Clinical Kidney Journal, 2024, vol. 17, no. 2, sfae026

https://doi.org/10.1093/ckj/sfae026
Advance Access Publication Date: 15 February 2024
Original Article



ORIGINAL ARTICLE

# Monoallelic pathogenic *IFT140* variants are a common cause of autosomal dominant polycystic kidney disease–spectrum phenotype

Chiara Dordoni[1], Letizia Zeni[2], Diego Toso[2], Cinzia Mazza[3], Federica Mescia[2], Roberta Cortinovis[2], Laura Econimo[2], Gianfranco Savoldi[3], Federico Alberici[2], Francesco Scolari[2] and Claudia Izzi[1,4]

[1]Clinical Genetics Unit, Maternal-Infantile Department, ASST Spedali Civili, Brescia, Italy, [2]Division of Nephrology and Dialysis, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia and ASST-Spedali Civili of Brescia, Brescia, Italy, [3]Medical Genetics Laboratory, ASST-Spedali Civili of Brescia, Brescia, Italy and [4]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy

Correspondence to: Claudia Izzi; E-mail: claudia.izzi@unibs.it

## ABSTRACT

**Background.** Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder, characterized by development and enlargement of kidney cysts, eventually leading to end-stage kidney disease (ESKD). Pathogenic variants in the *PKD1* and *PKD2* genes are the major cause of ADPKD; additional rare variants in the *GANAB*, *DNAJB11*, *ALG5* and *ALG9* genes have been found in a minority of ADPKD patients. More recently, a significant number of ADPKD families have been linked to monoallelic variants in the *IFT140* gene.

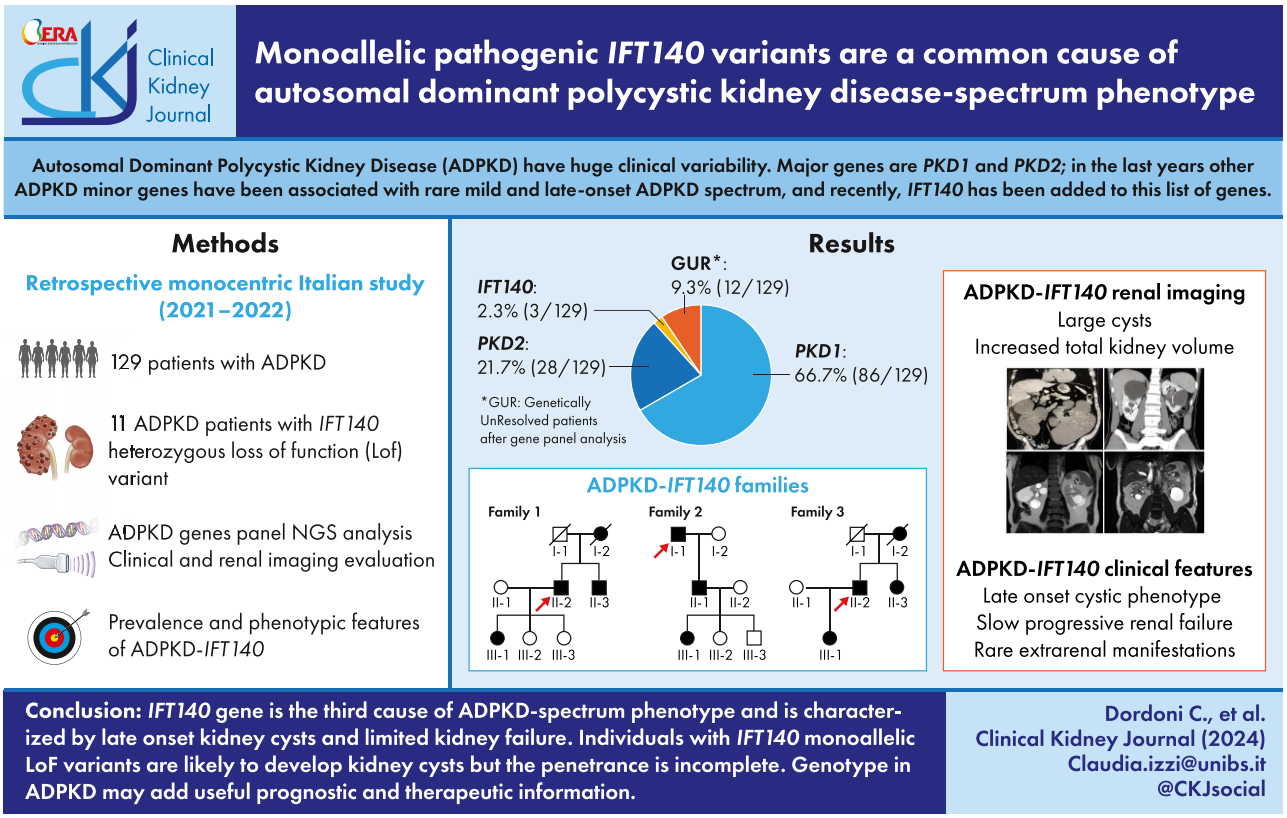
**Methods.** In this retrospective study, we tested the prevalence of the known causative genes of ADPKD-spectrum phenotype, including the *PKD1*, *PKD2*, *GANAB*, *DNAJB11*, *ALG5*, *ALG* and *IFT140* genes, in a cohort of 129 ADPKD patients who consecutively underwent genetic testing in a single centre in Italy. Genetic testing utilized a combination of targeted next-generation sequencing, long-range polymerase chain reaction, Sanger sequencing and multiplex ligation-dependent probe amplification. Clinical evaluation was conducted through renal function testing and imaging features, including ultrasonography, computer tomography and magnetic resonance imaging.

**Results.** Of the 129 enrolled patients, 86 (66.7%) had pathogenic variants in *PKD1* and 28 (21.7%) in *PKD2*, loss of function pathogenic variants in the *IFT140* gene were found in 3 unrelated patients (2.3%), no pathogenic variants were found in other ADPKD genes and 12 patients (9.3%) remained genetically unresolved (ADPKD-GUR). Familial clinical and genetic screening of the index patients with ADPKD due to an *IFT140* pathogenic variant (ADPKD-*IFT140*) allowed identification of eight additional affected relatives. In the 11 ADPKD-*IFT140* patients, the renal phenotype was characterized by mild and late-onset PKD, with large renal cysts and limited kidney insufficiency. Extrarenal manifestations, including liver cysts, were rarely seen.

**Conclusion.** Our data suggest the monoallelic pathogenic *IFT140* variants are the third most common cause of the ADPKD-spectrum phenotype in Italy, usually associated with a mild and atypical renal cystic disease.

*Received: 8.11.2023; Editorial decision: 12.1.2024*

## GRAPHICAL ABSTRACT




**Keywords:** ADPKD, genetic kidney disease, *IFT140*, kidney cysts, polycystic kidney disease

## KEY LEARNING POINTS

**What was known:**

- Autosomal polycystic kidney disease (ADPKD) is characterized by huge clinical variability, including early and late-onset disease. Major genes are *PKD1* and *PKD2*.
- In recent years, other cystogenes, including *GANAB*, *DNAJB11*, *ALG8* and *ALG* 5, have been associated with rare mild and late-onset ADPKD spectrum. Recently, *IFT140* has been added to the ADPKD genes.
- Thus the patient's genotype is becoming even more relevant to add prognostic information and to offer a personalized follow-up and family counselling.

**This study adds:**

- In our cohort, *IFT140* variants are the third leading cause of ADPKD spectrum.
- ADPKD-*IFT140* is a mild form of the disease, with large cysts and limited renal insufficiency occurring in older ages.

**Potential impact:**

- These results suggest that genetic testing of *IFT140* should be included in the clinical care of ADPKD patients.

## INTRODUCTION

Autosomal polycystic kidney disease (ADPKD) is the most common inherited renal disorder, mainly characterized by progressive bilateral renal cyst development, leading to end-stage renal disease (ESRD) in ≈50% of patients, at a median age of 58 years. A well-recognized feature of ADPKD is the variability of the renal phenotype, mainly due to locus and allelic effects. In a few ADPKD patients, onset of the disease is in late adulthood, with rare progression to ESRD [1, 2].

Pathogenic variants in *PKD1* [Online Mendelian Inheritance in Man (OMIM): 601313] or *PKD2* genes (OMIM: 173910) are the major cause of ADPKD (≈78% and ≈15% of cases, respectively) [1, 2]. About 7% of ADPKD patients do not carry pathogenic variants in the known genes, forming the group of 'genetically unresolved' (GUR) patients. ADPKD-GUR patients may be explained

by the presence of mosaicism or rare undetected pathogenic variants in the known genes. Alternatively, ADPKD phenocopies associated with other hereditary renal diseases, i.e. autosomal dominant tubulointerstitial kidney disease (ADTKD) or atypical Alport syndrome with cystic phenotype [3, 4], can be hypothesized. Finally, additional genetic heterogeneity may be taken into account.

In recent years, next-generation sequencing (NGS) studies have allowed identification, in some ADPKD-GUR patients, of the presence of heterozygous pathogenic variants in other cystogenes, including *GANAB* (OMIM: 104160), *DNAJB11* (OMIM: 611341), *ALG5* (OMIM: 604565), *ALG8* (OMIM: 608103) and *ALG9* [5–9], partially accounting for the ≈7% of non-*PKD1* or -*PKD2* families.

Typically these patients show a milder ADPKD phenotype compared with ADPKD due to *PKD1* variants (ADPKD-*PKD-1*) and *PKD2* variants (*ADPKD-PKD2*). For example, ADPKD due to *GANAB* variants (ADPKD-*GANAB*) is characterized by variable liver cystic disease and few renal cysts, with slow progressive renal disease [6]; patients with ADPKD related to *DNJAB11* variants (*ADPKD-DNJAB11*) show normal-sized cystic kidneys and progressive interstitial fibrosis resulting in adult ESKD [7]; and patients with ADPKD due to *ALG9* variants (ADPKD-*ALG9*) manifest a mild–moderate cystic kidney disease, with or without polycystic liver [8].

In a recent report, Senum *et al.* [10] found heterozygous *IFT140* variants in a large cohort of families with ADPKD-like phenotype, characterized by large renal cysts, few liver cysts and mostly mild kidney impairment, suggesting that *IFT140* monoallelic pathogenic variants may likely account for >1% of the ADPKD phenotype.

The *IFT140* gene encodes a protein involved in intraflagellar transport (IFT). The role of IFT140 protein in the genesis, resorption and signalling of primary cilia [11, 12]. It should be noted that biallelic *IFT140* variants are known to cause the syndromic ciliopathy short-rib thoracic dysplasia type 9 (SRTD9; OMIM: 266920) [13–16], a group of autosomal recessive skeletal diseases encompassing the disease previously designated as asphyxiating thoracic dystrophy (ADT), short rib-polydactyly syndrome (SRPS) and Mainzer–Saldino syndrome (MZSDS) and showing a phenotype characterized by short stature, rhizomelic limb shortening, narrowing of the thorax and renal involvement, including a cystic phenotype and fibrosis [13–16]. In this study employing NGS, we describe the genetic landscape of ADPKD in an Italian tertiary referral centre, focusing on the prevalence and phenotypic features of ADPKD-*IFT140*.

## MATERIALS AND METHODS

### Patients

Participants were recruited from January 2021 to December 2022 from the outpatient clinic of genetic kidney diseases of the Division of Nephrology, Brescia, Italy. Patients had a family history of ADPKD and met the unified criteria for ultrasonographic diagnosis of ADPKD or, in the absence of a positive family history, had renal cysts on imaging as per the unified criteria for ultrasonographic diagnosis of ADPKD [17, 18]. Medical histories were obtained as part of patients' clinical workup. Clinical and genetic data were collected according to national laws. All enrolled patients underwent genetic testing and clinical, laboratory and radiological assessment, including renal function tests and imaging. Kidney function was calculated as the estimated glomerular filtration rate (eGFR; ml/min/1.73 $m^2$) according with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [19]. Renal imaging included at least one of the following examinations: abdominal ultrasound (US), abdominal magnetic resonance imaging (MRI) or computed tomography (CT). Total kidney volume (TKV) was measured by stereology from the most recent abdominal MRI or CT. At-risk family members underwent molecular and clinical workup, including renal function tests and abdominal US.

### Genetic analysis

Since January 2022, the targeted gene panel has been updated with the *IFT140* gene. All patients also had multiple ligation probe amplification (MPLA) analysis of the *PKD1* and *PKD2* genes. Patients who did not have the updated ADPKD panel were re-analysed for the *IFT140* gene. At-risk family members were offered genetic testing for the familial pathogenic *IFT140* variant.

Data for genetic analysis (panel genes list, methodology of NGS analysis, data analysis pipeline, informed consent) are shown in the Supplementary data.

### Ethics approval

The study was approved by our institutional review board and all participants signed informed consent (protocol NP 4945, Ethics Committee of Spedali Civili of Brescia).

## RESULTS

### Genetic analysis

The APDKD NGS panel including the *IFT140* gene was analysed in 129 ADPKD patients. Pathogenic variants in *PKD1* were found in 86/129 patients (66.7%); 60% of *PKD1* patients had a truncating variant and 40% had a missense variant. Pathogenic variants in *PKD2* were identified in 28 patients (21.7%); 78% had a truncating variant and 22% had a missense variant. No pathogenic *PKD1* or *PKD2* variants were identified in 12 families (9.3%). Pathogenic variants in the *IFT140* gene were found in three unrelated patients (patient II-2 in family 1, patient I-1 in family 2 and patient II-2 in family 3; Fig. 1), representing 2.3% of all ADPKD patients and accounting for the 20% of the 15 non-*PKD1* or -*PKD2* families. No pathogenic variants were identified in the *GANAB*, *DNAJB11*, *ALG5*, *ALG8* and *ALG9* genes; 12 patients (9.3%) remained GUR.

### Classification of *IFT140* gene variants

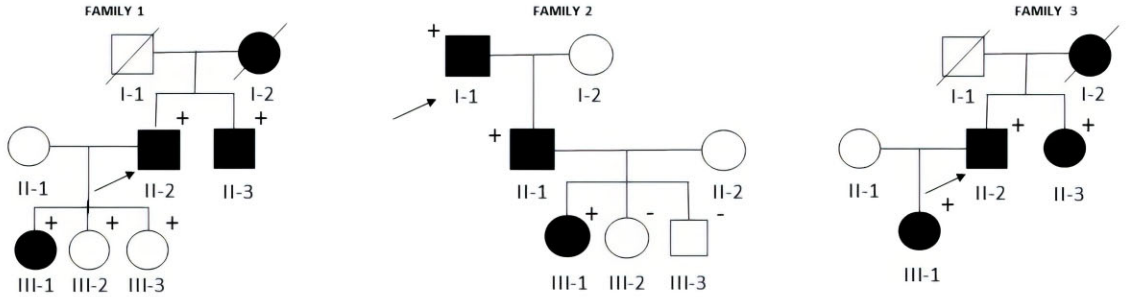
Patient II-2 of family 1 harboured a heterozygous novel variant in *IFT140*: c.[3824delA] (p.[Lys1275Argfs*35]). The variant is not listed in the population-based exome sequencing project (ExAC, gnomAD) and was not found in 169 ethnically matched controls.

Patient I-1 of family 2 had the c.[919C>T] (p.[Arg307*]) *IFT140* variant in heterozygosis; the variant has been described in a patient with Mainzer–Saldino syndrome in a compound heterozygous or homozygous state (ClinVar accession RCV001951871.1).

Patient II-2 of family 3 carried the *IFT140* heterozygous variant c.[2500C>T] (p.[Arg834*]); the variant has already been described by Senum *et al.* [10] in one patient with an ADPKD phenotype. All the variants co-segregate with the renal disease in affected offspring.

Taking these data together provides strong evidence of pathogenicity for the loss-of-function (LoF) variants p.[Lys1275Argfs*33], p.[Arg307Ter] and p.[Arg834Ter] according to the proposed classification of pathogenicity by the

(A)




(B)

| | IFT140 variant | Protein effect | ACMG classification and criteria | Clinvar accession # | Novel/Described |
|---|---|---|---|---|---|
| Family 1 | c.[919C>T];[=] | p.[Arg307*];[=] | Pathogenic: PVS1, PP5, PM2 | RCV001951871.1 | Described [9] |
| Family 2 | c.[3824delA];[=] | p.[Lys1275Argfs*23];[=] | Pathogenic: PVS1, PM2 | NOT LISTED | Novel |
| Family 3 | c.[2500C>T];[=] | p.[Arg834*];[=] | Pathogenic: PVS1, PP5, PM2 | VCV001069388.1 | Described [9] |

**Figure 1: (A)** Pedigrees of the three families with ADPKD-*IFT140*. The arrow indicates the proband for each family. Squares indicate males and circles indicate females. Fully black symbols identify individuals with multiple bilateral cysts. Plus symbols define carriers of *IFT140* heterozygous pathogenic variants, minus symbols indicate individuals with negative genetic test. Roman numerals under the pedigree denote generations. **(B)** Molecular data of the three families with ADPKD-*IFT140*.

American College of Medical Genetics (ACMG) [20]. Patients' molecular data are summarized in Fig. 1.

## Clinical features

### Family 1

The index case (II-2), a 56-year-old man, was referred because of an incidental finding of large bilateral renal cysts. His medical history was unremarkable for an extrarenal phenotype except for inguinal hernioplasty at age 55 (Table 1). In the proband, eGFR slowly declined from 104 ml/min/1.73 $m^2$ at age 43 to 74 ml/min/1.73 $m^2$ at age 55. MRI showed increased kidney volume [TKV 1042 cc, height-adjusted TKV (htTKV) 585 ml/m] with large cysts and a single liver cyst. Hypertension was diagnosed at age 55 (Table 1, Figs 1 and 2C). ADPKD was hypothesized and genetic analysis for *PKD1* and *PKD2* genes was performed, with negative results. The patient was considered for disease-modifying therapy with tolvaptan. Despite the increased TKV, the patient did not fulfil the criteria for ADPKD with rapid progression (slow decline of eGFR; Mayo class 1B). To acquire other prognostic data, an extended NGS ADPKD panel was performed. The updated genetic analysis revealed a heterozygous pathogenic LoF variant in the *IFT140* gene: c.919C>T p.Arg307* (Fig. 1B). Considering the diagnosis of ADPKD-*IFT140*, which is usually associated with mild renal disease, tolvaptan therapy was ruled out.

Three daughters and one son had abdominal US, which showed large renal cysts and normal kidney volume only in the 31-year-old daughter (III-1); her serum creatinine (SCr) was 0.97 mg/dl (eGFR 77.6 ml/min/1.73 $m^2$) and a history of kidney stones was reported at age 18. Molecular segregation analysis confirmed the presence of the familiar *IFT140* variant in the affected daughter (III-1) and also in the two asymptomatic daughters, ages 24 and 26 years (III-2 and III-3, respectively). A history of renal cysts and normal TKV with hypertension (onset at age 65) and preserved kidney function (0.98 mg/dl; eGFR 78 ml/min/1.73 $m^2$) was reported in the older brother (II-3; age 70 years). The segregation analysis confirmed the presence of a familial *IFT140* variant. The parents were not investigated.

### Family 2

The index case (I-1) came to our attention at age 73 with chronic kidney disease (CKD), stage 3b (SCr 1.96 mg/dl, eGFR 32.9 ml/min/1.73 $m^2$) and hypertension (onset at age 60). A CT scan detected increased TKV (5520 cc, htTKV 3154 ml/m) and multiple large cysts (diameter of the largest cyst was 16.5 cm) (Fig. 2A); no liver cysts were detected. The 46-year-old son (II-1) was found to have hypertension, abdominal US revealed multiple large cysts with increased kidney volume and no liver cysts and renal function was normal (eGFR 91.3 ml/min/1.73 $m^2$) (Fig. 2B). Previously, at age 36, he was diagnosed with pelviureteric junction obstruction (PJO) and treated by pyeloplasty; at age 37, resection of a large right renal cyst was performed. Extended NGS ADPKD panel analysis identified a novel heterozygous pathogenic frameshift variant in the *IFT140* gene (c.3824delA, p.Lys1275Argfs*23) in the index case and his son (Fig. 1B). The oldest daughter of patient III-1 (age 22) showed on US bilateral renal cysts with normal kidney function. Segregation analysis confirmed the presence of the paternal variant.

### Family 3

The proband (II-2) was noted to have renal impairment at age 55, when eGFR was 52 ml/min/1.73 $m^2$. The clinical history was characterized by recurrent kidney stones and hypertension (onset at age 56). At referral, at age 67, eGFR was 42 ml/min/1.73 $m^2$. A CT scan showed an only slightly increased TKV (447 cc; htTKV 255.4 ml/m), with large renal cysts and few liver cysts (Table 1, Fig. 2D). The deceased mother (I-2) reached ESRD at age 83 and presented with increased TKV and large

**Table 1: Phenotype of ADPKD-*IFT140* patients**

| | Family 1 | | | | | Family 2 | | | Family 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Characteristics | II-2 | II-3 | III-1 | III-2 | III-3 | I-1 | II-1 | III-1 | I-2 | II-2 | III-1 |
| Sex/age (years) | M/56 | M/70 | F/31 | F/24 | F/26 | M/73 | M/46 | F/22 | F/82 | M/67 | F/38 |
| eGFR (ml/min/1.73 $m^2$)/age (years) at onset | 104/43 | – | 99/30 | 100/24 | 99/26 | 38/68 | 84/40 | – | – | 52/55 | 97/26 |
| eGFR at last follow-up (ml/min/1.73 $m^2$)/CKD stage/age (years) | 75/CKD2/56 | 78/CKD2/70 | 78/CKD2/31 | – | – | 33/CKD3b/73 | 91/CKD1/46 | 98/CKD1/22 | ESRD/82 | 42/CKD3/67 | 98/CKD1/34 |
| Hypertension/age (years) at onset | Yes/55 | Yes/65 | No | No | No | Yes/60 | Yes/46 | No | Yes/60 | Yes/56 | No/38 |
| Type of imaging/age years)/main findings | MRI/55/large cysts | US/70/bilateral cysts | US/30/large cysts | US/24/no cysts | US/26/no cysts | CT/69/large cysts | CT/46/large cysts | US/bilateral cysts | US/65/large cysts | MRI/67/large cysts | US/37/large cysts |
| htTKV (ml/m) | 585 | – | – | – | – | 3154 | – | – | – | 255 | – |
| Urologic event/age (years)[a] | No | No | Kidney stones/18 | No | No | No | No | No | No | Kidney stones/24 and 57 | No |
| Liver cysts | 1 | No | No | No | No | No | No | No | No | Few cysts | No |
| Mitral valve prolapse | No | – | No | – | – | – | – | – | – | No | No |
| Intracranial aneurysm | Negative (MRA[2] 2021) | – | Negative (MRA 2021) | – | – | – | – | – | – | Negative (MRI 2022) | – |
| Other | Inguinal hernia | – | – | – | – | Renal artery aneurism | UPJO | – | – | – | – |

F: female; M: male; –: not available; MRA: magnetic resonance angiography; UPJO: ureteropelvic junction obstruction.
[a]Urologic events: flank pain, macroscopic haematuria, kidney stones, cyst infection.

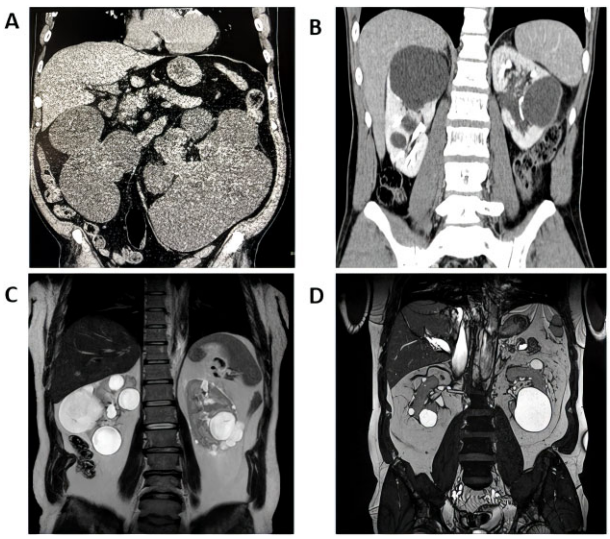



**Figure 2:** Renal imaging of four patients with ADPKD-*IFT140*, showing the bilateral presence of large renal cysts. **(A)** I-1, family 2, abdominal CT scan at the age of 69, htTKV 3154 ml/m. **(B)** II-1, family 2, abdominal CT scan at the age of 46, TKV not calculated. **(C)** II-2, family 1, abdominal MRI at the age of 55, htTKV 585 ml/m. **(D)** II-2, family 3, abdominal MRI at the age of 67, htTKV 255 ml/m.

renal cysts. The 55-year-old sister (II-3) showed kidney cysts on renal US. The 38-year-old daughter (III-1) had normal kidney function (Table 1); US revealed a few large bilateral kidney cysts (the largest cyst measured 7.5 cm). Genetic analysis was performed in the proband, disclosing a nonsense pathogenic *IFT140* variant (c.2500C>T, p.Arg834*) (Fig. 1B). The pathogenic variant was also detected in the daughter (III-1). Given the family history and the presence of cystic diseases, diagnosis of ADPKD-*IFT140* was retrospectively posed in the mother.

## DISCUSSION

Cystic kidney diseases encompass a broad group of disorders with variable phenotypic expression and multiple aetiologies, including developmental, genetic and acquired [21]. Among the 50 different monogenic disorders associated with cystic kidney disease (Human Phenotype Ontology, https://hpo.jax.org/app/, HP:0005562), ADPKD spectrum is the most frequent clinical diagnosis, with an estimated prevalence at birth of ≈1:1000 [1, 2].

In this report, for the first time, we comprehensively describe the genetic landscape of ADPKD in an unselected cohort of 129 ADPKD patients from Italy, evaluating the contributions of the major causative genes *PKD1* and *PKD2* and of the minor ADPKD-spectrum genes identified so far. Moreover, we provide a detailed clinical analysis of the phenotype of ADPKD linked to *IFT140*, the most recently described causative ADPKD gene [10].

The key findings of our study were 3-fold. First, in our cohort, the majority of ADPKD cases were attributed to *PKD1* (66.7) and *PKD2* (21.7%). These results agree with previous studies in cohorts from Italy, Ireland and the USA, where *PKD1* and *PKD2* were responsible for 60–77% and 12–19% of ADPKD cases, respectively [22–24]. The large majority of *PKD1* and *PKD2* variants were truncating. In 15 families (11.6%), ADPKD was unrelated to pathogenic variants in either *PKD1* or *PKD2*; in 3 of these families, accounting for 2.3% of the entire ADPKD cohort and for 20% of the non-*PKD1* and -*PKD2* families, the disease was found to be linked to *IFT140* pathogenic variants. In our cohort, we did not detect any pathogenic variant in the other minor ADPKD genes, including *ALG5*, *ALG9*, *DNAJB11* and *GANAB*. The mild and late cystic kidney phenotype causing a delayed diagnosis might explain the underrepresentation of ADPKD related to *ALG5*, *ALG9*, *DNAJB11* and *GANAB*. However, since ADPKD-*IFT140* is a mild and late disease, the occurrence of referral bias cannot be excluded. Overall, the results of the genetic studies in our cohort agree with the findings of Senum *et al.* [10], indicating that the above-mentioned minor ADPKD loci may account for some but not all non-*PKD1* or -*PKD2* ADPKD subjects and that the last identified ADPKD gene, *IFT140*, is the third most common ADPKD gene. Recently, ADPKD-*IFT140* was also reported in one patient from a small Kuwaiti cohort of ADPKD patients [25], suggesting that ethnic differences in its prevalence would be worth determining in future studies.

The second important finding of the study was the distinctive phenotype, characterized by mild PKD with large cysts and limited kidney insufficiency, few or no liver cysts, rare urological complications and late-onset hypertension. CKD stage 3b was documented only in the index cases of families 2 and 3, who showed an eGFR <60 ml/min/1.73 $m^2$ at ages 73 and 67, respectively. The remaining affected members identified through family screening had normal renal function. No patient reached ESRD. However, the mother of the index case of family 3 reached ESRD at age 83. Although detailed clinical data were not available, we cannot exclude that ESRD could be due to ADPKD-*IFT140*, a rarely described outcome. In the index cases, the diagnosis of ADPKD-*IFT140* was made usually incidentally at ≈60 years of age, a greater age when compared with *PKD2*-linked disease [1, 2]. Renal imaging revealed some large cysts accounting for most of the cystic disease, determining an increased TKV of variable degree. A few small, asymptomatic liver cysts were found in the index cases of families 1 and 3. No patients experienced pyelonephritis, cyst infections or episodes of macroscopic haematuria due to cyst rupture. However, two affected members suffered from kidney stones, a condition potentially related to ADPKD [1, 2]. The index cases had late-onset hypertension, with onset around or after the fifth decade, 15–20 years later than in ADPKD overall [1, 2]. Although we did not extensively study the vascular phenotype, we did not identify cardiac valve defects or thoracic/abdominal aortic aneurysms. The presence of intracranial aneurysms, described by Senum *et al.* [10], was investigated in three patients (II-2 family 1, III-1 family 1 and II-2 family 3), with no pathological findings.

Dilated cardiomyopathy, reported by Salhi *et al.* [26] in two ADPKD patients carrying *IFT140* heterozygous variants was not detected in our case series. The absence of cardiac involvement in our cohort certainly is not sufficient to exclude the possible association between an *IFT140* variant and development of cardiac disease, but other studies are needed to delineate the prevalence and prognosis of cardiac disease in ADPKD-*IFT140* patients and the timing of/need for cardiac screening.

Overall, from a clinical point of view, these features confirm that monoallelic variants in the *IFT140* gene may cause a form of ADPKD with an atypical milder phenotype, consisting of some large cysts, along with later onset of disease; renal functional decline occurs in older age, in the absence of extrarenal manifestations [2, 10]. The finding of a few large cysts in ADPKD-*IFT140* suggests the focal nature of cyst formation, compatible with the classic 'two-hit' model of cystogenesis, and supports a causal role of ciliary defects in the pathogenetic pathway of ADPKD. However, since our understanding of how IFT-140 protein influences renal development and cystic disease is limited, the true mechanism of cyst development in ADPKD-*IFT140* is unknown [10].

The third intriguing finding of our study was the absence of kidney cysts in two subjects of family 1 harbouring the familial pathogenic *IFT140* variant. Only abdominal US (with lower resolution than CT scan or MRI) was performed and the renal imaging was obtained at a young age, not excluding a possible later appearance of kidney cysts. Despite these observations, since in ADPKD the penetrance is age and genotype dependent, the negative renal imaging might reflect the reduced penetrance of ADPKD-*IFT140* compared with ADPKD-*PKD1* and ADPKD-*PKD2*. It should be noted that, while truncating *PKD1*/*PKD2* variants are reported to have 100% disease penetrance, the penetrance of variants in the minor ADPKD genes, including *IFT140*, is largely unexplored. However, very recently Chang *et al.* [27], using a genotype-first approach, combined exome sequencing results for >170 000 people, ages 44–72 years, with their electronic health records in order to evaluate the prevalence of ADPKD and kidney and liver cysts in carriers of LoF variants in 11 genes related to cystic/liver disease (*PKD1*, *PKD2*, *IFT140*, *ALG8*, *ALG9*, *DNAJB11*, *GANAB*, *HNF1B*, *PKHD1*, *PRKCSH*, *SEC63*). In that study, 97% and 100% of patients with LoF variants in *PKD1* and *PKD2*, respectively, had ADPKD. LoF variants of *IFT140* were identified in 205 individuals; however, only 2.5% of these subjects had a diagnosis of ADPKD and 13.7% had kidney cysts. These data suggest that although individuals with *IFT140* monoallelic LoF variants are likely to develop kidney cysts, the penetrance of the *IFT140* variants is low, being greatly genotype and age dependent.

The present study has some limitations. The ADPKD cohort size is relatively small. Moreover, the ADPKD families linked to the minor ADPKD genes other than *IFT140* are underrepresented, probably due to referral bias. Finally, US is a less accurate imaging method than CT and MRI to identify kidney cysts.

In conclusion, our study offers further evidence for the involvement of *IFT140* LoF variants in ADPKD in an Italian cohort. *IFT140* is the third most common ADPKD gene, representing 2.3% of the ADPKD cohort and accounting for 20% of the non-*PKD1* and -*PKD2* families. Clinically, ADPKD-*IFT140* is a mild form of disease, with large cysts and limited renal insufficiency occurring at older ages. The molecular diagnosis of ADPKD-*IFT140*, in addition to imaging and clinical data, may add useful prognostic information. The extent to which variants of *IFT140* cause cystic kidney disease requires additional studies, along with deeper phenotyping, using CT or MRI. Future studies are also needed to investigate the mechanism of cyst development in ADPKD-*IFT140* in order to identify the underlying pathogenetic pathway of cystogenesis.

## SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

## ACKNOWLEDGEMENTS

We thank all study participants and their families for their contributions to the study.

## FUNDING

None declared.

## DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and its supplementary material.

## CONFLICT OF INTEREST STATEMENT

F.A. has received consulting fees from GSK, Vifor Pharma, AstraZeneca and Novartis. All other authors have declared no conflicts of interest.

## REFERENCES

1. Bergmann C, Guay-Woodford LM, Harris PC *et al.* Polycystic kidney disease. *Nat Rev Dis Primers* 2018;**4**:50.
2. Harris PC, Torres VE. Polycystic kidney disease, autosomal dominant. In: Adam MP, Feldman J, Mirzaa GM *et al.* (eds). *Gene Reviews*. Seattle, WA: University of Washington, 1993.
3. Izzi C, Dordoni C, Econimo L *et al.* Variable expressivity of HNF1B nephropathy, from renal cysts and diabetes to medullary sponge kidney through tubulo-interstitial kidney disease. *Kidney Int Rep* 2020;**5**:2341–50. https://doi.org/10.1016/j.ekir.2020.09.042
4. Savige J, Mack H, Thomas R *et al.* Alport syndrome with kidney cysts is still Alport syndrome. *Kidney Int Rep* 2021;**7**:339–42. https://doi.org/10.1016/j.ekir.2021.11.004
5. Harris PC, Hopp K. The mutation, a key determinant of phenotype in ADPKD. *J Am Soc Nephrol* 2013;**24**:868–70. https://doi.org/10.1681/ASN.2013040417
6. Porath B, Gainullin VG, Cornec-Le Gall E *et al.* Mutations in *GANAB*, encoding the glucosidase IIα subunit, cause autosomal-dominant polycystic kidney and liver disease. *Am J Hum Genet* 2015;**98**:1193–207. https://doi.org/10.1016/j.ajhg.2016.05.004
7. Cornec-Le Gall E, Olson RJ, Besse W *et al.* Monoallelic mutations to *DNAJB11* cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet* 2018;**102**:832–44. https://doi.org/10.1016/j.ajhg.2018.03.013
8. Besse W, Chang AR, Luo JZ *et al.* *ALG9* mutation carriers develop kidney and liver cysts. *J Am Soc Nephrol* 2019;**30**:2091–102. https://doi.org/10.1681/ASN.2019030298
9. Cornec-Le Gall E, Torres VE, Harris PC. Genetic complexity of autosomal dominant polycystic kidney and liver diseases. *J Am Soc Nephrol* 2018;**29**:13–23. https://doi.org/10.1681/ASN.2017050483
10. Senum SR, Li SML, Benson KA *et al.* Monoallelic *IFT140* pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype. *Am J Hum Genet* 2022;**109**:136–56. https://doi.org/10.1016/j.ajhg.2021.11.016
11. Ishikawa H, Marshall WF. Ciliogenesis: building the cell's antenna. *Nat Rev Mol Cell Biol* 2011;**12**:222–34. https://doi.org/10.1038/nrm3085
12. Absalon S, Blisnick T, Kohl L *et al.* Intraflagellar transport and functional analysis of genes required for flagellum formation in trypanosomes. *Mol Biol Cell* 2008;**19**:929–44. https://doi.org/10.1091/mbc.e07-08-0749
13. Jonassen JA, SanAgustin J, Baker SP *et al.* Disruption of IFT complex A causes cystic kidneys without mitotic spindle misorientation. *J Am Soc Nephrol* 2012;**23**:641–51. https://doi.org/10.1681/ASN.2011080829
14. Tan W, Lin A, Keppler-Noreuil K *et al.* Cranio-ectodermal dysplasia. In: Adam MP, Feldman J, Mirzaa GM *et al.* (eds). *Gene Reviews*. Seattle, WA: University of Washington, 1993.
15. Schmidts M. Clinical genetics and pathobiology of ciliary chondrodysplasias. *J Pediatr Genet* 2014;**3**:46–94.
16. Schmidts M, Frank V, Eisenberger T. Combined NGS approaches identify mutations in the intraflagellar transport gene *IFT140* in skeletal ciliopathies with early progressive

kidney disease. *Hum Mutat* 2013;**34**:714–24. https://doi.org/10.1002/humu.22294
17. Pei Y, Obaji J, Dupuis A *et al*. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009;**20**:205–12. https://doi.org/10.1681/ASN.2008050507
18. Pei Y, Hwang YH, Conklin J *et al*. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016;**26**:746–53. https://doi.org/10.1681/ASN.2014030297
19. Levey A, Stevens L, Schmid C *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
20. Richards S, Aziz N, Bale S *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405–24. https://doi.org/10.1038/gim.2015.30
21. Goksu SY, Leslie SW, Khattar D. Renal cystic disease. Treasure Island, FL: StatPearls, 2023.
22. Heyer CM, Sundsbak JL, Abebe KZ *et al*. Predicted mutation strength of nontruncating *PKD1* mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016;**27**:2872–84. https://doi.org/10.1681/ASN.2015050583
23. Benson KA, Murray SL, Senum SR *et al*. The genetic landscape of polycystic kidney disease in Ireland. *Eur J Hum Genet* 2021;**29**:827–38. https://doi.org/10.1038/s41431-020-00806-5
24. Mantovani V, Sofia Bini S, Graziano C *et al*. Gene panel analysis in a large cohort of patients with autosomal dominant polycystic kidney disease allows the identification of 80 potentially causative novel variants and the characterization of a complex genetic architecture in a subset of families. *Front Genet* 2020;**11**:464. https://doi.org/10.3389/fgene.2020.00464
25. Salhi S, Doreille A, Dancer MS *et al*. Monoallelic loss-of-function IFT140 pathogenic variants cause autosomal dominant polycystic kidney disease: a confirmatory study with suspicion of an additional cardiac phenotype. *Am J Kidney Dis* 2023;doi: 10.1053/j.ajkd.2023.08.019.
26. Ali H, Naim M, Senum SR *et* al. The genetic landscape of autosomal dominant polycystic kidney disease in Kuwait. *Clin Kidney J* 2023;**16**:355–66. https://doi.org/10.1093/ckj/sfac236
27. Chang AR, Moore BS, Luo ZJ *et al*. Exome sequencing of a clinical population for autosomal dominant polycystic kidney disease. *JAMA* 2022;**27**:2412–21. https://doi.org/10.1001/jama.2022.22847

*Received: 8.11.2023; Editorial decision: 12.1.2024*