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Monoallelic *IFT140* variants causing childhood onset Autosomal Dominant Polycystic Kidney disease

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Abstract

IFT140 is a component of the intraflagellar transport-complex A involved in retrograde ciliary trafficking of proteins into primary cilia. Monoallelic IFT140 variants have been identified as an important cause of adult-onset Autosomal Dominant Polycystic Kidney Disease (ADPKD), accounting for ~2% of prevalent cases. Patients with ADPKD-*IFT140* usually present in later life with small numbers of large cysts and rarely develop kidney failure. Here, we report three genetically resolved cases of ADPKD-*IFT140* diagnosed in childhood or infancy from three unrelated pedigrees with ages at presentation ranging from *in utero* to 14 years of age. Each pedigree had a different familial *IFT140* variant, with no evidence of a second ADPKD gene variant on whole genome sequencing. All three children had normal kidney function and normal blood pressure although one child presented initially with a high cyst burden *in utero* and had impaired function on a DMSA scan. Despite the negative family history, cascade screening of first-degree relatives revealed previously undiagnosed ADPKD with features typical of adult-onset ADPKD-*IFT140*. Our findings highlight the need to consider *IFT140* as a potential cause of childhood early-onset ADPKD and expand the phenotypic spectrum of ADPKD-*IFT140*.

Index words: ADPKD, IFT140, early-onset PKD, intrafamilial variability, renal cysts

Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited kidney disease, affecting approximately 1:1000 individuals¹. It is characterised by the development of fluid filled cysts through the kidney along with extra renal manifestations such as Polycystic liver disease and intracranial aneurysms².

Germline variants in two genes, *PKD1* (78%) or *PKD2* (15%), which encode for Polycystin-1 and Polycystin-2, account for over 90% of ADPKD. The polycystin proteins form a complex localised to primary cilia, leading ADPKD to be described as a ‘ciliopathy’¹. Recently, several new minor genes for ADPKD have been identified, including *GANAB*³, *DNAJB11*⁴, *ALG5*⁵, *NEK8*⁶, *ALG9*⁷ and *IFT140*⁸. Apart from *NEK8*, patients with new gene variants tend to be older and have a milder, atypical cyst pattern. An increased prevalence of kidney cysts with reduced penetrance has been reported with other monoallelic gene variants (*ALG6*, *ALG8*, *PKHD1*)². Other diseases classically associated with other kidney presentations may also occasionally phenocopy ADPKD².

The IFT140 protein is a component of the intraflagellar transport-complex A, which localises to cilia and functions as a retrograde ciliary trafficking protein⁹. Kidney cells and tissue derived from *ift140* null mice have shortened, malformed cilia⁹ and patients with biallelic *IFT140* variants are associated with Short-rib Thoracic Dysplasia 9 with or without Polydactyly (SRTD9). SRTD9 is characterised by skeletal abnormalities, retinal dystrophy and chronic kidney disease (with and without renal cysts)¹⁰. An analysis of cystic kidney disease probands in the UK Biobank demonstrated that monoallelic *IFT140* variants represented 1.9% of naive screened families and 5.5% of those in whom previous testing had not identified variants in *PKD1* or *PKD2*⁸. This, and further work, suggest *IFT140* variants are the third most common cause of ADPKD^{8,11}.

To date, ADPKD related to *IFT140* variants are reported to present clinically in older adults with impaired kidney function but not kidney failure^{8,11,12}. Radiological features are atypical with small numbers of large cysts. Here, we present 4 paediatric cases of ADPKD-*IFT140* from three independent pedigrees. In all families, the index case was a child and cascade screening identified ADPKD in the wider family.

Case reports

Case 1 (IFT-1 pedigree)

A 7-year-old boy (IFT1-IV-2) presented with frequent UTIs to the paediatric department. A renal ultrasound demonstrated 4 cysts in each kidney with a complex multi-cystic area at the left upper pole measuring 1.9x2.0x1.9cm (Table S1). There was no family history of ADPKD or CKD. The patient was kept under annual monitoring before transitioning to adult services at the age of 18 and has remained normotensive with preserved renal function. An MRI at 18 years old demonstrated 12 cysts in the right kidney and 16 cysts in the left with a 4cm multi-septated cyst in the upper pole (Fig 1). Cascade screening (Fig 2) revealed his father (IFT1-III-2), uncle (IFT1-III-4) and grandfather (IFT1-II-2) having small numbers of large cysts (Table S1) and normal or near-normal kidney function (Table S2). The patient's two younger sisters had no cysts on ultrasound at 3 and 10 years of age.

Independently, the patient's younger cousin (IFT1-IV-4) presented with a *Staphylococcus Aureus* urinary tract infection at 10 months old. A renal ultrasound reported a small 0.3cm calculus in the left lower pole but no cysts. Follow-up ultrasound imaging four years later reported a multi-septated cyst measuring 5mm in the right mid-pole with two further cysts measuring 3 and 2mm (Table S1, Fig 1). The left kidney had no cysts, and no calculi were seen. Renal function was preserved (Table S2).

Genetic testing performed by next generation sequencing (17 gene cystic panel excluding *IFT140*) on the grandfather was initially negative¹³. Subsequent retesting by whole genome sequencing (WGS) identified a pathological monoallelic truncating *IFT140* variant in exon 21 (c.2598 C>G, p.Tyr866*). No other ADPKD associated variants were detected. Diagnostic testing confirmed the presence of this variant in the other affected adult family members. Testing for the patient's cousin (IFT1-IV-4) is currently pending.

Case 2 (IFT2 Pedigree)

The second case (IFT2-III-5) presented *in utero* due to abnormal foetal imaging. An ultrasound performed on the first day of life demonstrated an enlarged right kidney measuring 6.6cm with multiple tiny cysts and a 4.5cm left kidney with several tiny cysts. At 9 months of age, there were multiple cysts in the right with a 3cm cyst at the upper pole and a 0.7cm cyst on the left upper pole (Fig 1). His serum creatinine was 19 µmol/L and urea 9.6 mmol/L (Table S2). A DMSA scan performed at 3 months of age reported left kidney function at 74%, right kidney function at 26% with irregular uptake noted in both kidneys. Imaging at 9 years of age showed numerous cysts bilaterally but no liver cysts (Table S1). The patient remains normotensive with preserved renal function and is now 11 years old.

Cascade testing was offered to the wider family (Fig 2). His father (IFT2-II-5) underwent a renal ultrasound at 35 years old which demonstrated polycystic kidneys and an MRI revealing 25 cysts in each kidney and 1 liver cyst (Table S1, Fig S1). Nonetheless, he had normal kidney function and was normotensive. The mother had no detectable cysts.

Genetic testing of the father on a 17-gene cystic panel (excluding *IFT140*) was negative¹³ but as in the first case, subsequent retesting by WGS identified a pathogenic *IFT140* variant (c.1246C>T, p.Gln416*), later confirmed in the index case. Given the neonatal presentation,

the patient's mother (IFT2-II-6) also underwent WGS to exclude other ADPKD gene variants^{13,14}. All the patient's siblings remain asymptomatic but have not undergone ultrasound or genetic testing.

Case 3 (IFT3 Pedigree)

A 14-year-old girl (IFT3-III-1) was found to have renal cysts on imaging following a road traffic accident. CT imaging demonstrated a 5.3cm cyst in the left upper pole with several <1cm cysts in the lower pole and a single <1cm cyst in the right lower pole (Fig 1). She had normal renal function, blood pressure and urinalysis with no other medical history. WGS was performed on her and both parents. A pathological monoallelic *IFT140* variant (c.2399+1G>T) was detected in both the patient and her father (IFT3-II-1) (Fig 2) but no other ADPKD gene variants were found. Her latest ultrasound at 16 years old showed a 12cm right kidney with no cysts and a 11cm left kidney with 2 cysts (5.5cm largest). The father has normal kidney function and was found to have 3 cysts bilaterally, the largest being 3.5cm (Table S1, Fig S1). Her sister has had a normal ultrasound at 11 years but has not undergone genetic testing.

Discussion

In this report, we describe four cases of childhood onset ADPKD-*IFT140* from three different pedigrees. Recent work has identified *IFT140* variants as a common cause of ADPKD, accounting for approximately 2% of all cases^{8,11} and 4% in cases without a family history¹⁵. In patients with ADPKD-*IFT140*, kidney disease is usually mild with patients presenting later in life which rarely progresses to kidney failure¹².

Biallelic *IFT140* variants have been reported in several conditions including SRTD9¹⁰, male infertility¹⁶ and non-syndromic retinitis pigmentosa¹⁷. Although SRTD9 can lead to kidney

failure in childhood^{10,18}, the phenotype is clearly distinct from childhood-onset ADPKD-*IFT140* as reported here. There has only been one previous report of a monoallelic *IFT140* deletion variant in a child with ADPKD¹⁹. Our case series indicates that the true prevalence of ADPKD-*IFT140* in childhood may be underestimated.

The reason for the intrafamilial variability in all three pedigrees is unclear. Phenotypic discordance between generations in typical ADPKD pedigrees (*PKD1*, *PKD2*) has been reported with significant intra-familial variability in up to 12% of patients²⁰. The older patients in the families described here are in keeping with a typical late-onset ADPKD-*IFT140* presentation. One possible explanation is that these children were digenic for other ADPKD associated variants leading to early onset disease¹³. However, WGS did not detect a second variant in all 3 index cases. In two families, the unaffected mother also underwent WGS which was negative. The presence of the most common ADPKD-*IFT140* variant (c.2399+1G>T)⁸ in the second pedigree also suggests that the risk of early onset disease does not appear to be associated with specific variants.

To date, all the affected patients in this report have normal renal function with a low symptom burden. It is unclear if the patients who presented in childhood will progress more rapidly in adulthood than their older affected family members or if progression will mirror what is usually observed with atypical ADPKD. This may be the case for the children in the first and third pedigrees, but the prognosis is more uncertain in the child from the second pedigree given his neonatal presentation.

This report highlights the need to consider pathological *IFT140* variants as a potential cause of childhood-onset ADPKD. The prognostic implications of early-onset ADPKD-*IFT140* will become clearer with long-term follow-up. The present evidence does not however support predictive testing for pre-symptomatic children from ADPKD-*IFT140* families.

Supplementary material

Table S1: Summary of radiological features of the ADPKD-*IFT140* individuals

Table S2: Summary of clinical and genetic information about the ADPKD-*IFT140* individuals described

Figure S1: Radiology imaging of adult ADPKD-*IFT140* cases

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Financial disclosure

None declared.

Patient Protections

The authors declare that they have obtained written consent from the patients reported in this article for publication of the information about them that appears within this Case Report and any associated supplementary material.

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Figure legends

Figure 1. Radiology imaging of paediatric ADPKD-*IFT140* cases

Case IFT1-IV-2 (a and b): MRI imaging at 17 years of age showing 12 cysts on the right kidney and 16 on the left. The largest measures 26mm on the lower pole of the right and 4cm on the upper pole of the left. The majority are <5mm in length. Image a is a coronal T2 image (MRI) with the arrow pointing to the 4cm cyst with internal septation located at the upper pole of the left kidney. Images b is a coronal T2 MRI with the arrow pointing at the 26mm simple cyst on the lower pole of the right kidney.

Case IFT1-IV-4 (c and d): Ultrasound imaging at 4 years of age showing 3 cysts on the right kidney and none on the left. All cysts measured 2-5mm. Image c and d are longitudinal ultrasound pictures of the right kidney with the arrow pointing at the cysts.

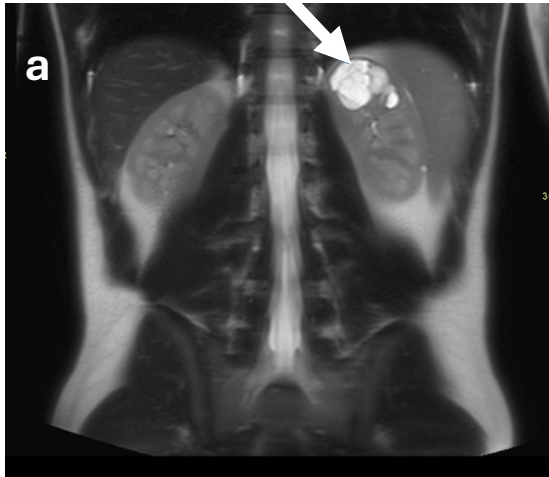
Case IFT2-III-5 (e and f): Ultrasound imaging at 9 months old showing multiple cysts on the right kidney with a 3cm cyst on the upper pole and a 0.7cm cyst on the left kidney. Image e is a longitudinal ultrasound picture of the right kidney with an arrow pointing at the 3cm cyst on the upper pole. Image f is a longitudinal ultrasound picture of the left kidney with the arrow pointing at the 7mm cyst at the upper pole.

Case IFT3-III-1 (g and h): Ultrasound (g) and CT (h) imaging at 14 years old showing normal right kidney and 2 cysts in the left, measuring 55mm and 5mm. Image g is a longitudinal ultrasound picture of the left kidney with the arrow pointing at the 5mm cyst on the interpolar region. Image h is a coronal CT with contrast with the arrow pointing at the 55mm cyst at the upper pole of the left kidney.

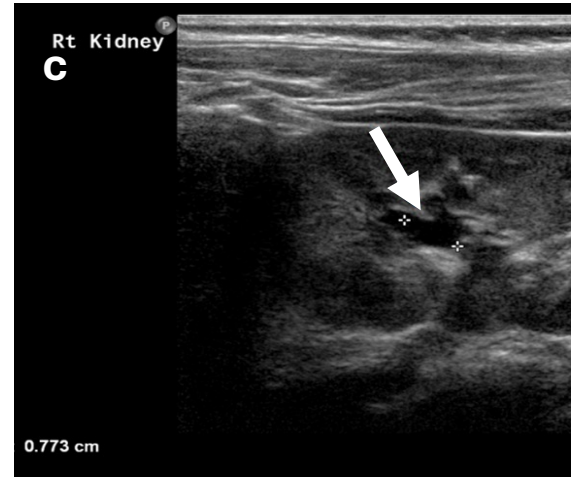
Figure 2: Pedigrees for the three childhood-onset ADPKD-*IFT140* cases

Pedigrees are numbered as IFT1, 2 and 3 and the affected individuals are shown as shaded symbols according to sex, known generations (I-IV) and numbered sequentially according to birth order (1-6). The index cases are indicated by arrowheads and the age at diagnosis or presentation for the individual shown.

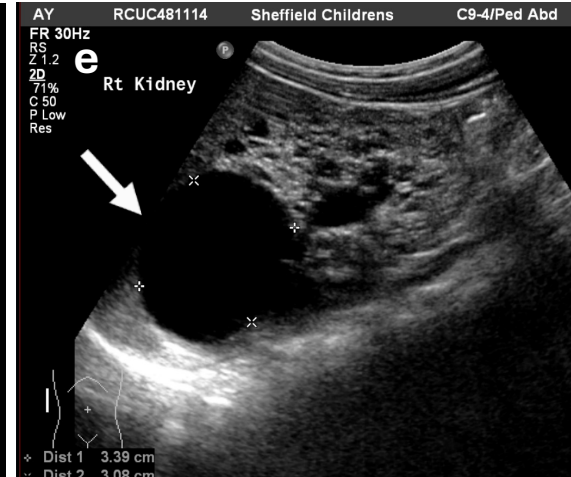
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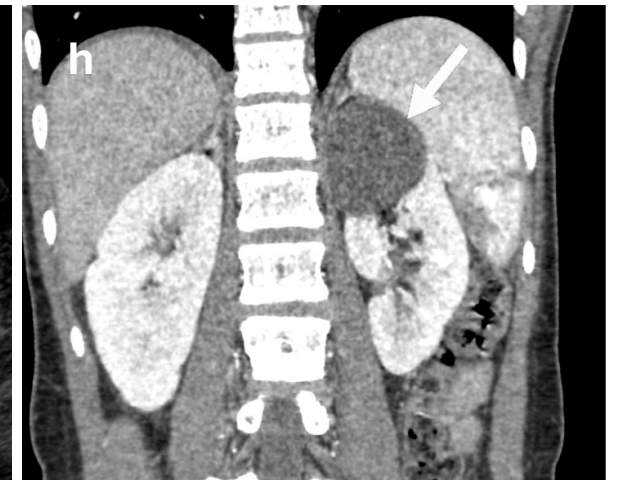
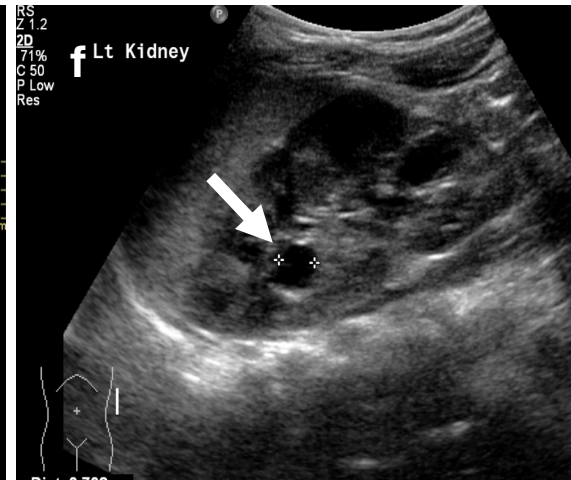
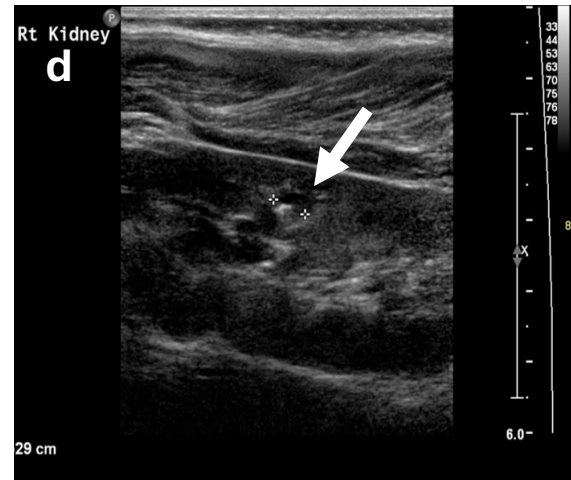
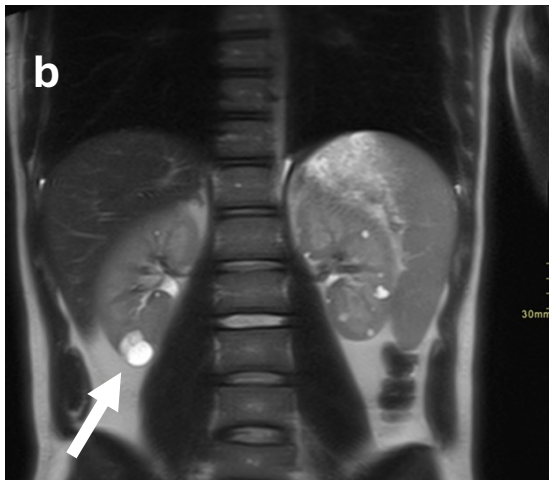
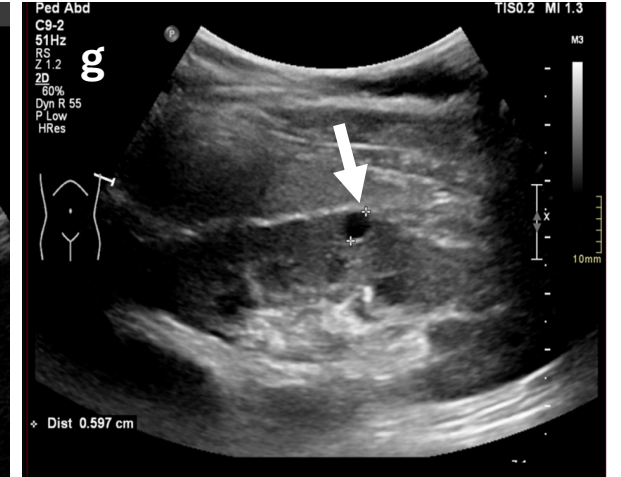
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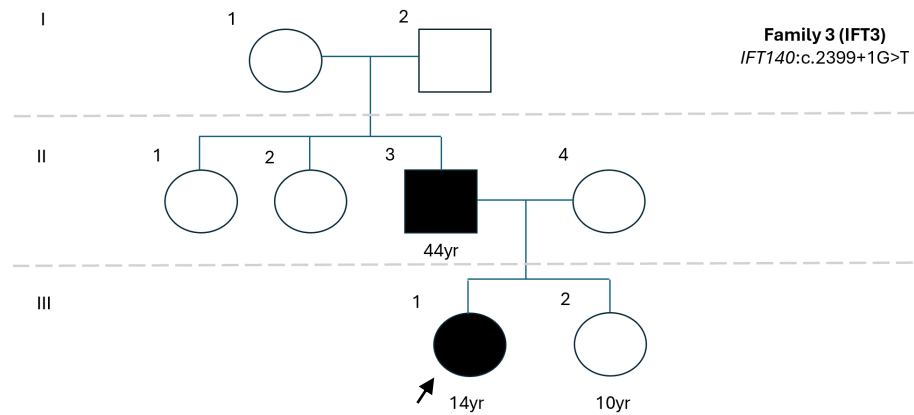
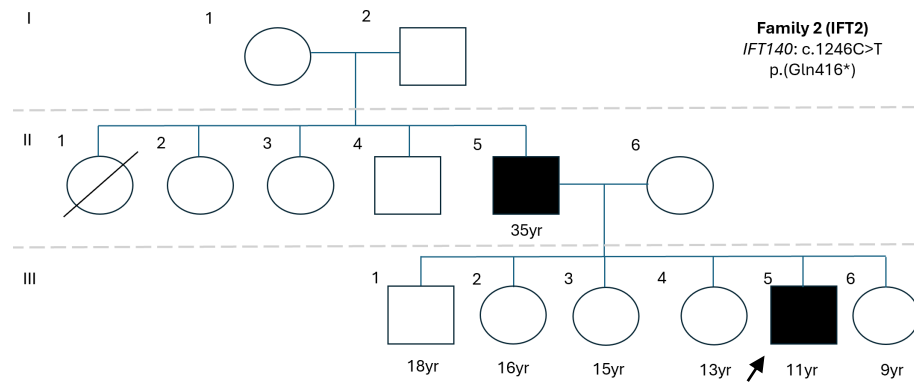
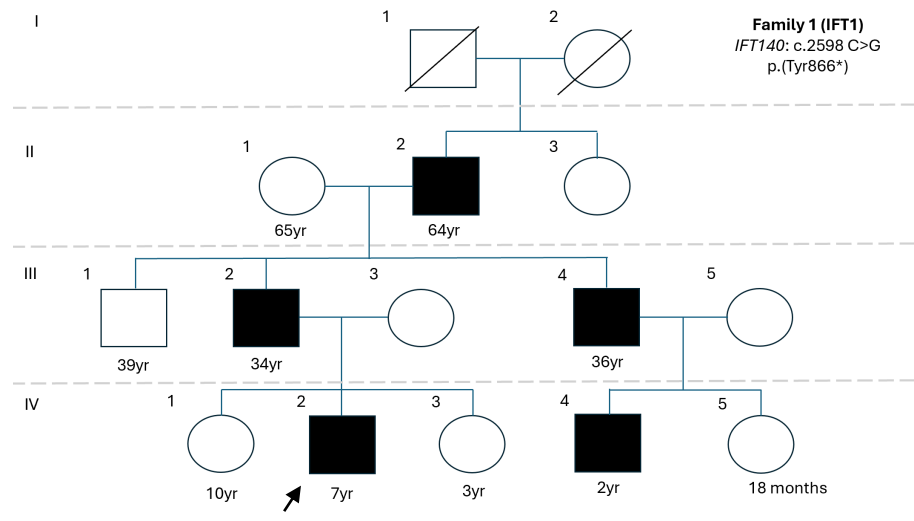


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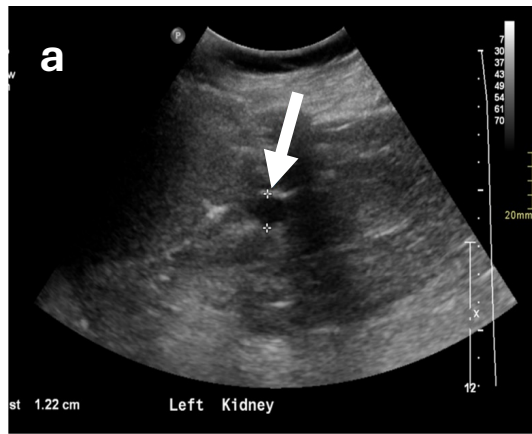


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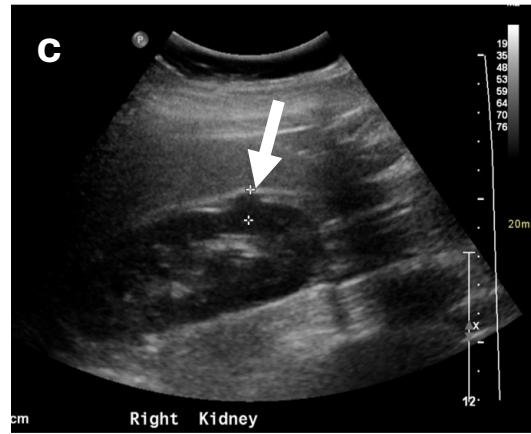




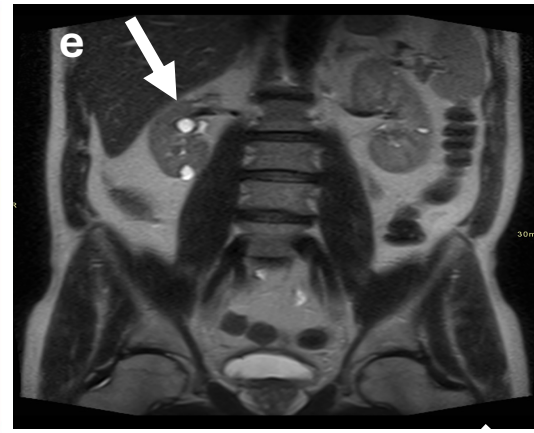
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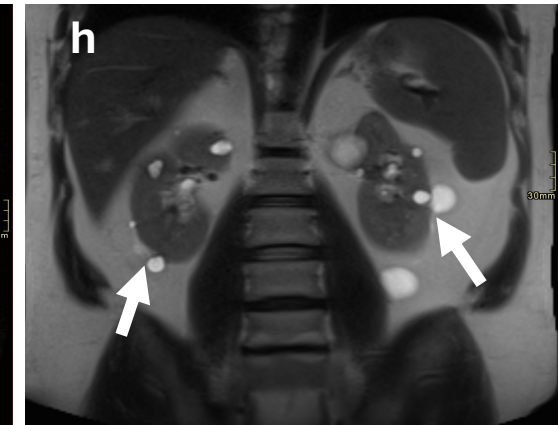
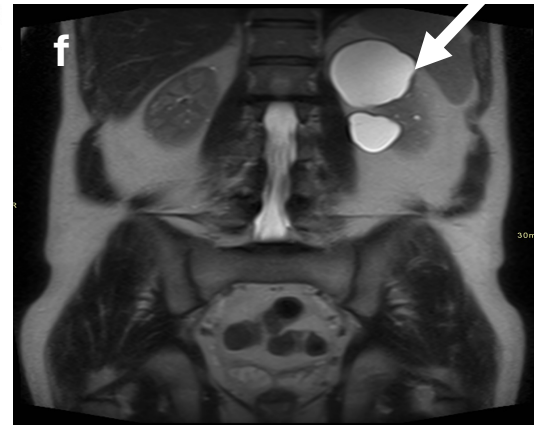
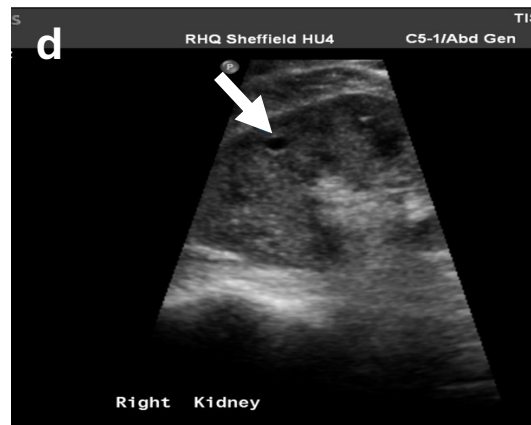
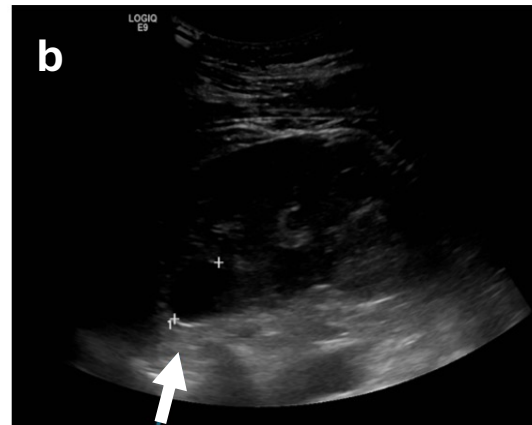
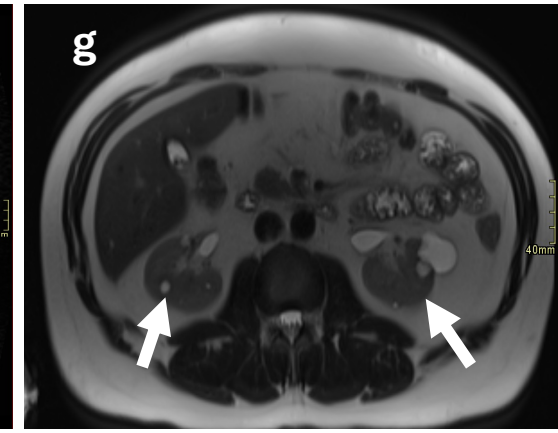
IFT1-III-4



IFT1-II-2



IFT2-II-5



IFT3-II-3

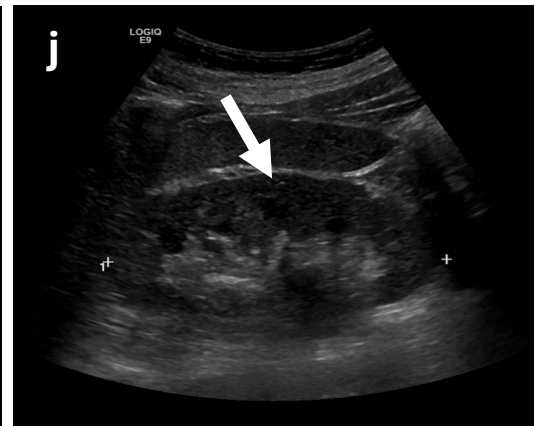
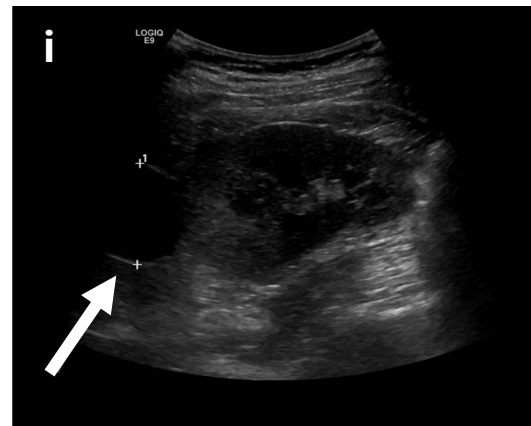


Table S1: Summary of radiological features of the ADPKD-*IFT140* individuals

Patient	Age at presentation	Cyst number at presentation (US)	Cyst number (MRI, CT)	Kidney length (US)	Kidney length and Total Kidney Volume in ml (MRI)	Extra renal cysts	Mayo class
IFT1-IV-2	7 years	4 right (largest 1.5cm, 0.3cm others), 4 left (with 4ml multicystic complex upper left pole) at 7 years	Right 12 (largest 2.6cm, majority <0.5cm); Left 16 (largest 4cm with multiple septations) at 17 years	8.3cm right, 8.3cm left at 4 years	12.6cm right, 12.3cm left (Total kidney volume 400ml) at 17 years	None	2A
IFT1-III-2	34 years	2 right (largest 1.3cm), 3 left (largest 1.2cm) at 34 years	NA	11cm right, 11.2cm left at 34 years	NA	None	NA
IFT1-III-4	36 years	1 right (0.8cm), 5 left (2cm largest) at 36 years	NA	11.1cm right, 11.3cm left at 36 years	NA	None	NA
IFT1-II-2	62 years	2 right (largest 1.6cm), 2 left (largest 4.6cm) at 63 years	Right 10, Left 9 (0.2-3cm) with large upper pole cyst (6.5cm) at 66 years	11.5cm right, 12cm left	11.5cm right, 12.4cm left (Total kidney volume 480ml)	None	2A
IFT1-IV-4	4 years	3 right (largest 0.5cm, multiseptated), 0 left at 4 years	NA	8cm right, 7.4cm left	NA	None	NA
IFT2-III-5	First day of life	Cystic dysplastic appearance bilaterally, largest cyst 19.2ml right upper pole, 0.7cm left upper pole at 9 months old.	NA	7.3cm right, 7cm left at 9 months old. 9.4cm right, 10.9cm	NA	None	NA

		Innumerable cysts bilaterally at 9 years old, largest cyst 4.9cm right upper pole.		left at 9 years			
IFT2-II-5	35 years	Less than 10 right (largest 0.8cm), less than 20 left (largest 2.2cm) at 35 years	Right 25 (all but 5 <1cm); Left 25 (largest 47mm, others <1cm) at 42 years	12.9cm right, 13.7 left at 35 years	Right 12.5cm, left 13cm at 42 years	Single liver cyst	2A
IFT3-III-1	14 years	2 left (largest 5.5cm), 0 right at 16 years	Left 6 (1-2mm) and 1 large (4.4cm) upper pole; Right 1 (2mm) at 14 years (CT)	12cm right, 11cm Left at 16 years		None	NA
IFT3-II-3	43 years	2 right (largest 3.5cm), 1 left (1.7cm)		10cm right, 11cm left at 43 years		None	NA

Table S2: Summary of clinical and genetic information about the ADPKD-*IFT140* individuals described

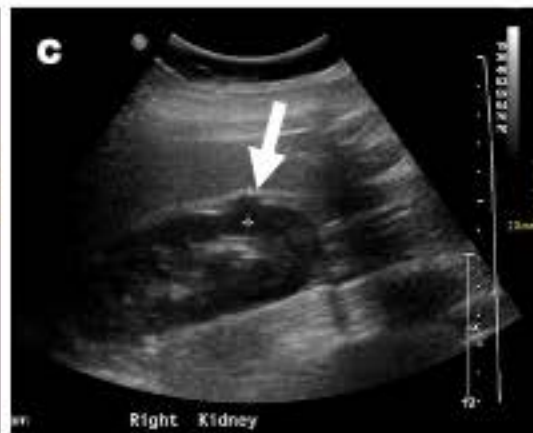
Patient	Age at presentation (years)	Creatinine in $\mu\text{mol/L}$ (Age)	eGFR (ml/min/1.73m^2)	Blood Pressure (mmHg)	Proteinuria (mg/mmol creatinine)	<i>IFT140</i> Variant
IFT1-IV-2	7	20 (7 years), 77(18 years)	>90 (7 years), >90 (18 years)	131/70	Urine Albumin/Creatinine Ratio- 4	c.2598 C>G, p.(Tyr866*)
IFT1-III-2	34	76 (34 years)	>90 (34 years)	131/77 (5mg Ramipril)	Normal urine Protein/Creatinine Ratio	c.2598 C>G, p.(Tyr866*)
IFT1-III-4	36	72 (34 years)	>90 (34 years)	130/80 (2.5mg Ramipril)	Normal urine Protein/Creatinine Ratio	c.2598 C>G, p.(Tyr866*)
IFT1-II-2	62	82 (62 years)	>90 (62 years)	130/80	Normal urine Protein/Creatinine Ratio	c.2598 C>G, p.(Tyr866*)
IFT1-IV-4	4	19 (4 years)	>90 (4 years)	101/76	Urine Protein/Creatinine Ratio- 9	Pending
IFT2-III-5	First day of life	19 (2 months), 48 (8 years)	>90 (8 years)	118/68	Urine Protein/Creatinine Ratio -17	c.1246C>T, p.(Gln416*)
IFT2-II-5	35	77 (35 years), 94 (46 years)	>90 (35 years), 84 (46 years)	137/85	Urine Protein/Creatinine Ratio -6	c.1246C>T, p.(Gln416*)

IFT3-III-1	14	40 (14 years), 54 (16 years)	108 (14 years), 94 (16years)	102 systolic	Nil on dip	c.2399+1G>T, p.?
IFT3-II-3	43	79 (34 years)	89 (43 years)	136/96	Urine Albumin/Creatinine Ratio- 4	c.2399+1G>T, p.?

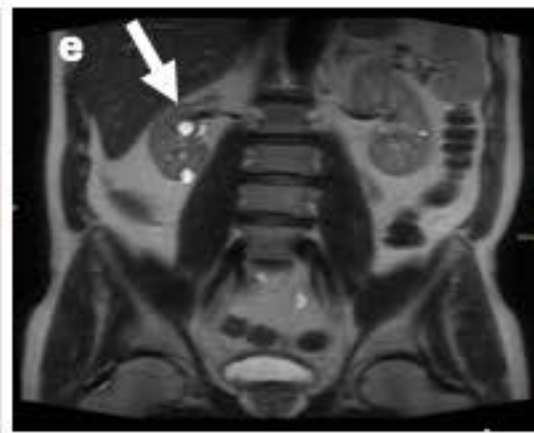
IFT1-III-2



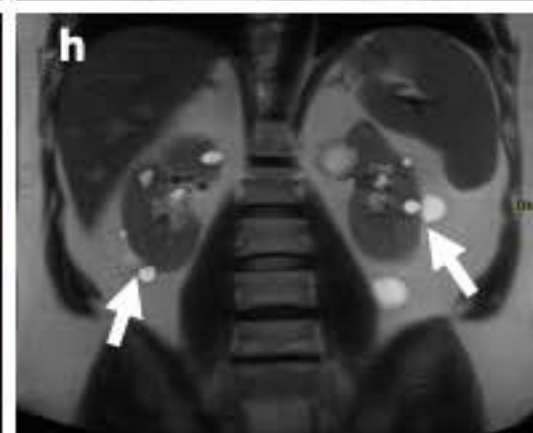
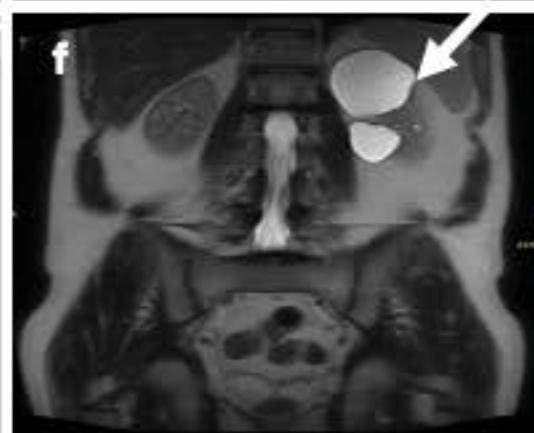
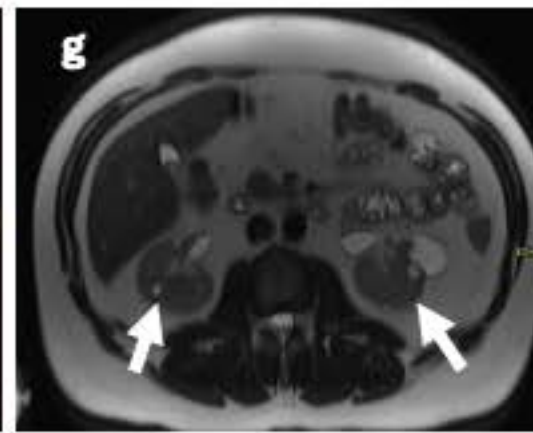
IFT1-III-4



IFT1-II-2



IFT2-II-5



IFT3-II-3



Figure S1. Radiology imaging of adult ADPKD-IFT140 cases

Case IFT1-III-2 (a and b): Ultrasound imaging at 36 years of age showing 1 cyst in the left kidney and 5 in the right with the largest measuring 2.7cm. Image a is a transverse ultrasound picture of the left kidney with an arrow pointing to a small simple cyst. Image b is a transverse ultrasound of the right kidney with the arrow pointing at a 27mm simple cyst located at the upper pole.

Case IFT1-III-4 (c and d): Ultrasound imaging at 34 years of age showing 3 cysts in each kidney the largest in each being 1.2-1.3cm. Image c is a longitudinal ultrasound of the right kidney with an arrow pointing at a 12mm simple cyst located at the lower pole. Image d is a transverse ultrasound of the right kidney with the arrow pointing at a simple cyst.

Case IFT1-II-2 (e and f): MRI imaging at 62 years of age showing 9 cysts in the right and 10 in the left kidney. The largest cyst was 6.5cm with the majority 2-3mm. Image e is a coronal T2 MRI with the arrow pointing at a 1cm cyst on the interpolar region of the right kidney. Image f is a transverse T2 MRI with the arrow pointing at the 47mm simple cyst located on the upper pole of the left kidney.

Case IFT2-II-5 (g and h): MRI imaging at 35 years of age showing 25 cysts in each kidney with the majority <1cm. The largest left cyst is 47mm and the largest right cyst is 36mm. Image g is an axial T2 MRI with both arrows pointing at the kidney which demonstrate multiple small simple cysts. Image h is a coronal T2 MRI with the arrows again pointing at both kidneys which demonstrate multiple simple cysts.

Case IFT3-II-3 (i and j): Ultrasound imaging at 43 years of age showing a 3.4cm simple cyst on the upper pole and an 8mm cyst on the lower pole of the right kidney (i). The left kidney with normal appearances (j). Image i is a longitudinal ultrasound of the right kidney with the arrow

pointing at a 34mm simple cyst located at the upper pole. Image j is a longitudinal ultrasound of the left kidney with the arrow pointing to the normal left kidney.