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Single Case

The First Pediatric Case of an IFT140 Heterozygous Deletion Causing Autosomal Dominant Polycystic Kidney Disease: Case Report

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Keywords
Autosomal dominant polycystic kidney disease · Child · IFT140 gene · Exon deletion

Abstract
Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, which is mainly caused by pathogenic variants in two particular genes: *PKD1* and *PKD2*. ADPKD caused by variants in other genes (*GANAB* or *IFT140*) is very rare. ***Case Report:*** In a 6-year-old girl examined for abdominal pain, a cystic mass in the upper part of the right kidney was detected during an abdominal ultrasound. She was referred to pediatric oncology and urology for suspicion of a tumorous mass and the condition was assessed as a cystic nephroma. A heminephrectomy was then performed on the upper cystic part of the right kidney. The histological examination was inconclusive; therefore, genetic testing was recommended. Kidney and liver cysts were detected sonographically in the mother, but DNA analysis of the *PKD1* and *PKD2* genes did not reveal any pathogenic variant; the cause of the pathological formation in the kidneys remained unclear. Nine years later, next-generation sequencing of a panel of genes for kidney disease was performed and a heterozygous deletion was found on chromosome 16; this included exon 13 of the *IFT140* gene. The same deletion was found in the patient's mother. Currently, the patient is 14 years old and has mild sonographic findings, normal glomerular filtration, mild proteinuria, and hypertension. ***Conclusion:*** Pathogenic variants of the *IFT140* gene very rarely cause ADPKD; however, they should be considered in all children with autosomal dominant forms of PKD and asymmetric/atypical cystic kidney involvement or negative findings of *PKD1* and *PKD2*.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, mainly caused by mutations in two genes in particular: *PKD1* (ca. 85% of patients) and *PKD2* (ca. 10% of patients) [1]. ADPKD caused by mutations in other genes is very rare. Among them, a pathogenic variant in the *IFT140* gene discovered in 2022 is the most common (ca. 2% of patients) [2]. Until now, all described patients with IFT140-ADPKD were adults [2, 3]. Here, we present the first pediatric patient with *IFT140*-ADPKD who broadened the age-related phenotype of patients with *IFT140* gene anomalies and the first patient with a deletion of exon 13.

Case Report

In the 6-year-old girl examined for abdominal pain, a cystic mass of the upper part of the right kidney (50 mm) was detected during an abdominal ultrasound and confirmed by an abdominal CT (Fig. 1, 2). The CT showed normal finding of the liver and other extra-renal abdominal organs. She had normal renal function (serum creatinine 39 μmol/L, Schwartz eGFR 115 mL/min/1.73 m^2), negative albuminuria and proteinuria (0.91 and 14 mg/mmol creatinine, respectively), and a normal blood pressure reading (106/68 mm Hg).

She was referred to pediatric oncology and urology for suspicion of a tumorous mass. There the condition was assessed and determined to be a cystic nephroma, so a hemi-nephrectomy was performed on the upper cystic part of the right kidney [4]. Histological examination was not conclusive, as it was suspected of localized/unilateral segmental cystic disease, and therefore, the exact etiology of the cystic lesion was unknown; genetic counseling was recommended. During the genetic testing phase, kidney cysts (maximal diameter 70 mm) and liver cysts were detected sonographically in the mother, but DNA analysis of the *PKD1* and *PKD2* genes did not reveal any pathogenic mutation/variant. The cause of the pathological formation in the kidney of the girl, therefore, remained unclear, as she did not fulfill the diagnostic criteria for pediatric ADPKD [5].

She was followed in pediatric nephrology where she was found to have normal serum creatinine and glomerular filtration rates (41–53 μmol/L and 108–119 mL/min/1.73 m^2), along with normal albuminuria and proteinuria. She developed mild arterial hypertension requiring treatment with the ACE inhibitor ramipril; echocardiography showed normal finding without left ventricular hypertrophy or cardiomyopathy. A kidney ultrasound showed the progression of cystic kidney disease; an increase in the number of small cysts without further large cyst formation. Since the first DNA analysis was performed in the 6-year-old female patient, additional genes have been identified with variants that very rarely (<5% of cases) cause ADPKD such as *GANAB, DNAJB11, BICC1, ALG5, ALG9,* or *IFT140.*

Nine years after the first DNA analysis done by Sanger sequencing, the implementation of next-generation sequencing (NGS, Illumina platform), consisting of a panel of 484 genes for kidney disease and ciliopathy, was performed on the patient and a heterozygous deletion was found on chromosome 16 in the 16p13 region; containing exon 13 of the *IFT140* gene. The same deletion was found in her mother with polycystic kidney and liver disease. The deletion was detected using copy number variation analysis during NGS (Varsome Clinical Programme, Saphetor S.A.). The exact localization and confirmation using MLPA could not be performed because MLPA is currently not available for the analysis of the IFT140 gene at the MPLA producer. Therefore, we confirmed the deletion using an alternative independent method of relative quantification for the confirmation of deletions/duplications. In both girl and her mother all the "classical" ADPKD genes (e.g., *PKD1, PKD2)* were wild type including deletions.

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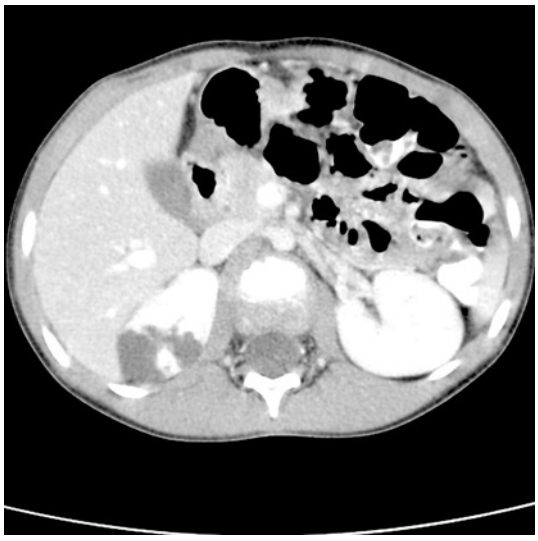

Fig. 1. Abdominal CT (axial images) with a large cystic mass of the upper part of the right kidney.

Currently, a 14-year-old girl has been found to have mild sonographic involvement (~15 cysts, max. size 10 mm), normal serum creatinine and glomerular filtration (60 μmol/L and 101 mL/min/1.73 m^2), mild proteinuria (24 mg/mmol creatinine), and mild hypertension which is being treated with ramipril 1.25 mg once daily.

Discussion

Here, we present the first pediatric case of *IFT140*-ADPKD and the first case of ADPKD caused by the deletion of exon 13 in the *IFT140* gene. Autosomal dominant polycystic kidney disease has a prevalence of 1:500–1,000 making it the most frequent monogenic chronic kidney disease. In adults, it leads to chronic renal failure in about 60% of patients [1], and in children, it can manifest with treatable complications such as proteinuria or hypertension in about 30% of them [6, 7]. ADPKD is caused by pathogenic variants in mainly two particular genes; *PKD1* and *PKD2*. ADPKD caused by variants in other genes are very rare.

In 2022, Senum et al. [2] described initial patients with autosomal dominant polycystic kidney disease with having heterozygous variants in the IFT140 gene on chromosome 16; the same chromosome where *PKD1* is localized. They consisted of 2% of all ADPKD patients and are, therefore, the 3rd most common gene mutated in ADPKD patients after the *PKD1* and *PKD2* genes. In both published studies dealing with IFT140-ADPKD, 39 cases are described [2, 3]. In all 39 patients, only pathogenic variants were described such as frameshift, nonsense or splicing variants. There have been no patients found with both the IFT140 gene and exon deletion, with neither being described in the literature; therefore, our patient is the first patient with exon 13 IFT140 gene deletion. More specifically, the extent of the deletion of our patient could not be assessed by the current molecular genetic methods. The *IFT140* gene is located on chromosome 16 in the 16p13.3 region and has 29 exons. Bialellic pathogenic variants are associated with a phenotype of Mainzer-Saldino syndrome which is yet another ciliopathy with an even more severe phenotype [8].

The clinical phenotype of IFT140-ADPKD in adult patients is described as atypical (contrary to the typical phenotype in *PKD1/PKD2* patients) and is characterized by fewer large kidney cysts, limited chronic kidney insufficiency, later onset hypertension and fewer liver cysts [2]. Recently, two adult patients with monoallelic IFT140 variants showed dilated cardiomyopathy suggesting a potential link between IFT140 and heart

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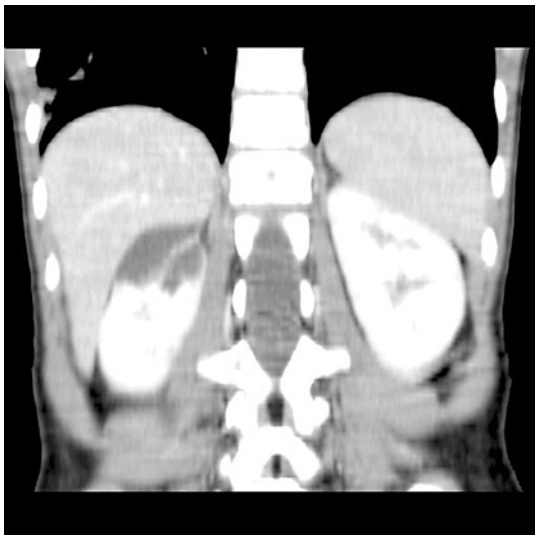

Fig. 2. Abdominal CT (coronal images) with a large cystic mass of the upper part of the right kidney.

disease [9]. The patients had several very large kidney cysts in both kidneys with some asymmetry. Kidney function which is usually normal or only mildly reduced in chronic kidney disease (CKD) stages 2-4, was only present in one of the patients who also had a solitary kidney along with IFT140-ADPKD and who was determined to actually have end-stage kidney disease (CKD stage 5). Kidney function is, therefore, better preserved than in patients with PKD1 and PKD2 [2]. Furthermore, IFT140-ADPKD patients are diagnosed at an older age (mean age of 53 years) in comparison to PKD1/PKD2 patients and are often diagnosed incidentally [2]. The reason for the less severe phenotype of this atypical form of ADPKD may be due to the reduced penetrance of the IFT140 variants [10]. Hypertension is diagnosed in only about 60% of these individuals and approximately 20 years later than in ADPKD patients overall [2].

Another adult patient with *IFT140*-ADPKD was described by Ali et al. [3] who was a 44-year-old female with only eight cysts in each kidney, normal kidney function, and no liver cysts. The youngest patient with *IFT140*-ADPKD described to date was a 29-year-old female who had normal kidney function, normal blood pressure, and only a few small cysts in both kidneys [2]. Therefore, our patient is the youngest patient with *IFT140*-ADPKD and the first pediatric case to date.

Our pediatric patient manifested with a solitary but very large kidney cyst that resembled a cystic nephroma. Due to the diagnostic uncertainty and suspicion of malignancy, a surgical removal of the cystic lesion was performed. Histological investigations did not confirm the suspicion of malignancy and the cystic lesion seemed to be only a large simple cyst and the first manifestation of *IFT140*-ADPKD. She had no extra-renal involvement including liver or heart.

Urinary findings showed no hematuria, albuminuria, or proteinuria. Renal function has remained normal during the entire 8 years of follow-up. Her blood pressure raised to hypertensive levels and she needed antihypertension therapy with the ACE inhibitor ramipril.

Our first pediatric patient with *IFT140*-ADPKD showed some similar phenotypical features of adults with *IFT140*-ADPKD, namely few (one) large cysts with asymmetric cystic involvement, normal-sized kidneys, normal renal function, and nearly normal proteinuria. Unexpectedly, our patient developed early hypertension which only occurs in about 30% of pediatric patients with ADPKD [7] and is less frequent in adults with *IFT140*-ADPKD than in ADPKD overall.

In conclusion, our first pediatric case shows that *IFT140*-ADPKD can also manifest in childhood. Furthermore, this case is the first patient with ADPKD caused by deletion of exon

13 of the *IFT140* gene. *IT140* gene anomalies should, therefore, be considered in all children with autosomal dominant forms of polycystic kidney disease, especially in those with asymmetric/atypical cystic kidney involvement, specifically with one or few very large cysts, or a negative DNA analysis of the two most common genes *PKD1* and *PKD2*.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the parent of the pediatric patient for publication of this case report and any accompanying images. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material at https://doi.org/10.1159/000539176.

Conflict of Interest Statement

All authors declared no conflict of interest.

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Author Contributions

T.S. and T.Š. made substantial contributions to the conception and design of the work. T.S. collected, analyzed, and interpreted the clinical data and wrote the manuscript; T.Š. and A.B. collected the clinical data. J.I. and D.G. made molecular genetic analysis and wrote part of the manuscript. All authors read and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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