashland, OR, USA) was used to analyze data.

2.7 Literature review

We searched in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), China National Knowledge Infrastructure (https://www.cnki.net/), Wanfang Database (http://www.wanfangdata.com.cn/index.html), VIP Database (http://www.vip.com/) with keywords “immune dysregulation, polyendocrinopathy, enteropathy, X-Linked syndrome” or “IPEX syndrome” or “IPEX”, considering studies published before August 22, 2020. Article selection criteria included: (1) original case reports of IPEX syndrome confirmed by molecularly, (2) renal biopsy was described in articles, (3) the time of renal biopsy was before taking drugs with nephrotoxicity, such as cyclosporine.

3 RESULTS

3.1 Case report

3.1.1 Clinical manifestations and laboratory features

The 5-year-old boy was the first parturition in three pregnancies of two healthy and nonconsanguineous Chinese parents. His mother had abortions at the first and second pregnancies because the fetus stopped growing in almost 10 weeks of gestational age. The growth was similar to that of children of the same age and sex in China. At 5 years old, he weighed 20.0 kg (p50–p75), was 110 cm (p25–p50) tall, and had a normal body mass index (BMI) of 16.5 kg/m² (p75–p90).

The onset of endocrinopathy appeared when he was 4 years 1-month-old, including polydipsia, polyphagia, polyuria, and diabetic ketoacidosis (DKA). Laboratory tests indicated that fasting plasma glucose (FPG) > 7.0 mmol/L, 2-h plasma glucose > 11.1 mmol/L, which were up to the standard of T1DM (American Diabetes Association, 2015). Glutamic acid decarboxylase (GAD) was higher than healthy people, while insulin autoimmune antibody (IAA) was normal. Free triiodothyronine (FT3) and free thyroxine (FT4) and had an unabiding reduction. The evidence of renal injury was negative at the onset (Table 1). Treated with insulin at the dosage of 0.5–1 U/kg·d, blood glucose was effectively controlled at 5–10 mmol/L for 1 year. He had neither intractable diarrhea nor recurrent infections. Despite elevated serum IgE levels, eczema, and asthma were absent in his childhood. The other laboratory features are shown in Table 1. The foamy urine was...
The patient was confirmed by WES, finding a missense mutation p.766A>G, as a novel FOXP3 mutation.

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3.1.2 | Sequencing with WES and pathogenicity analysis

Genomic DNA was extracted from the peripheral blood of the patient and his family. Based on human genome reference sequence hg19/GRCh37, We discovered a novel missense mutation c.766A>G (p.M256V) in exon7 of FOXP3 and his mother was a heterozygous carrier, while his father was normal (Figure 2a). The mutation (p.M256V) was localized in highly conserved amino acid sequences among representative species (Figure 2b). The family pedigree of the proband is shown in Figure 2c. Missense predictions from PolyPhen-2 and PROVEAN showed probably damaging with high sensitivity and specificity (Table 2). We had done the flow cytometry analysis in the peripheral blood of the patient and his pedigree. Peripheral blood was collected from the patient and his pedigree. Compared with isotype control, the CD4+ CD25+ FOXP3 positive T cells of this patient slightly decreased (Figure 2d). This patient was confirmed by WES, finding a missense mutation c.766A>G, as a novel FOXP3 mutation.

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Fusion of podocyte foot processes were observed on an electron microscope (Figure 1f).

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FIGURE 1 Renal pathology of the proband: (a) Slight proliferation in glomerular mesangial cells and mesangial matrix, slight renal tubulointerstitial lesions, HE × 100; (b) Incrassated GBM and spikes on the basement membrane, PAS × 400; (c) Deposition of C4d along the glomerular capillary wall, immunohistochemical × 400; (d) Granular IgG deposition along the glomerular capillary wall, immunofluorescence × 500; (e) IgG4 deposition in the glomeruli, immunofluorescence × 400; (f) Electron-dense deposition under epithelial cells and fusion of podocyte foot processes, electron microscope × 5000

FIGURE 2 Gene mutations and expressions of FOXP3 gene (NM_014009): (a) The whole exon sequencing in the family. The proband and his mother have a novel mutation (c.766A > G). The red arrow shows the mutation; (b) Conservative analysis in different species. The FOXP3 mutation of the proband was localized in highly conserved amino acid sequences (p.M256V); (c) Family pedigree of the proband. The mother of the proband is a carrier and his father is unaffected. There were two abortions before the proband; (d) Flow cytometry of CD4+ CD25+ FOXP3+ Treg cells in the family. Treg cells in the proband showed a decrease, which was more obvious after treatment
of c.766A>G in population data of 1000 Genomes met PM2. The predictions from PolyPhen-2 and PROVEAN met PP3. The family pedigree of the proband met PP4. One strong evidence (PS3), two moderate evidence (PM1, PM2), and two supporting evidence (PP3, PP4) met the ACMG criteria.

According to pathological features of MN (Ehrenreich et al., 1976), the patient was diagnosed as IPEX-associated MN stage II. Complete remission of urinary protein was achieved after 4 weeks of oral prednisone combined with mycophenolate-mofetil (MMF), as there was only a partial response to prednisone therapy during the first 4 weeks (Figure 3). The prednisone dose was gradually reduced to discontinuation over the course of 9 months and MMF has been taken orally continuously. The patient was followed for 12 months, with normal 24h urinary protein quantitation (38 mg/24h) and creatinine level at the last follow-up, but the expression of Treg cells decreased than before (Figure 2d).

3.2 | Literature review

We searched in PubMed, China National Knowledge Infrastructure, Wanfang Database, VIP Database with key words “immune dysregulation, polyendocrinopathy, enteropathy, X-Linked syndrome” or “IPEX syndrome” or “IPEX”, considering studies published before August 22, 2020. Total 362 articles were reviewed by topic selection. At first, 186 articles were excluded which were not articles about IPEX. Then, 72 articles were excluded which were not clinical studies. Eight review articles were excluded and 97 articles were reviewed by full text. Finally, 19 patients with renal pathology in 10 articles were identified in the literature review. The literature research strategy was showed in Figure 4. Including the case in our center, a total of 20 IPEX patients are summarized in Table 3. The patient’s serial number was arranged according to the location of the mutation and both patient 3 and 16 were patients in our center. Patient 16 had a novel gene mutation (c.766A>G) reported in this article, while the mutation (c.227delT) of patient 3 had been reported by Duclaux-Loras R (Duclaux-Loras et al., 2018). The data of clinical manifestation, renal pathological characteristics, and FOXP3 mutations are summarized in Table 3.

Analyzed cases with detailed renal clinical manifestations, proteinuria appeared in all patients (10/10), and half of them were diagnosed with nephrotic syndrome. Microscopic hematuria was observed in three patients. Renal insufficiency appeared in three patients and one of them got significantly remission after HSCT. Turning to the treatment, most of them were treated with immunosuppression (10/17). Only a few patients were combined immunosuppression and hematopoietic stem cell transplantation (4/17). Among four patients who died in the literature review, infection was the main factor, instead of end-stage renal disease and renal failure. Renal pathology of patient 1 showed the characteristics of both MN and interstitial nephritis. MN was the predominant pathological type (57.1%, 12/21), followed by tubulointerstitial nephritis (14.3%, 3/21), interstitial nephritis (14.3%, 3/21), minimal change nephrotic syndrome (9.5%, 2/21), and membranoproliferative glomerulonephritis (4.8%, 1/21). Furthermore, the depositions of immunoglobulin and complement in MN are summarized in Table 4. IgG deposition was present in five cases, with IgG4 deposition in three of these cases. IgG4, C3, and C4d deposits were observed in patient 16, while IgG4, C3, and C1q deposits were

**TABLE 2** Analysis in silico prediction

| Mutation   | PolyPhen-2 | PROVEAN  |
|------------|------------|----------|
| c.766A>G   | 0.969      | −3.817   |
| Possible pathogenic | Pathogenic |

*FIGURE 3* 24h urinary protein quantitation during follow-up
observed in patient 18. In Figure 5, there is a clear distribution of \textit{FOXP3} mutation in IPEX syndrome with renal biopsy. The detail of gene mutation in patient 20 was not described. The most mutation is located on exon 7 (8/19). The hot spot mutation is c.751-753delGAG (6/19) in the LZ domain. Mutation frequencies of different domains from high to low are 57.9\% (11/19) in LZ, 21.1\% (4/19) in repressor domains, 21.1\% (4/19) in the noncoding region, and 10.5\% (2/19) in FKH. As for mutation types, missense mutations (9/19) are the most common type.

4 | DISCUSSION

IPEX syndrome is regarding as an immunodeficiency disease in the early life of children. Despite various clinical feature has been observed in IPEX, the most common manifestation can be generalized as enteropathy, T1DM, and eczema. Renal involvement in IPEX is not infrequent, with morbidity from 16.4\% to 34.4\% in different studies (Barzaghi et al., 2018; Park et al., 2020). However, there were few articles focused on IPEX with renal involvement or renal pathology.

We reported a late-onset IPEX child with T1DM and nephrotic-range proteinuria, which differed from typical manifestations of IPEX with the absence of digestive symptoms and skin lesions. The renal pathology of the case showed MN stage II with negative PLA2R and THSD7A deposition. In the literature review, the most common clinical manifestation of renal injury was proteinuria, and the universal pathological type was MN.

MN is the most common pathological type. But the mechanism of MN with IPEX is unknown. The complement system plays a crucial role in the pathogenesis of IMN. In the Heymann nephritis rat model of MN, strong evidence showed C5b-9 membrane attack complex (MAC) led to glomerulus injury (Cybulsky et al., 1986). Back to humans, the activation of complements can be divided into the classical pathway, the alternative pathway, and the lectin pathway. The evidence presented thus far supports the idea that the classical pathway was activated by the combination of C1q and IgG1 in secondary MN (Diebolder et al., 2014; Huang et al., 2013), while IgG4 activates complement through mannose-binding lectin pathway leading to kidney injury (Haddad et al., 2021). As shown in Table 4, IgG4 and complement deposition was found in several IPEX-associated MN. IgG4 was the predominant deposition in the glomeruli of patient 16, with positive C4d and absence of C1q, which suggested that complement activation through mannose-binding lectin pathway may lead to IPEX-associated MN.

The essence of IPEX is the mutation of \textit{FOXP3}. Data from several studies suggested that \textit{FOXP3} is a crucial regulatory gene in the development and function of CD4+ CD25+ regulatory T cells (Bacchetta et al., 2018). Our study showed a novel mutation of \textit{FOXP3} (c.766A>G). Due to the match of PS3, PM1, PM2, PP3, and PP4, ACMG criteria were used to classify the variant as pathogenic. \textit{FOXP3} is one of the forkhead/winged-helix families, which is highly conserved. It comprises 12 exons, including an exon (exon 1) is in the 5’ untranslated region. In Table 3, a total of 20 IPEX patients were confirmed by molecular method, and all
of them were explicit except one. Comparing with total mutations in FOXP3 reported, the different mutation distributions of FOXP3 might show that LZ plays an important role in the renal injury of IPEX (Park et al., 2020). But a systematic review about IPEX did not find a genotype–phenotype correlation between LZ and renal injury either, while mutations in LZ domains were associated with hematologic presentations, protein-losing enteropathy, mega liver, and spleen (Park et al., 2020). The function of different domains in FOXP3 is not well understood yet. Similar with the LZ domain in FOXP1 and FOXP2, we predict the function of the LZ domain is affecting DNA binding as a consequence of heterodimer formation (Li et al., 2004). As a transcriptional repressor, FOXP3 protein play its role through DNA

| Patient | FOXP3 mutation | Renal pathology | Renal manifestation | Age at onset | Digestive symptom | Endocrinopathy |
|---------|----------------|-----------------|--------------------|--------------|------------------|----------------|
| 1       | c.-23 G > A    | MN,IN           | RI,MH, nephrotic-range proteinuria | 1 m          | Chronic diarrhea  | Polyendocrinopathy |
| 2       | c.227delT      | MN               | None described     | 3w           | Diarrhea         | None described  |
| 3       | c.264delC      | TIN              | None described     | 5 y          | Diarrhea         | Diabetes        |
| 4       | c.303–304 del TT | MN              | PU                 | 6 m          | Diarrhea, enteritis   | Hypothyroidism, T1DM |
| 5       | c.736–2 A > G  | MN stage I      | MH,NS, edema       | birth        | Diarrhea         | Hypothyroidism  |
| 6       | c.736–2 A > G  | MCNS            | NS                 | 2y           | None described   | None described  |
| 7       | c.736–1 G > A  | MN               | None described     | 8w           | Diarrhea         | DM              |
| 8       | c.748–750 del AAG | MCNS          | NS                 | 4 m          | Vomiting, enteropathy | T1DM            |
| 9       | c.751–753 delCAG | MN            | NS                 | 7 m          | Hematochezia     | Hypothyroidism  |
| 10      | c.751–753 delGAG | IN             | None described     | 6w           | Diarrhea         | Hypothyroidism, |
| 11      | c.751–753 delGAG | MN             | None described     | 1w           | Diarrhea         | DM              |
| 12      | c.751–753 delGAG | TIN           | None described     | 7 m          | Enteropathy      | DM              |
| 13      | c.751–753 delGAG | MPGN          | NS,hypertension.   | 2 m          | Diarrhea         | T1DM            |
| 14      | c.751–753 delGAG | IN             | None describe      | 6 w          | Enteropathy      | Hypothyroidism  |
| 15      | c.766A > G     | MN stage II    | Nephrotic-range proteinuria | 4 y1 m | None         | T1DM            |
| 16      | c.816 + 7G > C | MN               | None describe      | 11 y         | Bloody diarrhea  | DM, Hypothyroidism, GHD |
| 17      | c.1010 G > A   | MN               | RI, MH, Nephrotic-range proteinuria | 1 y       | Autoimmune enteropathy | None described |
| 18      | c.1010 G > A   | MN               | Edema, nephrotic-range proteinuria | 3 d       | Diarrhea         | Neonatal diabetes |
| 19      | c.1100 T > G   | TIN              | None described     | 1y 3 m       | Enteropathy      | DM              |
| 20      | Present, but no detail | MN       | None described     | 6 m          | Enteritis        | DM              |
**TABLE 3**  The clinical manifestation and gene mutation in IPEX-associated renal injury

| Patient | FOXP3 mutation | Immunoglobulin | Complement | Prognosis | Ref |
|---------|----------------|---------------|------------|-----------|-----|
| 20      | Present, but no| IgG4 positive | None       | Alive 3y9m| Moudgil et al. (2007) |
| 19      | c.1100 T>G     | TIN None      | None       | None      | None |
| 18      | c.1010 G>A     | Edema,nephrotic-range | None | Alive 18 | Sheikine et al. (2015) |
| 17      | c.1010 G>A     | RI,MH,Nephrotic-range | None | Alive 18 | Sheikine et al. (2015) |
| 16      | c.816+7G>C     | None described| None       | None      | None |
| 15      | c.766A>G       | NS,stage II   | None       | None      | None |
| 14      | c.751–753 delGAG | None | None | None | None |
| 13      | c.751–753 delGAG | NS | None | None | None |
| 12      | c.751–753 delGAG | NS | None | None | None |
| 11      | c.751–753 delGAG | NS | None | None | None |
| 10      | c.751–753 delGAG | NS | None | None | None |
| 9       | c.751–753 delGAG | NS | None | None | None |
| 8       | c.748–750 delAAG | MCNS | NS | None | None |
| 7       | c.736–1 delA  | MCNS | NS | None | None |
| 6       | c.736–2A>G    | IgG positive | None | None | None |
| 5       | c.303–304 del TT | IgG 3+ | C3 2+, Clq 1+ | Alive 5 y | Moudgil et al. (2007) |
| 4       | c.303–304 del TT | IgG 3+ | C3 2+, Clq 1+ | Alive 5 y | Moudgil et al. (2007) |
| 3       | c.303–304 del TT | IgG 3+ | C3 2+, Clq 1+ | Alive 5 y | Moudgil et al. (2007) |
| 2       | c.303–304 del TT | IgG 3+ | C3 2+, Clq 1+ | Alive 5 y | Moudgil et al. (2007) |
| 1       | c.303–304 del TT | IgG 3+ | C3 2+, Clq 1+ | Alive 5 y | Moudgil et al. (2007) |

**TABLE 4**  Deposition of immunoglobulin and complement in IPEX associated MN

| Patient | FOXP3 mutation | Immunoglobulin | Complement | References |
|---------|----------------|---------------|------------|------------|
| 1       | c.23 G>A       | IgG4 positive | None       | Sheikine et al. (2015) |
| 5       | c.303–304 del TT | IgG 3+ | C3 2+, Clq 1+ | Moudgil et al. (2007) |
| 6       | c.736-2A>G     | IgG positive | None       | Park et al. (2015) |
| 16      | c.766A>G       | IgG4 positive | C3 Suspicious positive, C4d positive, Clq negative | This article |
| 18      | c.1010G>A      | IgG4 positive | C3 2+, Clq 1+ | Sheikine et al. (2015) |
binding. Mutations located in the LZ domain might influence the ability of suppression. LZ was used to describe the periodic repetition of leucine at seven positions (Landschulz et al., 1988). Changes in amino acids between two leucines might have less influence on LZ structure. Hence, mutations in LZ are reflected in less serious clinical manifestations. This is a possible explanation for milder manifestation in our case.

In recent years, rapamycin has been considered as the first-line immunosuppressant of IPEX, and HSCT is considered to be a measure that can fundamentally solve the disease (Barzaghi et al., 2018). Our study indicates prednisone combined with MMF could relieve symptoms either. For the first time, we observed a decrease in Treg levels during IPEX treatment. We speculate that the reason is that Treg cells have a significant immunosuppressive effect, and immunosuppressive therapy may replace part of the function of Treg cells and downregulate the expression of Treg through its upstream negative feedback regulation. This is similar to the reduction of Treg cells found in other connective tissue diseases caused by glucocorticoids and other immunosuppressants (Banica et al., 2009).

In summary, we report a novel missense FOX3 mutation (c.766A>G) with MN stage II in IPEX. The immunosuppressive therapy of prednisone and mycophenolate-mofetil can alleviate symptoms of proteinuria. The deposition of IgG, C3, and C4d in the patient indicates that the activation of the mannose-binding lectin pathway may lead to IPEX-associated MN. In the literature review, MN is the most common pathological type in children with IPEX and proteinuria is the most prevalent clinical feature. Due to the high incidence of secondary MN in childhood, IPEX should be considered in the differential diagnosis of MN patients with related endocrine diseases and immune disorders.

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CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS
Liwen Tan, Yunfei An, and Mo Wang made substantial contributions to the conception or design of the work. Liwen Tan, Qin Yang, and Haiping Yang contributed the acquisition, analysis, and interpretation of data for the work. Liwen Tan and Yunfei An drafted the work and revised it critically for important intellectual content. Gaofu Zhang and Qiu Li interpreted the pathological images. Liwen Tan and Mo Wang made revision for final approval of the version to be published. All authors read and approved the final manuscript.

ETHICS APPROVAL
Ethical approval for this study was gained through the Institutional Review Board, Children’s Hospital of Chongqing Medical University (2020–220). Informed consent was obtained from the patient’s parents.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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