Clinical Case Report

Medicine®

OPEN

A human ciliopathy with polycystic ovarian syndrome and multiple subcutaneous cysts

A rare case report

Kangan Tan, MD[a], Peng Liu, PhD[b], Lili Pang, MD[a], Wanna Yang, PhD[a], Fengqin Hou, MD, PhD[a,c,*]

Abstract

Rationale: Ciliopathies is a group of clinically and genetically overlapping disorders due to cilia abnormalities and multiple organ systems are involved in.

Patient concerns: We present a young female patient who showed renal function impairment, Caroli syndrome (CS), liver cirrhosis, polycystic ovarian syndrome, and multiple subcutaneous cysts.

Diagnoses: The patient was diagnosed with ciliopathy according to the clinical manifestations and whole-genome sequencing.

Interventions: She received treatment of intravenous albumin, polyene phosphatidyl choline, furosemide, and antisterone.

Outcomes: The patient showed clinical improvement in her edema and liver tests, and ultrasonography revealed that the ascites had disappeared. Unfortunately, the edema relapsed a year later. The patient received the same treatment as before, and there was clinical improvement of the edema. Since the family cannot afford liver and kidney transplantation, the patient only accepted symptomatic treatment.

Lessons: Polycystic ovarian syndrome and multiple subcutaneous cysts have never before been reported to be associated with ciliopathy. This finding could remind doctors to consider the possibility of ciliopathy disease for patients suffering from similar conditions. In addition, the phenotype of the patient differs from those of patients reported with the same mutations, which also reminds doctors that the clinical manifestation of a given mutation may show patient-specific differences. This case report extends the phenotypic spectrum of ciliopathy, and these findings might represent a new ciliopathy syndrome, which could facilitate the diagnosis of ciliopathies.

Abbreviations: CS = Caroli syndrome, GFR = glomerular filtration rate, UTP = urinary total protein, ESRD = end-stage renal disease, NPHP = nephronophthisis, MKS = Meckel-Gruber syndrome, JS = Joubert syndrome, PKHD1 = polycystic kidney and hepatic disease gene 1, CHF = congenital hepatic fibrosis.

Keywords: Caroli syndrome, CC2D2A, ciliopathy, INVS, multiple subcutaneous cysts, PKHD1, polycystic ovarian syndrome, renal function impairment

1. Introduction

Ciliopathies include a group of disorders associated with genetic mutations encoding defective proteins resulting in either abnormal formation or function of cilia. Cilia are a cellular organelle with numerous biological roles, such as whole-cell locomotion, fluid movement, sensing and transducing environmental signals, and sexual reproduction.[1] Given the diverse functions and extensive distribution of cilia, disorders affecting cilia, including loss of cilia and DNA damage due to replication stress, can affect multiple organs.[2] The most frequently affected organs are the liver, skeleton, brain, eyes, kidneys, and ectoderm.[3] There are 2 subsets of renal ciliopathies: the common autosomal dominant polycystic kidney disease (ADPKD),[4] recessive ciliopathies collectively referred to as autosomal recessive polycystic kidney disease (ARPKD), and nephronophthisis-related ciliopathies (NPHP-RCs).[5] NPHP-RC is frequently associated with extrarenal manifestations and accounts for the majority of genetically mediated chronic kidney disease (CKD) during childhood and adolescence. The term NPHP-RCs include a group of rare autosomal recessive cystic kidney diseases including nephronophthisis (NPHP), Senior–Løken syndrome (SLS), Joubert syndrome (JS) and Meckel-Gruber syndrome (MKS).[6]

NPHP-RCs comprise the majority of genetic end-stage renal diseases (ESRDs) during the first three decades of life. The most prominent renal features of NPHP-RCs are increased echogenicity and corticomedullary cysts on ultrasound. Renal histology reveals tubular atrophy, basement membrane disintegration,

Editor: N/A.

Kangan Tan and Peng Liu contributed equally to this work.

The patient has agreed to publish this case, and informed consent has been obtained.

The authors have no conflicts of interest to disclose.

[a] *Department of Infectious Diseases and the Center for Liver Diseases, Peking University First Hospital, Beijing,* [b] *Department of Cardiology, Ordos Central Hospital, Ordos School of Clinical Medicine, Inner Mongolia Medical University, Inner Mongolia,* [c] *Department of Infectious Diseases, Peking University International Hospital, China.*

[*] *Correspondence: Fengqin Hou, No. 8, XiShiKu Street, XiCheng District, Beijing 100034, China (e-mail: houfqys@139.com).*

Medicine (2018) 97:50(e13531)

Received: 20 June 2018 / Accepted: 22 October 2018

http://dx.doi.org/10.1097/MD.0000000000013531

interstitial fibrosis, and cyst formation.[7] Approximately 15% of affected individuals with NPHP-RC show extrarenal organ involvement.[8] Ciliopathic features have been associated with mutations in over 40 genes to date. However, the phenotypes associated with ciliary dysfunction have yet to be fully elucidated and require continued investigation. Here, we report a new phenotype of ciliopathy to enrich the knowledge of ciliopathies.

2. Case presentation

An 18-year-old woman presented with severe peripheral edema for 7 months. The edema was associated with hematuria, proteinuria, increased nocturia, repeated fever with a maximal temperature 38 °C, and diarrhea with 3 or 4 loose stools a day. Due to the proteinuria, the patient restricted her own protein intake. She denied hemafecia, abdominal pain, chills or unintentional weight loss. She had been diagnosed with Caroli syndrome (CS) and renal lesions due to hematuresis at 7 years of age and polycystic ovarian syndrome by doctors in the Department of Gynecology at age 16 years but had no history of hypertension or diabetes mellitus. She denied a family history of CS, polycystic ovarian syndrome, and kidney disease. Her menarche did not occur until she took oral progesterone when she was 16 years old. Upon physical examination, multiple subcutaneous cysts were found in her face. On subsequent physical examination, her blood pressure was 110/55 mmHg with a pulse of 87 bpm. Her respiratory rate was 18/min. She was alert and answered questions appropriately. Her lungs were clear of auscultation. Cardiac examination revealed a regular rhythm. Laboratory workups showed creatinine 2.2 mg/dL, serum albumin 13.1 g/l and a glomerular filtration rate (GFR) 38.7 ml/min. Urine dipstick showed positive protein and low urine specific gravity (1.010). Urinalysis was remarkable for 70 to 80 red blood cells (RBCs) and nephritic sediment characterized by dysmorphic red cells; 24 h urine protein collection showed UTP of 0.31 g/l. Urine protein electrophoresis showed albumin 86.7% and large molecule protein 13.3%. The test for urine osmotic pressure was 307 mOsm/kg (600–800 mOsm/kg). Markers of livers function and hepatic enzymes were also abnormal, with alanine aminotransferase (ALT) 42U/L (7–40IU/L), aspartate aminotransferase (AST) 79U/L (13–35IU/L), total bilirubin 2.94 mg/dL, direct bilirubin 0.84 mg/dL, and prealbumin (PAB) 23.4 mg/L (200–400 mg/L). Coagulation showed prothrombin time activity (PA) 64%, prothrombin (PT) 13.5 s (9.0–11.5 s), prothrombin ratio (PTR) 1.34 s (0.89–1.13 s), international normalized ratio (INR) 1.35, and activated partial thromboplastin time (APTT) 40.2 s (26.9–37.6 s). Her blood lipid level was within normal limits. Autoantibodies were not detected, and the levels of serum IgG, IgM and IgA were in normal ranges; only the levels of complement 3 (C3) and complement 4 (C4) were below normal. Complete blood count showed a modestly low platelet count (93×10^9/L), normal white blood cells (3.6×10^9/L) and a low level of hemoglobin (86 g/L). Echocardiography revealed mild dilation of the left ventricle (5.4 cm) with a normal ejection fraction of 65%, but an electrocardiogram (ECG) obtained during the hospitalization did not show any obvious problems. The so-called "central dot sign," defined as small foci of strong contrast enhancement within dilated intrahepatic ducts, along

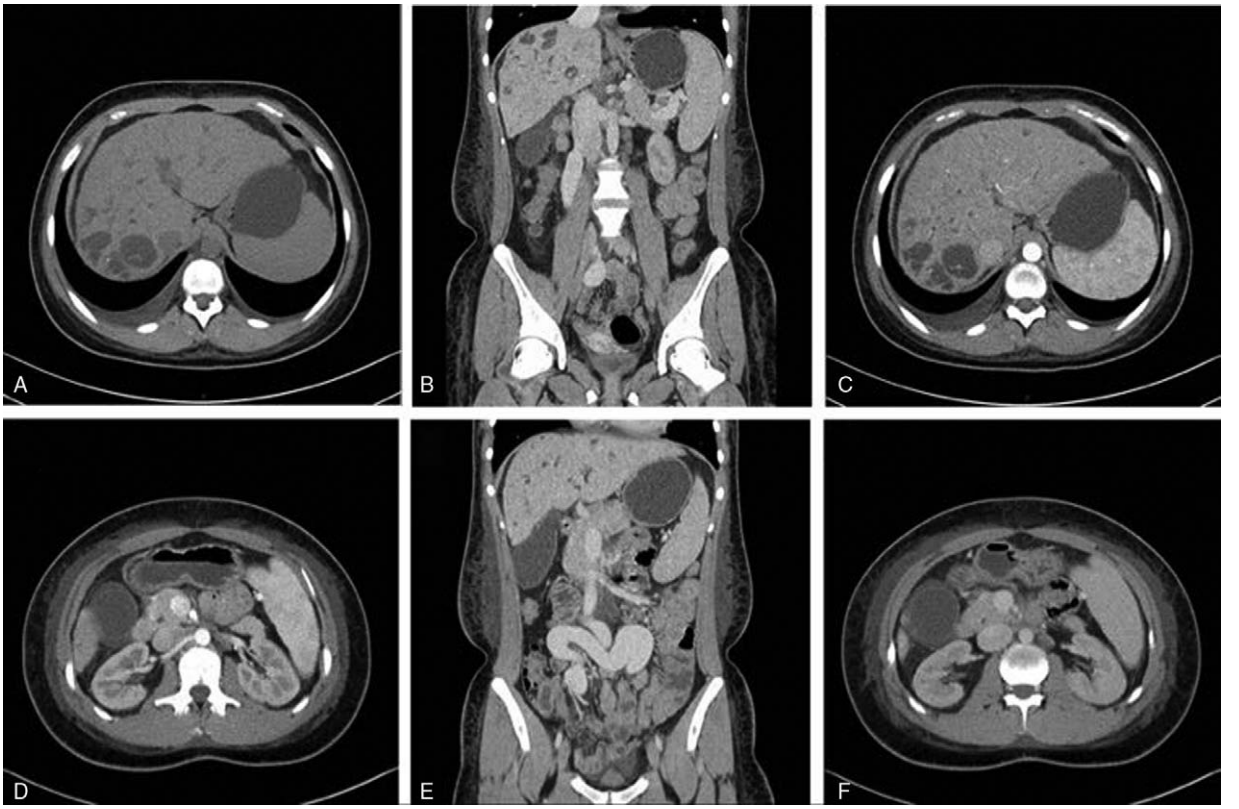

Figure 1. Pictures of CT scans of the patient. (A and B) Non-enhanced CT images of the patient through the abdomen demonstrating intrahepatic bile duct dilation. (C) Contrast-enhanced CT images of the patient through the upper abdomen demonstrating CS with the central dot sign. (D) Non-enhanced CT images through the abdomen demonstrating no enlargement of the kidneys or bilateral renal cysts. (E and F) Non-enhanced CT images through the abdomen demonstrating collateral vein circulation portal hypertension with splenoportoscintigraphy. CS = Caroli syndrome, CT = computed tomography.

with liver cirrhosis, portal hypertension, splenomegaly, and ascites was found on computed tomography (CT) scan (See Fig. 1). Renal ultrasonography and CT showed diffuse renal lesions without observed cysts. Brain CT was normal.

2.1. Mutation analysis

Next-generation sequencing library preparations were constructed following the manufacturer's protocol (NEBNext Ultra DNA Library Prep Kit for Illumina), and whole-genome sequencing was performed by Genewiz company. For each sample, 1 μg genomic DNA was randomly fragmented to <500 bp by sonication (Covaris S220). The fragments were treated with End Prep Enzyme Mix for end repairing, 5' phosphorylation and dA-tailing in one reaction, followed by a T-A ligation to add adaptors to both ends. Size selection of adaptor-ligated DNA was then performed using AxyPrep Mag PCR Clean-up (Axygen), and fragments of ~410 bp (with an approximate insert size of 350 bp) were recovered. Each sample was then amplified by PCR for 8 cycles using P5 and P7 primers, with both primers carrying sequences that can anneal with the flowcell to perform bridge PCR and the P7 primer carrying a six-base index allowing for multiplexing. The PCR products were cleaned up using AxyPrep Mag PCR Clean-up (Axygen), validated using an Agilent 2100 Bioanalyzer (Agilent Technologies, PaloAlto, CA, USA), and quantified by Qubit2.0 Fluorometer (Invitrogen, Carlsbad, CA, USA). Then, libraries with different indexes were multiplexed and loaded on an Illumina HiSeq instrument according to the manufacturer's instructions (Illumina, San Diego, CA, USA). Sequencing was carried out using a 2x150 paired-end (PE) configuration; image analysis and base calling were conducted by the HiSeq Control Software (HCS) + OLB + GAPipeline-1.6 (Illumina) on the HiSeq instrument.

Data analysis: Cutadapt (V1.9.1) was used to remove the sequences of the adaptors, polymerase chain reaction (PCR) primers, content of N bases greater than 10%, and bases of quality lower than 20. BWA (V0.7.12) was used to map clean data to the reference genome. The mapping results were processed by Picard (V1.119) to remove duplication. The Unified Genotyper was used to call SNV/InDels with GATK(V3.4.6) software. SNV/InDel annotation was performed by Annovar (V21 Feb 2013). Pindel and CNVnator were used to conduct genomic structure variation analysis.

Whole-genome sequencing revealed 4 mutations in 3 genes that have ever previously been reported to be associated with ciliopathies (see Table 1). Then, PCR was performed to sequence her parents' 4 mutations in three genes by Genewiz company. PCR was conducted using the following primers: CC2D2A (c. 1268G>A:p.R423Q) forward, 5'- TGGTTTCTTTTCTAACTCCCAGT-3', and reverse, 5'-TCCCTTTTGTCTCTAGCTGGA-3'; CC2D2A(c.1127A>C:p.E376A) forward, 5'-TGTTGACACAGAATTTTCAAGAA-3', and reverse, 5'-CCACTGCACTCCAACCTG-3'; INVS (rs7024375) forward, 5'-CGTCCGTCATCTAGAACTTCC-3', and reverse, 5'-AGAGCAGAAAGAAGAGGCAG-3'; PKHD1 (c. 8518C>T:p.R2840) forward, 5'-AAAGAAGAGTGAATACCTGGTGA-3', and reverse, 5'-TGCTGACACTATAAAGCTGTGTG-3'.

The patient's mutations included a homozygous variant c.1127A>C:p.E376A (rs16892095) in coiled-coil and C2 domain containing 2A (CC2D2A) originating from her healthy parents, who were both heterozygous for the same mutation; a homozygous variant (rs7024375) in INVS (NPHP2); a heterozygous variant c. 8518C>T:p.R2840 in PKHD1; and a heterozygous variant c. 1268G>A:p.R423Q in CC2D2A. The latter three mutations were found in either her mother or her father but not both.

Based on the above tests and imaging results, the following diagnoses were established: CS, liver cirrhosis, portal hypertension, splenomegaly, ascites, diffuse renal disease, polycystic ovarian syndrome, and multiple subcutaneous cysts.

After treatment with intravenous albumin (20 g/d), polyene phosphatidyl choline and oral furosemide (40 mg/d), and antisterone (60 mg/d) for 5 days, she showed an apparent clinical improvement in her symptom of edema. Serum albumin showed obvious elevation to 23.8 g/l and creatine also declined to normal (1.2 mg/dL), but 24 h urine protein collection showed that UTP was elevated to 4.46 g/l. We failed to perform renal biopsy because coagulation function had not been restored. The reexamination of liver function showed no obvious improvement, but hepatic enzymes had returned to normal. Ultrasonography revealed that the ascites had disappeared. Unfortunately, her edema relapsed a year later. The patient received the same treatment as before, and there was clinical improvement of the edema and liver tests. Since the family cannot afford the liver and kidney transplantation, the patient only accepted symptomatic treatment.

Table 1

Mutations in CC2D2A, INVS(NPHP2) and PKHD1 in the patient and her parents.

Chromosome	Gene	Variant	Nucleotide change	Amino acid change	dbSNP	ID	hom/het	Alleles	Flanking Sequence
chr9	INVS (NPHP2)	5'UTR	–	–	rs7024375	patient	hom	T/G	TCTGACCTGGCTGGATATAG(T/G)GTACCGGCCCGGCAGGAGGG
						mother	none	–	–
						father	het	G/T	TCTGACCTGGCTGGATATAG(G/GT)GTACCGGCCCGGCAGGAGGG
chr4	CC2D2A	NM_001080522	c.1127A>C	p.E376A	rs16892095	patient	hom	A/C	GGAGCAGAGCATTAAGGCAG(A/C)GCTTGAAACACTGTATAAAA
						mother	het	A/G	GGAGCAGAGCATTAAGGCAG(A/AG)GCTTGAAACACTGTATAAAA
						father	het	A/G	GGAGCAGAGCATTAAGGCAG(A/AG)GCTTGAAACACTGTATAAAA
		NM_001080522	c.1268G>A	p.R423Q	unknown	patient	het	G/A	TCATCATCCCTGTTTTAGCC(G/GA)AGAGCATGTTTTGGCAGCCA
						mother	none	–	–
						father	het	G/A	TCATCATCCCTGTTTTAGCC(G/GA)AGAGCATGTTTTGGCAGCCA
chr6	PKHD1	NM_138694	c.8518C>T	p.R2840C	unknown	patient	het	G/A	GTCTCCCTCAGAAAACACTG(A/AG)CATACTTACCTTAAGTATAA
						mother	het	C/T	CAGAGGGAGTCTTTTGTGAC(C/CT)GTATGAATGGAATTCATATT
						father	none	–	–

CC2D2A = coiled-coil and C2 domain containing 2A, INVS = inversin, PKHD1 = polycystic kidney and hepatic disease 1.

3. Discussion

Ciliopathies have numerous clinical phenotypes or syndromes and involve many genetic mutations. Clinically, our patient presented kidney injury, CS, liver cirrhosis, polycystic ovarian syndrome, and multiple subcutaneous cysts. The diagnoses of CS, liver cirrhosis, polycystic ovarian syndrome, and multiple subcutaneous cysts were unquestionable, only the nature of the kidney injury was unclear because of the lack of a renal biopsy due to the abnormal coagulation. However, the renal damage was characterized by interstitial nephropathy (including increased nocturia, low urine specific gravity, and low urine osmotic pressure), though urine protein was mainly albumin, which did not conform to renal tubular urinary protein. There is previous evidence that ciliopathy can manifest as albumin-based proteinuria,[9,10] and thus the patient's renal manifestations conformed clinically to ciliopathy.

We found in our patient 4 mutations associated with ciliopathy in three genes. The 4 mutations all play pathogenic roles, but the specific roles of the mutations are not clear because the previously reported clinical symptoms corresponding to each mutation are not consistent with our patient's symptoms.

The first mutation was a homozygous mutation of CC2D2A (NM_001080522: c.A1127C:p.E376A, SNP (rs16892095)), which is reported to present as JS.[11] JS is a class of neurodegenerative diseases, and the main neuroimaging feature is the "molar tooth sign" (MTS), which is an essential criterion for the diagnosis of JS.[12] JS and related disorders (JSRD) is a wider classification for any individual who displays MTS together with additional non-neurological features. The non-neurological manifestations include polydactyly, oral frenulae and tongue tumors, hepatic fibrosis, and renal diseases. There have been reports that mutation of CC2D2A often causes JS or Meckel–Gruber syndrome (MKS). The features of MKS include encephalocoele, hepatic fibrosis, polydactyly, cleft palate, neural tube defects, and kidney cysts. There have also been reports of simultaneous variants in CC2D2A and polycystic kidney and hepatic disease gene 1 (PKHD1) in a patient diagnosed with MKS, which suggests a digenic or triallelic inheritance model and emphasizes the genetic complexity of ciliopathy.[13] Our patient with the homozygous mutation of CC2D2A, however, did not present any classical characteristics of MKS, JS or JSRD; only hepatic fibrosis and renal diseases were found.

The second mutation was a heterozygous mutation of CC2D2A (NM_001080522: c.G1268A:p.R423Q), which has been described in two patients who also presented as JS.[14]

The third mutation was a homozygous mutation of TrG at position rs7024375 in the 5'UTR of INVS (NPHP2),[15] which was previously reported in a heterozygous form. The common presentations between the girl and the reported patient were that both patients had renal damage, and all had preservation of renal function past childhood. Patients with mutations of NPHP2 usually show enlarged cystic kidneys, and renal cysts are a significant feature of NPHP. However, these were not observed in some patients with NPHP2 mutations.[16] Our patient had a similar situation in that her kidneys were not found to be enlarged, and no cysts were found. Patients with mutations of NPHP2 progress to ESRD around 5 years of age in most cases, but there have also been adult patients,[17] as was our patient. To date, the observed phenotypic spectrum of the NPHP2 gene is wide, and the extrarenal manifestations include abnormal left-right axis, cardiac abnormalities such as heart valve and septal defects, situs inversus, hepatic involvement, developmental delays and, recurrent bronchitis.[18] These studies suggest a previously proposed hypothesis that additional modifier genes might be present and oligogenicity may occur in cases of NPHP.[19]

The fourth mutation was in PKHD1 (NM_138694 c.C8518T: p.R2840C), which has been described many times in previous mutational studies and has always been associated with ARPKD.[20,21] PKHD1 is the only known gene responsible for all classical forms of ARPKDs, which belong to the group of ciliopathies characterized by the bilateral renal cystic disease with kidney enlargement and congenital hepatic fibrosis (CHF). A previous study even showed that PKHD1 might be a major gene for Caroli disease (CD).[15] Our patient had CD and CHF, perhaps resulting from this genetic mutation.

From what has been discussed above, though the corresponding clinical symptoms of the 4 mutations in three genes found in our patient are not fully consistent with those previously reported, the diagnosis of ciliopathy could be established for the following reasons:

1. the renal damage and CS began in the patient's childhood, which conforms to a genetic disease;
2. clinically, the patient's renal manifestations conform to ciliopathy;
3. the 4 mutations in 3 genes we found in the patient have been reported to be associated with ciliopathy;
4. ciliopathy is a genetically heterogeneous disease, mutations in a given gene may result in markedly different phenotypes, and a given manifestation can be induced by distinct genes[22–24];
5. it has been speculated that genetic interactions between distinct ciliopathy genes can result in new phenotypes that are not found in any of the single mutants alone, as previously proposed.[25]

The phenotype of our patient can be explained by this viewpoint, and this case may represent a new ciliopathy syndrome.

The diagnosis of ciliopathy complicated with renal lesions could be established, but the type of renal lesion was not very clear. Ciliopathies with renal lesions often manifest as renal cysts, but ultrasound and even CT scan did not find evidence of cystic changes. Many ciliopathy cases have been reported to possess microcysts, which might be better detected by renal biopsy rather than ultrasound.[26] However, we failed to perform renal biopsy due to the patient's abnormal coagulation function. Therefore, we cannot rule out the possibility that microcysts could be present in her kidneys. CS has been reported to be associated with ciliopathies, but polycystic ovarian syndrome and multiple subcutaneous cysts have not been reported to be associated with ciliopathies. In spite of this, several similar manifestations have been reported, such as diseases of the reproductive system and ectodermal abnormalities.[27,28] Because the ovary belongs to the reproductive system and skin is derived from the ectoderm, we cannot exclude the possibility that these 2 manifestations are associated with ciliopathy.

Ciliopathy is an autosomal recessive disease. We speculate that homozygous mutations of CC2D2A NM_001080522: c. A1127C:p.E3, SNP (rs16892095) and homozygous mutations of TrG at position rs7024375 in the 5'UTR of INVS might be the causative mutations because the former is present in both her parents, which combined to generate the homozygous mutation in the daughter, and the latter is also a homozygous mutation that has been previously reported to induce renal lesions while preserving renal function past childhood, as in our patient. Although the other two heterozygous mutations in CC2D2A and

PKHD1 in the patient came only from her mother or father, we could not rule out the pathogenic potential of these variants because they have all been reported to be associated with ciliopathy. Thus, genetic interactions between mutations in distinct cilia-related genes might contribute to the presence of multiple affected organs, as previously proposed.[29] This point could also explain why the patient's parents, with many of the same mutations as her, have remained healthy.

This is the first report of a human ciliopathy with polycystic ovarian syndrome and multiple subcutaneous cysts, which extends the phenotypic spectrum of ciliopathy and may represent a new ciliopathy syndrome. The main causative genes are hypothesized to be CC2D2A and INVS (NPHP2), which show homozygous mutations. Other heterozygous mutations in CC2D2A and PKHD1 might also affect the clinical manifestation. Further experiments are required to determine the mechanism of the rare phenotype this patient suffered from in her childhood.

Acknowledgments

The authors are grateful to the reviewers and editors for their critical reading of the manuscript and suggestions.

Author contributions

Data curation: Lili Pang and Wanna Yang.
Writing – original draft: Kangan Tan and Peng Liu.
Writing – review & editing: Fengqin Hou.
Kangan Tan orcid: 0000-0001-7060-8714.

References

[1] Badano JL, Mitsuma N, Beales PL, et al. The ciliopathies: an emerging class of human genetic disorders. Annu Rev Genom Hum G 2006;7:125–48.
[2] Slaats GG, Giles RH. Are renal ciliopathies (replication) stressed out? Trends Cell Biol 2015;25:317–9.
[3] Kempeneers C, Chilvers MA. To beat, or not to beat, that is question! The spectrum of ciliopathies. Pediatr Pulmonal 2018;53:1122–9.
[4] Szabó T, Orosz P, Balogh E, et al. Comprehensive genetic testing in children with a clinical diagnosis of ARPKD identifies phenocopies. Pediatr Nephrol 2018;33:1713–21.
[5] Stokman MF, van der Zwaag B, van de Kar NCAJ, et al. Clinical and genetic analyses of a Dutch cohort of 40 patients with a nephronophthisis-related ciliopathy. Pediatr Nephrol 2018;33:1701–12.
[6] Schueler M, Halbritter J, Phelps IG, et al. Large-scale targeted sequencing comparison highlights extreme genetic heterogeneity in nephronophthisis-related ciliopathies. J Med Genet 2016;53:208–14.
[7] Srivastava S, Molinari E, Raman S, et al. Many genes—one disease? Genetics of nephronophthisis (NPHP) and NPHP-associated disorders. Front Pediatr 2018;5.
[8] Hildebrandt F, Attanasio M, Otto E. Nephronophthisis: disease mechanisms of a ciliopathy. J Am Soc Nephro 2009;20:23–35.
[9] Walczak-Sztulpa J, Wawrocka A, Sobierajewicz A, et al. Intrafamilial phenotypic variability in a Polish family with Sensenbrenner syndrome and biallelicWDR35 mutations. Am J Med Genet A 2017;173:1364–8.
[10] Bacchetta J, Chapurlat R, Bouvier R, et al. Nephronophthisis-like nephritis associated with fibrous dysplasia of bone. Pediatr Nephrol 2008;23:1559–63.
[11] Lehman AM, Eydoux P, Doherty D, et al. Co-occurrence of Joubert syndrome and Jeune asphyxiating thoracic dystrophy. Am J Med Genet Part A 2010;152A:1411–9.
[12] Lee N, Nam SO, Kim YM, Lee YJ. A neonate with Joubert syndrome presenting with symptoms of Horner syndrome. Korean J Pediatr 2016;59(Suppl 1):S32–6.
[13] Rossetti S, Torra R, Coto E, et al. A complete mutation screen of PKHD1 in autosomal-recessive polycystic kidney disease (ARPKD) pedigrees. Kidney Int 2003;64:391–403.
[14] Bachmann-Gagescu R, Ishak GE, Dempsey JC, et al. Genotype-phenotype correlation in CC2D2A-related Joubert syndrome reveals an association with ventriculomegaly and seizures. J Med Genet 2012;49:126–37.
[15] Courcet JB, Minello A, Prieur F, et al. Compound heterozygous PKHD1 variants cause a wide spectrum of ductal plate malformations. Am J Med Genet A 2015;167A:3046–53.
[16] Tory K, Rousset-Rouviere C, Gubler MC, et al. Mutations of NPHP2 and NPHP3 in infantile nephronophthisis. Kidney Int 2009;75:839–47.
[17] Okada M, Sugimoto K, Shimada Y, et al. Association of INVS (NPHP2) mutation in an adolescent exhibiting nephronophthisis (NPH) and complete situs inversus. Clin Nephrol 2008;69:135–41.
[18] Moalem S, Keating S, Shannon P, et al. Broadening the ciliopathy spectrum: motile cilia dyskinesia, and nephronophthisis associated with a previously unreported homozygous mutation in the INVS/NPHP2 gene. Am J Med Genet A 2013;161A:1792–6.
[19] Hoefele J, Wolf MTF, O'Toole JF, et al. Evidence of oligogenic inheritance in nephronophthisis. J Am Soc Nephrol 2007;18:2789–95.
[20] Losekoot M, Haarloo C, Ruivenkamp C, et al. Analysis of missense variants in the PKHD1-gene in patients with autosomal recessive polycystic kidney disease (ARPKD). Hum Genet 2005;118:185–206.
[21] Bergmann C, Senderek J, Windelen E, et al. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). Kidney Int 2005;67:829–48.
[22] Drivas TG, Wojno AP, Tucker BA, et al. Basal exon skipping and genetic pleiotropy: a predictive model of disease pathogenesis. Sci Transl Med 2015;7:291r–7r.
[23] Szymanska K, Berry I, Logan CV, et al. Founder mutations and genotype-phenotype correlations in Meckel-Gruber syndrome and associated ciliopathies. Cilia 2012;1:18.
[24] Al-Hamed MH, Kurdi W, Alsahan N, et al. Genetic spectrum of Saudi Arabian patients with antenatal cystic kidney disease and ciliopathy phenotypes using a targeted renal gene panel. J Med Genet 2016;53:338–47.
[25] Pellissier LP, Lundvig DMS, Tanimoto N, et al. CRB2 acts as a modifying factor of CRB1-related retinal dystrophies in mice. Hum Mol Genet 2014;23:3759–71.
[26] Sun L, Tong H, Wang H, et al. High mutation rate of NPHP3 in 18 Chinese infantile nephronophthisis patients. Nephrology (Carlton) 2016;21:209–16.
[27] Ul Hassan A, Hassan G, Khan SH, et al. Ciliopathy with special emphasis on kartageners syndrome. Int J Health Sci 2009;3:65–9.
[28] Konstantinidou AE, Fryssira H, Sifakis S, et al. Cranioectodermal dysplasia: a probable ciliopathy. Am J Med Genet Part A 2009;149A:2206–11.
[29] Masyukova SV, Winkelbauer ME, Williams CL, et al. Assessing the pathogenic potential of human Nephronophthisis disease-associated NPHP-4 missense mutations in C. elegans. Hum Mol Genet 2011;20:2942–54.