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Exceptional Case

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Novel *NUP160* mutations related to simultaneous congenital nephropathy and ovarian insufficiency

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ABSTRACT

Nucleoporins, as major components of nuclear pore complex, have been recently discovered to participate in organ development. Here, we report a young female patient with nephrotic proteinuria resistant to immune suppressant treatment and congenital ovarian insufficiency. Renal pathology confirmed focal segmental glomerulosclerosis and whole-exome sequencing revealed compound heterozygous mutations in Nucleoporin 160 (*NUP160*), NM_015231.2 c.4154C>T (p.Pro1385Leu) and c.1102–9T>G. Notably, *NUP160* mutations have been associated with congenital nephropathy in four families. We also ruled out competing genetic variants implicated in focal segmental glomerulosclerosis and ovarian dysgenesis. Our identification of two novel *NUP160* mutations associated with congenital nephropathy and ovarian insufficiency simultaneously contributes to a deeper understanding of nuclear pore complex function in the urogenital system.

Keywords: congenital nephropathy, focal segmental glomerulosclerosis, Nucleoporin 160, ovarian dysgenesis

BACKGROUND

The nuclear pore complex (NPC) is a macromolecular assembly consisting of >30 types of nucleoporins (Nup), facilitating bidirectional traffic between the cytoplasm and nucleoplasm. The core scaffold of the NPC consists of inner and outer ring complexes, with the NUP107-160 complex serving as the major subunit of the outer ring structure. The NUP107-160 complex is evolutionarily conserved and is composed of nine distinct subunits including Nup160/Nup120, Nup133, and Nup107 [1]. While nucleoporins are best understood as part of the NPC, recent discoveries have highlighted their additional functions in embryogenesis and organ development [2].

Nucleoporin 160, encoded by the *NUP160* gene located on chromosome 11p11.2, plays a crucial role in early stages of NPC assembly. In a significant proportion of steroid-resistant nephrotic syndrome (SRNS), renal pathology reveals focal segmental glomerulosclerosis (FSGS). More than 50 genes have been associated with monogenic FSGS and mutations in several NUPs, such as *NUP160*, *NUP 107*, and *NUP 85*, have been identified causative for SRNS [3].

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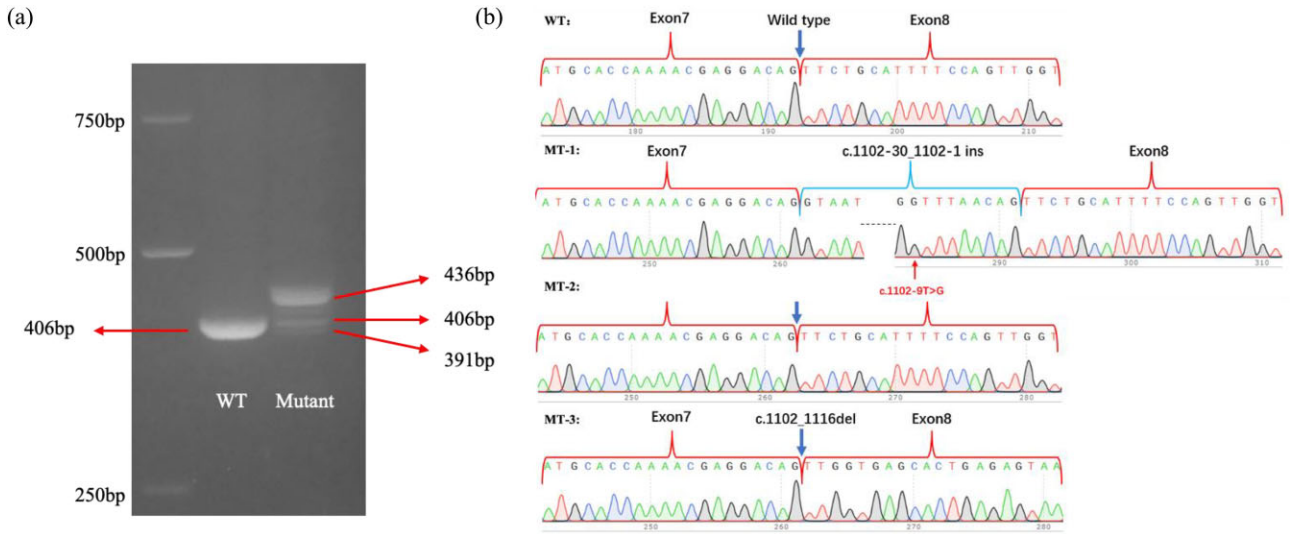

Figure 1: Verification of the effects of *NUP160* c.1102–9T>G on mRNA splicing. (a) The WT appears as a single band while the mutant *NUP160* generates three bands in the minigene splicing assay. (b) Sanger Sequencing image of the gel recovery products in (a) confirms the WT mRNA splicing product includes exons 7, 8, and 9 without any abnormal splicing events. By contrast, the *NUP160* c.1102–9T>G mutation leads to two additional abnormal splicing products: one with a partial deletion of exon 8 (c.1102_1116del) and another with an insertion (c.1102–30_1102–1 ins) between exons 7 and 8.

CASE PRESENTATION

Here we report a 22-year-old female patient who first discovered proteinuria (urine protein-to-creatinine ratio 4400 mg/g Cr) during a routine health examination. Her serum albumin level was 34.9 g/l, and her glomerular filtration rate was within the normal range. A renal biopsy was performed, and light microscopy identified 57 glomeruli, of which eight were sclerosed, 27 showed ischemic sclerosis, and one displayed ischemic wrinkling. Segmental sclerosis was specifically observed in nine glomeruli. Electron microscopy revealed segmental fusion of podocyte foot processes, intact basement membranes, and no electron-dense deposits. FSGS was thus diagnosed, and the patient was prescribed Tacrolimus and Losartan. However, despite continuous treatment and appropriate drug concentrations, there was no alleviation of proteinuria after 6 months of treatment.

Moreover, ovarian dysgenesis was another vital clinical manifestation of the patient. She did not experience spontaneous menstruation, and was diagnosed of uterine hypoplasia at the age of 17 despite normal chromosome karyotype. Low levels of estradiol (<15 pg/ml) and progesterone ($P < .08$ ng/ml) were evident with increased luteinizing hormone (37.67 IU/l) and follicle stimulating hormone (86.7 IU/l).

Whole-exome sequencing (WES) was performed to explore the mutual cause for immune suppressant-resistant FSGS and ovarian insufficiency. Compound heterozygous mutations in *NUP160*, specifically NM_015231.2 c.4154C>T (p.Pro1385Leu) and c.1102–9T>G, were identified. Further pedigree analysis revealed that the patient's biological mother also carried the heterozygous c.4154C>T variant but she did not exhibit any renal or ovarian manifestations. The patient's father was out of reach, and her half-siblings were claimed to be free of any similar symptoms.

A minigene assay was conducted. Plasmids containing either the wild-type (WT) *NUP160* minigene or the NM_015231.2 c.1102–9T>G variant were generated and transfected into 293T cells. Reverse transcription was performed following RNA extraction. Polymerase chain reaction and gel electrophoresis revealed one band in the WT and three bands in the mutant cells (Fig. 1a). Sanger sequencing of the products was performed to identify the exact splicing alterations (Fig. 1b). In conclusion, the intron NM_015231.2 c.1102–9T>G mutation influences *NUP160* mRNA splicing.

DISCUSSION

The underlying mechanisms of NUP mutations in nephrotic syndrome are currently being explored. Knocking out genes encoding the NUP107-160 complex (*NUP107*, *NUP85*, or *NUP133*) in immortalized human podocytes has been shown to activate the Rho-like small guanosine triphosphatase Cdc42, a regulator for actin cytoskeleton plasticity, and disrupted podocyte physiological function [3]. Moreover, specific knockdown of *NUP160* inhibited mouse podocyte proliferation, and disrupted the integrity of the slit diaphragm, leading to a drastic increase in proteinuria and glomerulosclerosis in mice [4]. To summarize, modulation of podocyte cytoarchitecture and filtration membrane could be potential pathogenic mechanisms of *NUP* mutations in nephrotic syndrome. A summary of *NUP160* mutations reported in four families to cause nephrotic syndrome is presented in Table 1.

Furthermore, as >50 genes have been linked to FSGS [5], we checked the patient's WES data and additional 24 variants in 16 reported genes were identified with allele frequency less than 1/1000. According to American College of Medical Genetics and Genomics guidelines, one variant (*ALG1*: NM_001330504.1 c.C959A) was of uncertain significance with BP4 evidence, one variant (*INF2*: NM_022489.4 c.1259_1270del) was likely benign with BP3 evidence, and the other 22 variants were all benign with BA1+BS2, BA1, or BS1 evidence. Since no other pathogenic/probably pathogenic FSGS-related variants were found in the patient, her renal phenotype was largely ascribed to her *NUP160* mutations.

Interestingly, the patient also experienced ovarian dysgenesis in addition to proteinuria. Therefore, genes recorded to

Table 1: Characteristics of patients with congenital nephropathy and *NUP160* mutations.

Patient	Onset age/sex/ethnicity	NUP 160 mutation	Renal symptoms and Pathology	Extrarenal symptoms	Family history	Ref
Patient 1	7/F/Chinese	Compound heterozygous mutation of c.2407G>A (p.Glu803Lys) and c.3517C>T (p.Arg1173*)	24hUP 8.34 g, Alb 24 g/l, TC 4.55 mmol/l, SCr 53μmol/l; resistant to prednisone, cyclophosphamide, and *Tripterygium wilfordii*; ESRD at 15; FSGS	Not evident	One sister and one brother died of unknown causes in early childhood; Two older siblings were affected with SRNS, and both died of ESRD at 17	[7]
Patient 2	16/M/Chinese	Compound heterozygous mutation of c.2407G>A (p.Glu803Lys), and c.2728C>T (p.Arg910*)	Nephrotic syndrome resistant to steroids or other immuno-suppressant; FSGS	Not evident	A younger sister with the same mutation had proteinuria at 7	[3]
Patient 3	3.5/F/Chinese	Compound heterozygous mutation of c.3656T>G (p.Leu1219Trp), and c.2241+1G>T	24hUP 2.83 g, Alb 20 g/l; resistant to prednisone and tacrolimus; eGFR decrease during follow-up; FSGS	autism spectrum disorder; cord-like uterine	NA	[8]
Patient 4	11/M/Arabian	Homozygous c.1179+5G>A (p.Phe368_Gln393del)	Nephrotic syndrome resistant to steroids	Developmental delay, epilepsy	19-year-old sister had similar seizure and FSGS	[9]

cause ovarian dysgenesis in Online Mendelian Inheritance in Man and Kyoto Encyclopedia of Genes and Genomes (KEGG) DISEASE Database were also checked in her WES data. Only two variants (*SPIDR*: NM_001080394.4 c.776+401T>C, *SPIDR*: NM_001080394.4 c.2341+2700T>A) were identified and both were benign with BA1+BS2 evidence. Homozygous mutations in *NUP107*, which encodes another major component of the NUP107-160 complex, have been reported in patients with ovarian dysgenesis or premature ovarian insufficiency, and mice carrying the same *Nup107* mutation exhibited a similar subfertile phenotype [6]. The underdevelopment of the ovary in *NUP107*-mutated patients potentially occurred in an NPC-dependent manner. Therefore, we hypothesize that the *NUP160* mutations are also responsible for the patient's ovarian insufficiency.

To summarize, we present a case of a young female with immune suppressant-resistant FSGS and ovarian dysgenesis. The patient carries compound heterozygous mutations in *NUP160*, specifically NM_015231.2 c.4154C>T (p.Pro1385Leu) and c.1102–9T>G, which have not been reported to date and highly likely linked to her clinical manifestations. Our report adds two novel potential pathogenic *NUP160* variants to the existing cases of congenital nephropathy previously documented in four families and deepens the understanding of NUP function in urogenital system development.

ETHICS APPROVAL AND PATIENT CONSENT

This study was approved by Ethics Committee of Peking Union Medical College Hospital. A written informed consent was obtained from the patient.

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AUTHORS' CONTRIBUTIONS

Y.L., M.N., and M.L. contributed to the diagnosis, clinical data collection, and manuscript writing of the case. Y.L. and X.H. did literature searches and reviews. L.X. instructed the genetic data analysis. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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