

The New Compound Heterozygous Mutation of NUP Nephropathy: Report of Two Cases and Literature Review

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Research

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Abstract

Backgrounds: NUP nephropathy is identified as a rare monogenic cause of steroid-resistant nephrotic syndrome recently. To explore the relationship between NUP mutation and renal disorders, we provide two cases and a literature review of the genotypical and phenotypical features in patients with NUP nephropathy.

Results: We reported two patients with newly diagnosed NUP nephropathy who carried a compound heterozygous mutations in NUP107 and NUP93 gene respectively. Both patients were diagnosed steroid-resistant nephrotic syndrome and progressed to end-stage renal disease in childhood. While the mutation c.1537+1G>A in NUP93 gene was previously described, the mutations c.460A>G and c.1085C>T in NUP107 gene and c.1472A>T in NUP93 gene were novel. We also summarized the phenotypic and genetic spectrum of NUP nephropathy in eighty-six reported patients who carried 50 different mutations in 6 NUP genes (NUP107, NUP93, NUP205, NUP85, NUP133, NUP160). The majority of them were Asians (66/86, 76.7%). The mutation c.2492A>C and c.1079-1083del in NUP107 had been identified as the founder mutations in East Asian[1-3], while c.1772G>T and c.1886A>G in NUP93 might be the founder mutations in Western Europe and Turkish respectively. Nephrotic syndrome was the most common renal manifestation (68/86, 79.1%). Although the renal prognosis was poor that 80.8% (59/73) of them developed end-stage renal disease within the first two decades, the outcome of renal transplantation in NUP nephropathy is better than patients with other steroid-resistant nephrotic syndrome. Focal segmental glomerulosclerosis was the most prevalent renal biopsy pathologic type (56/65, 86.1%). Various extra-renal manifestations were found in 44.8% (26/58) of patients. Neurological involvement was the most common extra-renal presentation (22/26, 84.6%), including microcephaly (13/22, 59.1%), intellectual disability (12/22, 54.5%), and global developmental delay (10/22, 45.5%). Diverse abnormalities of the facial appearance (8/26, 30.8%), short stature (5/26, 19.2%), and contain convergent strabismus (4/26, 15.4%) had also been reported. There are significant differences in extra-renal manifestations between different genomics.

Conclusions: The renal manifestation of NUP nephropathy is highly consistent that most patients suffered early-onset SRNS with FSGS. More than half of the patients had extra-renal symptom concomitantly. Asians showed potential susceptibility to NUP nephropathy. Despite the limited reports, some genotype-phenotype correlations have been gradually revealed.

Background

Nuclear pore complexes (NPCs) are the largest protein assemblies in eukaryotic cells that embedded in nuclear membrane ubiquitously. It plays important role in gene expression, protein synthesis and macromolecular transmembrane process. Relatively stable sub-units that are composed of nucleoporins make up NPCs supramoleculares. Despite there are distinct categories of nucleoporins among different species, the structure of NPCs is conservatively evolved[4]. There are more than 30 nucleoporins (NUPs) discovered in human NPCs. Recent studies revealed that mutations of nucleoporin (NUP) genes can affect the binding and interaction between different NPCs sub-units, which may alter the structure or function of NPCs leading a range of diseases[5]. Since the first case of nephrotic syndrome (NS) caused by NUP107 mutation reported in 2015[1], dozens of cases who were conjectured to be NUP nephropathy have been reported worldwide. However, the role of NUP gene mutations in nephropathy is still unclear[6]. In this report, the clinical characteristics of two Chinese cases with steroid-resistant nephrotic syndrome (SRNS) who discovered NUP93 and NUP107 gene biallelic mutations respectively were summarized. In addition, to explore the relationship between NUP mutation and renal disorders, we provide a literature review of the genotypical and phenotypical features in patients with NUP nephropathy reported to date.

Methods

Two children with SRNS that progressed to end-stage renal disease (ESRD) were presented. Gene detection approval and Written informed consents were obtained from the patients' parents.

Exome sequencing

Genomic DNA was isolated from peripheral blood leukocytes. The purified DNA fragments were amplified with PCR reactions after ligation of adaptor. Exome sequencing was performed after SeqCap EZ Choice XL Library (Roche NimbleGen) targeted capturing on Illumina HiSeq 2000. Sequencing data were analyzed by NextGene Software (V2.3.4). Nucleotide positions refer to GRCh37/hg19 (<http://grch37.ensembl.org>). Genome Aggregation Database (gnomAD, <http://gnomad.broadinstitute.org/>) was used to determine the prevalence of identified variants in coding regions. To confirm the variants, Sanger sequencing was performed in patients and their parents.

Case reports

Patient 1

This patient was a 3-year-7-month-old girl who is the first child of a non-consanguineous family without family history of renal disease. She developed seizures when she was 3 months old. Although multiple anti-epileptic drugs were used, seizures was not well controlled. She presented with global developmental delay and detected proteinuria by regular physical examinations at the age of 2 years. One year later, she was admitted to the emergency department for edema and oliguria. The patient was diagnosed NS because of macroalbuminuria (3+ protein on urine dipstick), hypoalbuminemia (serum albumin 13.6g/L) and hypercholesterolemia (serum cholesterol 20.42mmol/L). Prednisone with daily dose of 2mg/kg/d was given orally for four weeks, but no response was observed. Due to steroid-resistant, prednisone was gradually tapered off after 3 months of mycophenolate and 1.5 months of tacrolimus were used sequentially. Despite those treatments, the patient's symptoms and signs were not improved. Her renal function deteriorated with serum creatinine increased to 398 μ mol/L at the age of 3 years 5 months and hemodialysis was initiated due to hyperkalemia and anuria. Whole-exome sequencing of the proband showed a compound heterozygous NUP107 missense mutation (c.460A>G and c.1085C>T) inherited from her unaffected father and mother

respectively. Neither of these mutations have been reported previously. The allele frequency of this variant in the general population is very low. The variant sequence was highly conserved across different species (see Fig. 1.). The patient is currently waiting for kidney transplantation.

Patient 2

A 1-year-2-months old girl was admitted to local hospital with severe bilateral lower extremity edema. Laboratory test revealed severe proteinuria (urine protein/creatinine ratio > 2) and hypoalbuminemia (< 2.5 g/dL). Value of serum creatinine was not recorded initially and normal renal function was self-reported. Prednisone 2mg/kg for 4 weeks was prescribed, but her proteinuria persisted. Renal biopsy was performed at the age of 1 year and 4 months and focal segmental glomerulosclerosis (FSGS) was found. Cyclosporine and tacrolimus were used successively but stopped because of ineffectiveness. Five months since the onset of symptoms, her serum creatinine level elevated to 344 μ mol/L gradually and commenced peritoneal dialysis. Targeted exome sequencing revealed NUP93 compound heterozygous mutations (c.1537 + 1G > A/c.1472A > T). Sanger sequencing confirmed that the novel mutation c.1472A > T was inherited from her unaffected father while the reported mutation c.1537 + 1G > A[7, 8] was inherited from her unaffected mother while c.1472A > T was inherited from her father. Corticosteroids and immunosuppressive agents were then progressively tapered off in two months. During the waiting period for kidney transplantation, her urine output decreased gradually. Cardiac ultrasound showed progressively enlarged left heart, mild mitral valve insufficiency and left ventricular ejection fraction decreased (43%). However, no clinical signs of cardiac insufficiency was observed. She underwent allograft renal transplantation when she was 1-year-9-month old. After kidney transplantation, she had transient proteinuria for about one month. Her renal function became normal 3 days post-operation and maintained stable until now. During follow-up, echocardiogram returned to normal 5 months later.

Literature review

Since the discovery of the linkage between NUP107 gene mutation to SRNS syndrome in 2015, renal involvement resulting from NPC's mutation has been observed in six NUP genes (NUP107 [OMIM #616730][1–3, 9–13], NUP93 [OMIM #616892][7, 8, 10, 13–17], NUP205 [OMIM #616730][8], NUP85 [OMIM #618176][8], NUP133 [OMIM #618177][9, 18], NUP160 [OMIM #618178][9, 19, 20]). We studied the correlations between NUP gene mutations and clinical manifestations by reviewing the literatures published on PubMed Database (<http://www.pubmed.com>) up to January 2021. The retrieval strategy is provided in Table S1. Seventy-four articles were retrieved initially and 21 articles were included finally after manual screen. We summarized the clinical manifestations by using standardized vocabulary provided in Human Phenotype Ontology (<https://hpo.jax.org/>).

Results

Genotypical spectrum of NUP nephropathy

There were eighty-six cases with NUP nephropathy carrying 50 different mutations have been reported to date, including 2 of our cases. The most frequent type of mutation was missense mutation (35/50, 70%), followed by frameshift mutation (8/50, 16%) and splicing mutation (5/50, 10%). Nup107 and Nup93 gene mutations were seen in most of the reported cases (68/86, 79.1%) (see Table 1 and Table 2). The majority of them were Asians, accounting for 76.7% (66/86) in total patients. NUP107 mutation was more prevalent in East Asians (35/46, 76.1%) in total patients, however, this trend was not evident in other NUP genes. Thirty-three (38.4%) patients carried homozygous mutations while others (53/86, 61.6%) carried biallelic heterozygous mutations. Of those who had provided family information, 43.3% (26/60) had consanguineous parents, and 57.8% (48/83) have a family history of renal disease. Homozygous patients trend to come from consanguineous families (26/31, 83.9%). However, neither the average age of disease onset (4.9 ± 3.9 years vs. 5.5 ± 4.9 years, $P = 0.26$) nor the age progressed to end-stage renal disease (7.0 ± 4.0 years vs. 8.0 ± 5.0 years, $P = 0.44$) were observed significantly different between homozygotes and heterozygotes.

Table 1
Nucleotide changes of reported patients with renal involvement in NUP107.

Reported Cases (n)	Ethnic origin	Age at onset time	Parental Consanguinity(n)	Family history (n)	Nucleotide change	Exon / Intro	Zygosity (n)	AA change	Renal Manifestations (n)	Renal biopsy (n)	ESF (n)
31	EAS	1.7–11	N (9), UN (22)	Y (20), N (11)	c.2492A>C	Exon 26	hom (1) het (30)	p.D831A	NS (20), P (6) CKD (1), ESRD (4)	FSGS (24), MCD (2)	28
18	EAS	1.7–4.4	N (6), UN (12)	Y (11), N (7)	c.1079-1083del	Exon 12	het	p.E360Gfs*6	NS (12),P (2), ESRD (4)	FSGS (11), MCD (2)	16
9	Tur (3) Pak (6)	4.0–14.3	Y (9)	Y (8), N (7)	c.303G>A	Exon 4	hom(11)	p.M101I	NS (6) P (3)	FSGS (4), MCD (1), ESRD (1)	4
3	EAS	10–11	N (2), UN (1)	Y (3)	c.469G>T	Exon 6	het (3)	p.D157Y	SRNS (2), CKD (1)	FSGS (2)	2
3	EAS	2.9–4.3	UN (3)	Y (3)	c.2071C>T	Exon 23	het (3)	p.Q691*	NS (3)	FSGS 3	3
3	EAS	4–5	UN (3)	Y (3)	c.1735-3T>G	Intron 20	het (3)	splice site	NS (2), P(1)	FSGS 3	3
2	EAS	2–3.8	UN (2)	N (2)	c.627_663dup37	Exon 7	het (2)	p.L225Ffs*15	P (2)	FSGS (2)	2
1	EAS	11.8	UN	UN	c.727T>G	Exon 8	het	p.T243P	SRNS		UN
1	EAS	11.8	UN	UN	c.1273A>T	Exon 15	het	p.R425X	SRNS		UN
1	EAS	3	UN	N	c.1547A>G	Exon 18	het	p.Q516R	P		0
1	EAS	2	N	N	c.969+1G>A	Intron 11	het	splice site	SRNS	FSGS	1
1	EAS	4.8	UN	N	c.934delT	Exon 11	het	p.Y312Tfsa	P	FSGS	1
1	Tur	4.5	Y	N	c.2666A>G	Exon 27	hom	p.Y889C	SRNS	DMS	1
1	Pak	2.1	Y	N	c.1325G>A	Exon 16	hom	p.C442Y	NS	FSGS	1
1	Euro	4	N	N	c.1021dup	Exon 12	het	p.E341Gfs*3	HU	GS	1
1	Euro	4	N	N	c.2129_2131delAAG	Exon 24	het	p.E710del	HU	GS	1

n: number, Tur: Turkish, Pak: Pakistani, Euro: European, EAS: East Asian, AA: amino acid, Y: yes, N: no, P: proteinuria, HU: hematuria, CKD: chronic kidney disease, NS: nephrotic syndrome, SRNS: Steroid resistant nephrotic syndrome, NA: not affected, MC: Microcephaly, ID: Intellectual disability, DF: dysmorphic face, DD: Developmental delay, S: Sporadic, F: Familial, Hom: Homozygous, Het: Heterozygote

UN: unknown, FSGS: Focal Segmental Glomerulosclerosis, MCD: minimal change disease, GS: Glomerulosclerosis

Table 2
Nucleotide changes of NUP93 reported in patients with renal involvement.

Reported Cases (n)	Ethnic origin	Age at onset time (years)	Parental Consanguinity(n)	Family history (n)	Nucleotide change	Exon / Intro	Zygosity (n)	AA change	Renal Manifestations (n)	Extra-renal phenotype	Renal biopsy (n)
10	Serbian (1), German (2), Turkish (3), CS (4)	1.8-7	Y (3), N (7)	Y (2), N (8)	c.1772G > T	Ex16	Hom (4), het (6)	p.G591V	HU (4), SRNS (10)	MGS (1)	FSGS (8), IgA (1)
5	Turkish (4), Japanese (1)	0.9-4	Y (3), N (2)	Y (1), N (4)	c.1886A > G	Ex17	Hom (4), het (1)	p.Y629C	HU (3), SRNS (5)	convulsion (1), RA (1)	FSGS (2), IgA (1)
2	German (1), CS (1)	3	N	N	c.1537 + 1G > A	Int13	Het (2)	splice site	SRNS (2), HU (1)	MGS (1)	FSGS (1), MCD (1)
1	Serbian	6	N	N	c.1162C > T	Ex11	het	p.R388W	HU,SRNS	N	FSGS
1	Chinese	1	UN	UN	c.1235A > C	Ex11	het	p.Y412S	SRNS	N	UN
1	Chinese	1	UN	UN	c.1286A > G	Ex12	het	p.Y429C	SRNS	N	UN
1	CS	3.9	N	N	c.1298delA	Ex12	het	p.D433Afs	SRNS	N	FSGS
1	German	~ 3	N	N	c.1326delG	Ex12	het	p.K442Nfs	HU,SRNS	N	FSGS
1	Chinese	7	UN	UN	c.1528A > C	Ex13	hom	p.K510Q	CG	N	UN
1	Japanese	4	N	N	c.1573C > T	Ex14	het	p.R525W	HU,SRNS	convulsion, RA	FSGS
1	Mestizos*	5	N	N	c.1605C > G	Ex14	het	p.Y535*	SRNS, ESRD	DD, autistic, HF	UN
1	CS	1.8	N	N	c.1916T > C	Ex18	het	p.L639P	SRNS, HU	N	FSGS
1	Arabic	1	Y	Y	c.2017C > T	Ex18	hom	p.R673W	CNS	UN	FSGS
1	White	6.1	N	N	c.2084T > C	Ex19	het	p.L695S	SRNS	N	UN
1	White	6.1	N	N	c.2267T > C	Ex21	het	p.L756S	SRNS	N	UN
1	Mestizos*	5	N	N	c.575A > G	Ex7	het	p.Y192C	SRNS, ESRD	DD, autistic, HF	UN
1	Russian	2	N	N	c.2137-18G > A	Int19	het	splice site	SRNS	optic nerve atrophy	FSGS
1	Russian	2	N	N	c.727A > T	Ex8	het	p.K243*	SRNS	optic nerve atrophy	FSGS

*: This child is a mestizos of African American and Hispanic. #: This patient recurred NS after kidney transplantation.

n: number, AA: amino acid, Tur: Turkish, Pak: Pakistani, CS: Czech and Slovak, EAS: East Asian, Y: yes, N: no, HU: hematuria, Hom: Homozygous, Het: Heterozygous, end stage renal disease, NS: nephrotic syndrome, SRNS: Steroid resistant nephrotic syndrome, CG: chronic Glomerulonephritis, CKD: chronic kidney disease, IgA: IgA disease, FSGS: Focal Segmental Glomerulosclerosis, RA: rheumatoid arthritis, DD: developmental delays, MGS: Marcus-Gunn-Syndrome, HF: heart failure.

Phenotypical spectrum of NUP nephropathy

Childhood-onset renal disease was most commonly reported as the initial symptom (82/86, 95.3%). 84.9% (73/86) of the patients experienced initial manifestation during their first decade. The mean age of disease onset was 4.9 ± 3.9 years. The vast majority of patients had proteinuria (79/86, 91.9%), with 86.1% (68/79) of them satisfied the diagnostic criteria of nephrotic syndrome. For those who received treatments of steroid, calmodulin inhibitor or angiotensin-converting enzyme inhibitor, only few patients achieved partial responses. Hematuria was occasionally observed (13/86, 15.1%). Renal prognosis

was poor that 80.8% (59/73) patients developed end-stage renal disease within the first two decades, and among them 72.9% (43/59) occurred even in the first decade. Fortunately, compared with other SRNS patients, the outcome of renal transplantation in NUP nephropathy is excellent that only one case suffered relapse of NS post-transplantation. Sixty-five patients performed renal biopsy and 86.1% (56/65) of patients showed FSGS. Electron microscopy revealed partial effacement of foot processes without electron dense deposition. Various extra-renal manifestations were found in 44.8% (26/58) of patients while 32.6% (28/86) of them did not mention relevant information. Neurological involvement was the most common extra-renal presentation (22/26, 84.6%) (see Table 3). For those who harboured NUP107 gene mutations, some were presented with microcephaly, impaired intellectual development and steroid-resistant nephrotic syndrome, which this triad is similar to Galloway-Mowat Syndrome (OMIM #616730) but lack of structural abnormality of brain. Abnormalities of the facial appearance including sloping forehead, narrow forehead, smooth philtrum, micrognathia, cleft lip and palate were seen in patients with NUP107 or NUP133 mutations. Short stature (5/26, 19.2%), contain convergent strabismus (4/26, 15.4%), and muscle hypotonia (4/26, 15.4%) had also been reported.

Table 3
Comparison between NPC associated renal diseases (including our cases).

	NUP93 (n = 22)	NUP107 (n = 46)	NUP160 (n = 5)	NUP85 (n = 4)	NUP133 (n = 7)	NUP205 (n = 2)
Age of onset (years)	3.2 ± 2.1	5.2 ± 3.8	10.0 ± 7.3	7.5 ± 2.9	3.6 ± 4.2	2.5 ± 0.7
Ethnic origin						
Asian	11	44	3	0	6	2
East Asian	4	34	3	0	4	0
European	8	1	0	2	1	0
Arabic	1	0	2	2	0	0
Mestizos	1	0	0	0	0	0
Not available	1	1	0	0	0	0
Parental Consanguinity	7/20	11/22	2/5	1/4	5/7	0/2
Family history	4/20	28/45	5/5	3/4	6/7	2/2
Zygosity						
Homozygous	10	12	2	2	5	2
Heterozygote	12	34	3	2	2	0
Renal manifestations						
Proteinuria (HP: 0000093)	21	40	5	4	7	2
NS (HP: 0012588)	21	30	4	4	4	2
Hematuria (HP: 0000790)	8	1	0	3	1	0
ESRD (HP: 0003774)	11/15	33/42	2/5	3/4	7/7	1/2
Age of ESRD (years)	5.4 ± 3.3	7.1 ± 3.3	17.0 ± 2.8	9.7 ± 2.5	7.2 ± 6.8	7.0
Performed renal biopsy	14	37 [§]	4	3	5	2
FSGS (HP: 0000097)	12	30	4	3	5	2
MCD (HP: 0012579)	1	3	0	0	0	0
Extra-renal manifestations						
Abnormality of the nervous system (HP: 0000707)	2	12	2	2	4	0
Microcephaly (HP: 0000252)	0	11	0	0	2	0
Seizure (HP: 0001250)	1	1	2	0	3	0
Global developmental delay (HP: 0001263)*	1	3	2	0	4	0
Intellectual disability (HP: 0001249) #	0	8	2	2	0	0
Abnormality of the face (HP: 0000271)	0	6	0	0	2	0
Growth abnormality (HP: 0001507)	1	4	0	1	0	0
Abnormality of the eye (HP: 0000478)	1	0	0	0	4	0
Hearing loss (HP: 0000365)	0	0	0	0	1	0
Abnormality of the musculoskeletal system (HP: 0033127)	0	1	0	0	4	0
Abnormality of the cardiovascular system (HP:0001626)	2	1	0	0	0	1
Abnormality of the skin (HP: 0000951)	0	2	0	0	0	0

*: This child is a mestizos of African American and Hispanic. #: This patient recurred NS after kidney transplantation. §: One patient received renal biopsy twice which showed MCD at first time and FSGS at second time. Both results are recorded in this table. ESRD: end stage renal disease, NS: nephrotic syndrome, FSGS: Focal Segmental Glomerulosclerosis, MCD: minimal change disease.

Discussion

SRNS account for 30% of the primary nephrotic syndrome in children, it is challenging due to that 30% – 50% of them gradually progress to ESRD within 10 years. This progress may be more rapid in patients with genetic background[11]. NUP nephropathy is identified as a rare monogenic cause of SRNS recently. Due to the limited cases reported previously, the association between clinical and genetic features remain unclear. Hence, the diagnosis of NUP nephropathy are mainly based on genetics analysis. In this study, we presented the clinical and genetic data of two Chinese children with early-onset SRNS. Three novel mutations in NUP genes (two in NUP107 and one in NUP93) were detected in these patients, thus expanding the variant spectrum of NUP nephropathy and raising concern about carrier screening and genetic counselling for their family members in the future. Furthermore, we summarized the clinical, pathologic and genetic features of 86 reported cases to explore the correlation between phenotype and genotype in NUP nephropathy.

NUP nephropathy was initially reported in 9 patients with NUP107 gene biallelic mutations by Miyake et al.[1]. The results from the in vitro assays showed that the p. D831A substitution weak the binding between NUP107 and NUP133. Although mutations in NUP nephropathy varied among the reported cases, founder mutations in some regions emerged gradually. The mutation c.2492A > C and c.1079-1083del in NUP107 had been identified as the founder mutations in East Asian[1–3], while c.1772G > T and c.1886A > G in NUP93 might be the founder mutations in Western Europe and Turkish respectively[8, 16]. Including our cases, East Asian race accounting for more than half of the reported cases with NUP nephropathy. A multicenter study in Korean revealed that NUP107 gene is one of the top 5 causative genes of SRNS or FSGS in pediatric patients[2]. However, as a novel genetic etiology of early-onset renal disease, it has not been given adequate attention at present. Current researches on genetic spectrum of renal disease in children did not include[21–24] or only include part of[11] NUP genes mutation detection. For the potential susceptibility of NUP nephropathy in Asians, NUP gene detection should be considered in gene panel of renal disease in Asia.

Both renal clinical and pathologic manifestations of NUP nephropathy are highly consistent that most patients suffered SRNS with FSGS in their early life. Apoptotic cells in the glomeruli and renal tubules cells were mentioned in some cases, which it might be the typical change of NUP nephropathy[1]. Small amount of immune complex deposition was observed in some cases but massive deposition of immune complex was reported in only one patient with IgA 4+ by immunofluorescence[19]. Two patients underwent repeated renal biopsy. One patient was found to have increased IgA deposition[19] and the other had pathological transformation from minimal change disease (MCD) to FSGS after 2 years[1], suggesting that performing renal biopsy at different time points may give different impressions of the pathological types. According to the limited reports, patients with NUP nephropathy were unresponsive to either steroids or immunosuppressants. Thus, it is recommended to perform genetic examination early in patients with SRNS or FSGS to avoid unnecessary long-term administration to steroids or immunosuppressants.

Rapidly progressive renal insufficiency, which it may be a result of treatment failure, is not uncommon and can increase the therapeutic difficulty for children with NUP nephropathy, especially in young children. Yet not all reported cases had ESRD. A girl presented SRNS at the age of 10 years and renal function remained normal until the last follow-up at the age of 24 years, dissimilar from her sister who carried the same biallelic heterozygous mutation in NUP107 had SRNS at the age of 11 years but progressed to ESRD one year later[1]. The pathophysiology of renal function deterioration in NUP nephropathy has not yet been studied, thus further researches are required to clarify the interacting mechanisms. In progressed patients, the effect of renal transplantation were better than those without NUP gene mutation[3, 11]. Only 1 case suffered plasma exchange dependent recurrent NS after renal transplantation. Fortunately, his proteinuria disappeared after comprehensive treatment therapy including rituximab and PE[25].

Extra-renal manifestations have made the comprehensive management of children with NUP nephropathy even more challenging. This study concluded that the involvement of nervous system is common, but there are significant differences between different genomics. All of the patients who carried c.303G > A mutations in NUP107 had microcephaly, and most of them with concomitant global developmental delay or intellectual disability[9, 12, 13]. However, no extra-renal involvement was reported in patients with mutations of c.2492A > C and c.1079-1083del in NUP107, which they are considered as the founder mutations in East Asia[1, 11]. The differences mentioned above exhibit a potential correlation between phenotype and genotype. Besides, nearly one-third of the cases did not provide relevant information about the extra-renal involvement. Due to the high expression of NUP in vivo, systemic symptoms deserve further attention from physicians during disease course.

Conclusion

Timely genetic testing may guide early diagnosis of NUP nephropathy to avoid prolonged steroid or immunosuppressant exposure in patients with SRNS. In Asian population, NUP genes detection should be routine considered in children with SRNS or FSGS. Extra-renal involvement in patients with NUP nephropathy is not uncommon, which it should be given more attention. Although patients with NUP nephropathy often progress to ESRD, their long-term prognosis after renal transplantation are favorable.

Declarations

Ethics approval and consent to participate

Ethics approval was not required for this study protocol since it was a retrospective analysis of observational data and does not use any tissue collected from human subjects.

Consent for publication

All authors read and approved the final manuscript.

Availability of data and materials

Written informed consent was obtained from the parents.

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Competing interests

The authors have declared no conflicts of interest.

Authors' contributions

All authors contributed to the study conception and design. This subject was designed by Xiaoyun Jiang and Lizhi Chen. Data collection and literature review were performed by Yuxin Pei and Liping Rong. Literature manual screen was performed by Zhilang Lin. Data analysis was performed by Cheng Cheng and rechecked by Mengjie Jiang. The first draft of the manuscript was written by Yuxin Pei and all authors commented on previous versions of the manuscript. The corresponding authors had full access to all the study data and had final responsibility for the decision to submit.

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Conflict of interests

The authors have declared no conflicts of interest.

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Figures

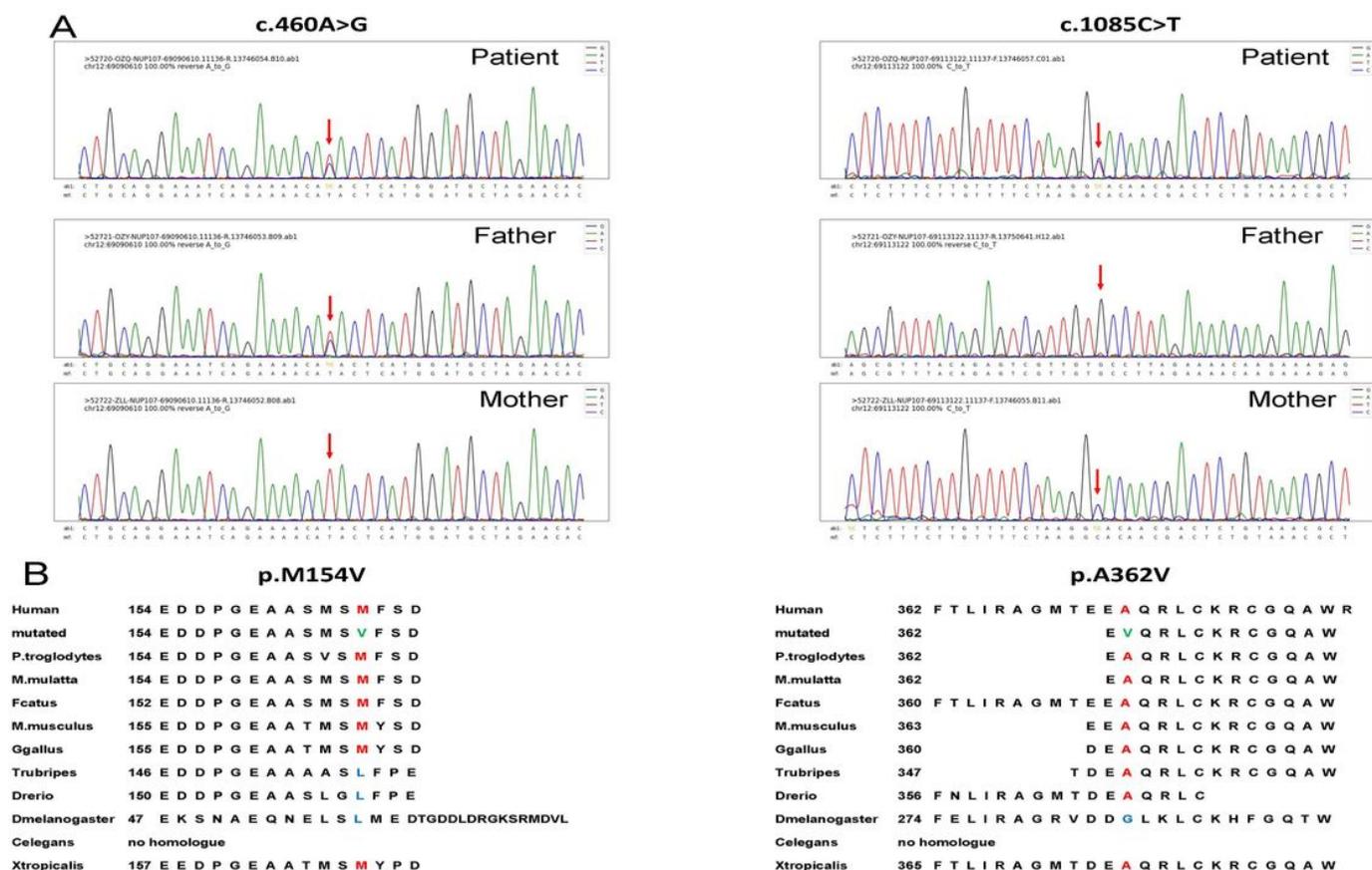


Figure 1

Identification of a novel biallelic heterozygosity compound heterozygous mutation in NUP107. (A). Sequence chromatograms for the patient and her family. (B). Protein alignment plot of the nucleoporin (NUP) 107 amino acid (AA) sequence for residue. The amino acids altered in this patient are largely conserved.

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