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Clinical Spectrum and Prognosis of Atypical Autosomal Dominant Polycystic Kidney Disease Caused by Monoallelic Pathogenic Variants of *IFT140*

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Abstract

Rationale & objective: Monoallelic predicted Loss-of-Function (pLoF) variants in *IFT140* have recently been associated with an autosomal dominant polycystic kidney disease (ADPKD)-like phenotype. This study sought to enhance the characterization of this phenotype.

Study design: Case series

Setting & participants: Seventy-five among 2797 European individuals with ADPKD-like phenotypes who underwent genetic testing that revealed pLoF *IFT140*-variants.

Findings: The 75 individuals (median age 56 years, 53.3% females) were from 61 families and were found to have 41 different monoallelic pLoF *IFT140*-variants. The majority of individuals presented with large, exophytic kidney cysts (median [range] total kidney volume 688 ml [201-4139]), and 90.2% were classified using the Mayo Imaging Classification as Mayo Class 2A. Arterial hypertension was present in 50.7% of the individuals (median [range] age at diagnosis 59 years [29-73]). Only one patient developed kidney failure (at age 69 years). A significant difference in age-adjusted eGFR between male and female patients was observed (P<0.001). 56.3% of the individuals over the age of 60 years had an eGFR less than 60ml/min/1.73m². The estimated genetic prevalence of monoallelic pLoF *IFT140* variants was 19.76 (95%CI=18.8-20.7) and 27.89 (95%CI=23.8-31.9) per 10,000 in the Genome Aggregation Database and the 100,000 Genomes Project (100kG), respectively. Only CyKD (ICD-10 Q61) was associated with pLoF *IFT140* variants (P=2.9x10^{-9}, OR=5.6 (3.3-9.2)) in 100kG.

Study limitations: retrospective study; younger patients and patients with milder forms of IFT140-related CyKD may not be diagnosed.

Conclusions: Individuals with monoallelic *IFT140* pLoF variants are likely to develop kidney cysts atypical of classical ADPKD and generally have a favorable kidney prognosis.

Keywords: polycystic kidney disease, autosomal dominant polycystic kidney disease (ADPKD), ADPKD-like spectrum, *IFT140*, monoallelic *IFT140*-variants, loss of function variants, inherited kidney diseases, kidney function, case series

Plain-Language Summary

Monoallelic pathogenic variants in *IFT140* have been linked to a spectrum of kidney disease clinically similar to autosomal dominant polycystic kidney disease (ADPKD). This article describes a case series of 75 individuals with ADPKD-IFT140. Affected individuals typically presented with an atypical imaging pattern, had fewer but larger kidney cysts compared to classical ADPKD, and rarely developed liver cysts. Although the kidney prognosis appeared better than in classical ADPKD, 70% of individuals over 60 years of age had stage 3 or more severe CKD. Individuals with ADPKD-*IFT140* variants are likely to develop kidney cyst patterns atypical of ADPKD. Their kidney prognosis appears favorable.

Introduction

The Autosomal Dominant Polycystic Kidney Disease (ADPKD)-spectrum includes disorders of varying severity, characterized by the development of fluid-filled cysts in the kidneys, with or without associated liver cysts.[1,2] Disease severity is highly variable and depends strongly on the gene and allelic variant responsible for the disease.[3,4] The major genes are *PKD1* (chr.16.p13.3) and *PKD2* (chr.4p21), involved in ~75% and 18% of the pedigrees, respectively, encoding polycystin-1 and polycystin-2.[5, 6] In recent years, seven additional genes have been described in individuals or pedigrees presenting with atypical forms of ADPKD. These include genes involved in the endoplasmic reticulum (ER) glycosylation machinery and/or ER folding pathway such as *GANAB* (MIM: 104160), *DNAJB11* (MIM 611341), *ALG5* (MIM 604565), *ALG6* (MIM 603147*), ALG8* (MIM 617874), *ALG9* (MIM 608776) and two genes previously linked to recessively inherited ciliopathies, *IFT140* and *NEK8*.[7-14]

IFT140 (chromosome 16p13.3, less than 0.5 Mb distal to *PKD1*) encodes the protein IFT140, a principal component of the IFT-A core complex, responsible for dynein-associated retrograde trafficking of proteins from the tip of the cilia back to the cell body.[15, 16] Biallelic variants of *IFT140* are known to be associated with a rare severe ciliopathy most often referred to as short-rib thoracic dysplasia 9 with or without polydactyly (MIM: 266920), also described as Jeune asphyxiating thoracic dystrophy, Mainzer-Saldino syndrome or cranioectodermal dysplasia type 2. This syndromic presentation is characterized by a range of physical and developmental abnormalities (kidney disease due to nephronophthisis, skeletal malformations and retinal dystrophy).[17-19] The phenotype can also be restricted to eye, with isolated Leber congenital amaurosis or retinitis pigmentosa in a subset of affected individuals.[20, 21]

Interestingly, monoallelic predicted Loss-of-Function (pLoF) variants of *IFT140* have recently been linked to the ADPKD-spectrum. The disease presentation in 66 individuals included cystic kidney disease (CyKD) characterized by large bilateral cysts and preserved or a late decline in kidney function.[12] While this finding has helped clinicians and researchers to understand the highly variable phenotype of patients in ADPKD-spectrum, the characterization of larger cohorts with monoallelic pLoF *IFT140* variants is important in clarifying disease penetrance, prognosis and clinical management.

This study presents the clinical, radiologic, and genetic characterization of 75 individuals with monoallelic pLoF *IFT140*-variants. Additionally, the prevalence of *IFT140* variants in a large cohort of patients affected by various possibly inherited kidney diseases from the 100,000 Genomes (100kG) Project, and in the publicly available population-sequencing database Genome Aggregation Database (GnomAD) (Cambridge, MA) was explored.

Patients and Methods

Study participants and clinical analysis

The participants originated from the ADPKD cohorts, Genkyst/GeneQuest study and the European CYSTic study, and genetic laboratory cohorts where individuals with ADPKD-like phenotype were referred for genetic

testing (i.e. Brest University Hospital, Fundació Puigvert in Barcelona, Charité Berlin and Dijon's University Hospital).[22] Details of the study design and participant recruitment are shown in Figure 1A. The relevant Institutional Review Boards or ethics committees approved all studies, and participants gave informed consent. Clinical, imaging data and familial information were obtained by review of clinical and study records, and/or during medical interviews. Kidney function was estimated using CKD-EPI formula.[23] Kidney failure (KF) was defined as the need for kidney replacement therapy (dialysis or transplantation).

Molecular analyses

In Brest, genetic testing was performed in index cases by targeted next-generation sequencing (tNGS) of a customized capture-based gene panel containing 25 genes as previously described.[10] In Barcelona, a customized capture-based kidney disease gene panel containing 316 genes was employed.[24] In Berlin and Dijon, whole exome sequencing (WES) was performed as previously described.[25] We selected patients with pLoF *IFT140* variants (i.e. stop-gained, frameshifting, canonical splice site and large deletions). Copy number variants (CNVs) analysis was performed in NGS data. All pathogenic single-nucleotide variants (SNVs) were confirmed by Sanger sequencing. Segregation analysis of the variant of interest was performed when family samples were available.

Imaging classification

Abdominal computerized tomography (CT), magnetic resonance imaging (MRI) and ultrasound images and/or reports were retrieved from medical records. Total Kidney Volumes (TKV) were measured by semi-automatic segmentation (ITK-SNAP) from abdominal CT or MRI and Mayo imaging classification (MIC) was applied.[26]

Statistical analysis

Continuous and categorical variables were expressed as medians (with range) and number and proportions, respectively. Mann-Whitney U-test was employed for the comparison of medians between the groups. Linear regression was used for the analysis of the correlation between age and eGFR with comparison performed according to sex. Hypertension-free survival time was evaluated using Kaplan-Meier estimator. Statistical analyses were performed using MedCalc 22.019.

Genetic prevalence estimation

Genetic prevalence was estimated from the GnomAD collection of 734,947 exome and 76,215 genome data of unrelated individuals from different ethnic origins (Figure 1B).[27] GnomAD v4.0 data was downloaded from http://gnomad.broadinstitute.org. The pLoF variants of *IFT140* (including the CNVs) were inventoried, with their respective allele counts, and entered in the calculation of the genetic prevalence, after exclusion of low confidence variants. The 95% confidence intervals (CI) for prevalence rates were computed assuming that the observed number of cases followed a binomial distribution.

Genomics England 100kG Project

All participants in the 100kG Project provided written consent to access their anonymized clinical and genomic data for research purposes (approved by the National Research Ethics Service, Research Ethics Committee for East of England. Whole-genome sequencing (WGS) was performed with the Illumina TruSeq

DNA PCR-Free sample preparation kit (Illumina) and an Illumina HiSeq 2500 sequencer as previously described.[12] Variant annotation was performed with Ensembl Variant Effect Predictor with the following filter: canonical transcript (ENST00000426508.7) *IFT140* gene and high impact (stop_gained, splice_donor/acceptor, frameshift, start_lost). While a similar approach was undertaken in the original study by Senum et al., the variant calling and filtering was refined to include frameshifting insertion/deletions or duplications (INDELS).[12] Phenotypes of identified carriers were manually reviewed using the Genomics England Participant Explorer tool. We reviewed exit questionnaires, completed by clinicians at the NHS Genomics Medical Centers for each closed case, to detect subjects solved by variants in other genes and excluded those with pathogenic variants in *PKD1* and *PKD2.* To explore the possibility of other unrecognized clinical manifestations, we performed an unbiased analysis for ICD10 phenotype enrichment in carriers of *IFT140* pLoF SNV&INDELS compared this to carriers with *IFT140* synonymous (benign) variants.

Results

Patient characteristics and description of the pathogenic variant spectrum

Of 2797 unrelated individuals with ADPKD-like phenotypes, 58 (2.1%) had a monoallelic pLoF *IFT140* variant (Figure 1). Additionally, three families were diagnosed by WES at a center that sequences for various genetic conditions. In total, we identified 75 individuals from 61 families with pLoF *IFT140* variants (NM_014714.4). The median age at diagnosis was 56 years (ranging from 1 to 86), and 53.3% (n=40) were female. All patients displayed CyKD (results are summarized in Table 1 and Table S1). A family history of CyKD was positive in 16 (26.2%) of probands. Kidney cysts were incidentally detected in 35 (51.5%) individuals, while in others, cysts were found during screening due to positive family history (21, 30.9%) or workup of abdominal pain (10, 14.7%) or reduced kidney function (2, 2.9%). We identified 41 different pLoF variants of *IFT140*, including 14 nonsense, 7 splice, 14 frameshift deletions and insertions, and 6 large deletions (Figure 2). Seven variants were identified in more than one family, and the splice variant c.2399+1G>T was the most common allele identified (11 individuals from 9 pedigrees). The pedigrees of 14 families with monoallelic *IFT140* variants are provided in Figure S1. A list of rare variants in other genes of interest is presented in Table S2, none of the 75 individuals had class 4 or 5 variants in genes associated with diseases of autosomal dominant inheritance, and 2 individuals from two different pedigrees had a co-existing *PKHD1* class 4/5 heterozygous variant.

Kidney function

Of the 75 individuals (Table 1), only one patient with a past medical history of type 2 diabetes and heart failure reached KF at the age of 69 years. The distribution of patients' eGFR values according to age at the last follow-up evaluation is reported in Figure 3A. Figure 3B compares these eGFR values with those of Genkyst participants with *PKD1* or *PKD2* variants, highlighting a generally milder kidney disease progression. The majority of the individuals (72%) were classified as CKD stages 1 and 2. Individuals aged 60 years and above (N=32) exhibited reduced kidney function, with 25% of this age group classified as CKD stage 3a, 25% stage 3b, and 6.25% stage 4 or 5. The age-adjusted eGFR in individuals with the recurrent variant c.2399+1G>T

(n=11) was comparable to that observed in the remaining IFT140 individuals (P=0.843, Figure S2). Multivariable linear regression analysis revealed that males with ADPKD-IFT140 exhibited a significantly lower eGFR than females (P<0.001, Figure 3A).

Other kidney related outcomes and imaging presentation

A diagnosis of arterial hypertension was made in 50.7% of the individuals, with a median age at diagnosis of 59 years [range: 29-73] (Figure S3). No patient exhibited significant proteinuria. Table S1 reports the kidney morphology of the patients, where available, and examples of illustrative imaging are displayed in Figures 4 and S4. The most prevalent radiological presentation was the presence of multiple bilateral kidney cysts, frequently voluminous and exophytic, leading to nephromegaly in some individuals (see table S1 for details on kidney size). Some patients exhibited cysts exceeding 10cm in diameter, yet remained asymptomatic (Family 6, patient II.2 – Figure 4B). MIC was applied to 51 individuals with available images. The most frequent radiological presentation was that of Mayo 2A, which was observed in 90.2% of the cases. The majority of individuals classified as 2A exhibited a lopsided imaging pattern, characterized by a bilateral distribution of kidney cysts with mild replacement of kidney tissue by cysts where a maximum of 5 cysts account for a minimum of 50% of TKV.[26] The remaining five patients exhibited a typical presentation consistent with Mayo Class 1 (three patients in class 1A, one in class 1B and one in class 1C), and were all under 35 years of age. Of interest, tolvaptan (a vasopressin 2 receptor antagonist indicated in individuals with ADPKD at risk for progression to KF) was initiated in a 60-year-old female individual (individual III.2 from Family 17) with an eGFR of 60 ml/min/1.73m² (Figure 4E). The genetic results prompted her nephrologist to discontinue the treatment after six months.

Extrarenal manifestations

A small number of liver cysts (up to 10) were detected in 10 individuals (13.3%), with only one individual (I.1 from Family 38, also carrying a nonsense variant in *PKHD1*) exhibiting more than 10 liver cysts, all millimeter-sized. One individual (I.1 from Family 18) underwent a liver cyst fenestration at the age of 49 years for a 9cm cyst. Eight individuals underwent cerebral MRI as part of a systematic screening protocol for intracranial aneurysm (ICA). In Family 45, the 82-year-old mother (I.1) was found to have two ICAs: one measuring 3mm in the anterior communicative artery and another measuring 5mm in the medium cerebral artery. A saccular aneurysm was diagnosed in the cavernous portion of the left internal carotid artery in the subject's son (II.2). Furthermore, two additional individuals underwent imaging due to the presence of symptoms. One was evaluated for epilepsy, while the other was investigated following an acute headache, revealing subarachnoid hemorrhage due to ICA rupture (individual II.7 from Family 14). One patient was diagnosed with an arachnoid cyst incidentally. No cases of aortic dissection or other vascular phenotypes were reported. Abdominal hernias were observed in three subjects. One patient died from a ruptured diverticulitis at age 86.

Genetic prevalence of monoallelic loss-of-function variants of IFT140 using GnomAD data

A total of 280 pLoF IFT140 SNVs and 11 large deletions of IFT140 were identified in 1579 individuals from the GnomAD v4.0 database (Table S3&S4). Based on the aforementioned data, the estimated prevalence of monoallelic pLoF *IFT140* variants was determined to be 19.76 (95%CI=18.80-20.70) per 10,000 individuals within the entire GnomAD population (n=807,162). In the European population within the GnomAD database (n=622,057), the calculated prevalence was 18.42 (95%CI=17.36-19.49) per 10,000.

Prevalence of CyKD caused by monoallelic loss-of-function variants of IFT140 in 100kG Project

Monoallelic pathogenic *IFT140* variants were extracted from WGS of 64,534 subjects recruited under the rare disease domain and after annotation, 25 distinct predicted pathogenic monoallelic SNVs were identified in a total of 145 individuals (83 probands and 62 relatives) from 105 different families. These individuals, together with part of their phenotypic data have been previously described.[12] Further refinement of the script permitted the detection of an additional 17 distinct pathogenic/likely pathogenic monoallelic INDELS variants (11 deletions, 2 insertions, 4 duplications) in a total of 35 individuals (18 probands and 17 relatives) from 24 different families. In two families, the INDEL variant was observed to segregate with CyKD in 2 generations.. The estimated genetic prevalence of monoallelic pLoF *IFT140*-variants in the rare disease 100kG cohort is 27.89 per 10,000 (95%CI=23.8-31.9). When considering only probands recruited under the designation "CyKD" (N=1291), a total of 34 (2.63%) were found to have ADPKD related to a pLoF *IFT140* variant. When all carriers (probands and relatives) of likely pathogenic *IFT140* variants (pLoF SNVs and INDELS) were considered, kidney cysts were described in 50/180 (27.6%) and in 37/100 (37%) when only probands were considered. The prevalence of CyKD in *IFT140* positive individuals increased with age, reaching 51.9% in individuals over 60 years of age (Figure 5). Finally, an unbiased analysis conducted to ascertain enrichment of ICD10 phenotypes among carriers of *IFT140* pLoF SNV&INDELS compared with carriers of *IFT140* synonymous variants found no extrarenal associations. Of the total of 730 phenotype tests performed, only "CyKD" (ICD-10 code Q61) was associated with pLOF *IFT140* variants (12.37 vs 2.19%, P=2.9x10^{-9}, OR=5.6 (3.3-9.2)).

Discussion

This European multicenter study provides a detailed description of the clinical and radiological presentation of 75 individuals from 61 families with ADPKD-like presentations caused by a monoallelic pLoF variant of *IFT140*, representing the largest clinical case series reported to date. Monoallelic pLoF variants of *IFT140* are associated with a mild form of ADPKD, with fewer and larger cysts than in classical ADPKD caused by *PKD1* and *PKD2* variants, with absent or very few liver cysts. While high TKVs are observed in some individuals, this is attributed to a small number of large cysts in the majority of cases corresponding to a Mayo Class 2A category. Typically, diagnosis is made incidentally on abdominal imaging. A few individuals presented with abdominal pain due to larger cysts with some individuals requiring cyst aspiration. As underlined in the previous study, affected individuals have a good prognosis in terms of kidney function.[12] However, a small number had more severely impaired kidney function, potentially due to comorbidities or the coinheritance of modifier genes. In our cohort, only one individual required kidney replacement therapy at the

age of 69 years and it seems likely that type 2 diabetes and heart failure could accelerated the loss of kidney function. It should be noted, however, that 56.3% of the individuals aged over 60 years had an eGFR of less than 60ml/min/1.73m², and 6.25% of less than 30 ml/min/1.73m². This indicates that ADPKD-*IFT140* is not a benign condition, and that individuals with this condition should be educated about preventive measures to protect kidney function and undergo regular follow-up.

Vascular phenotypes (intracranial or aortic aneurysms) were previously identified as potential correlates of monoallelic IFT140, although the available data lacked sufficient detail to draw definitive conclusions.[12] While a systematic screening approach for ICA was not employed in our cohort, ICA were documented in three individuals from two pedigrees, with one case diagnosed in the context of a subarachnoid hemorrhage. Further study is required to explore the potential association with ICA, as observed in individuals with classical ADPKD. Currently, there is no evidence to recommend the systematic screening for ICA in individuals with *IFT140* variants. It is established that biallelic *IFT140* variants are associated with retinal degeneration.[20, 21] While some individuals from the previous cohort presented with a range of ophthalmological conditions, no specific eye disease was reported in our cohort.[12] A recent paper has suggested a link between dilated cardiomyopathy and monoallelic pLoF variants of *IFT140*.[28] Among 1340 individuals evaluated by whole exome sequencing for various kidney diseases, 130 had a cystic kidney disease, and six of those were found to harbor a monoallelic pLoF variant in *IFT140*. In contrast, no case of dilated cardiomyopathy were observed among the 75 new cases reported here. Furthermore, phenotype enrichment analysis performed in the 100kG cohort did not identify any cardiac phenotype association.

The GnomAD database indicates that 19.76 out of every 10,000 individuals are carriers of monoallelic pLoF *IFT140*-variants. This figure is higher than the estimated prevalence of ADPKD, which is between 1 and 10 out of every 10,000 individuals.[28-30] It is possible that individuals with only a few uncomplicated cysts might be carriers of such variants. Nevertheless, it remains unclear whether all individuals carrying monoallelic pLoF *IFT140*-variants will ultimately develop kidney cysts. Constraint metrics from the GnomAD database indicates that *IFT140* is not intolerant to heterozygous pLoF variants.[31] However, it has been observed that genes associated with milder adult-onset dominantly inherited condition may appear not to be constrained to pLoF variants, and this is the case for several cystic genes (e.g. *PKD2, DNAJB11, ALG9*…). The determinants of disease penetrance remain to be elucidated. A study by Chang et al. found that only 2.5% of pLoF *IFT140* carriers who underwent WES had a diagnosis of ADPKD according to electronic medical records.[32] Data from the 100kG project indicate that at least 52% of the individuals over the age of 60 with a heterozygous pLoF variant of *IFT140* have multiple kidney cysts. However, this figure is likely an underestimate, as abdominal imaging was not performed systematically in all patients.

Although we provide a more comprehensive characterization of the ADPKD-*IFT140* phenotype through the description of the 75 individuals diagnosed in the clinical setting, it is important to note that this description is limited to the probands who were referred to nephrology centers and underwent genetic testing, as well as their affected family members. Consequently, it may have led to an ascertainment bias towards a

more severe presentation, and likely does not apply to all individuals with pathogenic variants of *IFT140*. Other study limitations include non-uniform genetic testing across the different cohorts with either tNGS panel or WES and absence of systematic screening for ICAs. Finally, it should be noted that only protein truncating variants were considered in this study. A total of 178 pathogenic or likely pathogenic *IFT140* variants have been reported in the ClinVar database, 18 of which are missense variants. While some missense *IFT140* variants may be associated with the ADPKD spectrum, determining their pathogenicity is challenging due to the need for functional studies and/or large familial co-segregation analyses.

The classification of individuals with polycystic kidneys due to monoallelic variants of *IFT140* as having ADPKD might be considered questionable. Although affected individuals have inherited bilateral kidney cysts in a dominant fashion, their risk of progressive kidney disease leading to KF is low, which differs from the typical presentation of classical ADPKD. Being diagnosed as having progressive disease may result in unintended consequences in term of insurability or employment, especially in some countries. The use of a dyadic terminology comprising both the clinical condition and the gene name, ADPKD-*IFT140* has been suggested.[12] Using such terminology would enable accurate identification of the specific condition and offer flexibility for patients and caregivers.[33] However, it is important to emphasize that the diagnostic criteria, disease progression, and treatment approaches are distinct from those applied in classical forms of ADPKD (ADPKD-*PKD1* or ADPKD-*PKD2*). In particular, there is no evidence to support the use of vasopressin V2R antagonists in IFT140-affected individuals. In one participant of our study, the treatment was discontinued after the results of the genetic testing. This example illustrates the importance of an accurate diagnosis prior to initiating specific therapies.[34]

In conclusion, our study indicates that individuals with ADPKD-*IFT140* generally have a favorable renal prognosis, exhibit a lower number of kidney cysts that are larger in size compared to those observed in classical ADPKD, and rarely develop liver cysts, which are generally asymptomatic. Blood-pressure monitoring, preventive measures to protect kidney function, and regular eGFR follow-up after the age of 50, are advisable. It is crucial to emphasize that, due to the probable incomplete disease penetrance and the delayed onset of clinical features, the detection of a monoallelic pLoF *IFT140* variant without visible kidney cysts on abdominal imaging should not prompt a diagnosis of ADPKD-*IFT140*. For the aforementioned reasons, we believe that pre-symptomatic genetic diagnosis should not be performed in minors with a familial risk of ADPKD-*IFT140*. The implementation of genetic testing into the routine diagnostic workup of CyKD, where feasible, could provide precise diagnosis, lead to adequate pre-therapeutic evaluation, risk stratification, and may inform genetic counselling.

Disclosures

The authors declare that they have no relevant financial interests.

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Research idea and study design: NZ, AC, ECLG. Data acquisition: NZ, AC, MD, EO, SO, JAS, VGP, ASDP, FTMT, SN, LF, EA, RT, ACMO, OD, NP, AMD, HL, JF, RB, AH, BK, NM, JH. Data analysis and interpretation: NZ, AC, EO, SO, JAS, VGP, ASDP, FTMT, SN, LF, EA, RT, ACMO, OD, NP, YLM, M-PA, JH, ECLG. Statistical analysis: NZ, EO, ECLG. Supervision or mentorship: JAS, YLM, ECLG. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Data Sharing Statement

All data used to support the findings of this study is included in the article and its supplementary materials. Scripts for statistical analyses or generation of figures are available upon request

Supplementary Material:
Supplementary File (PDF)

Table S1. Clinical presentation and pathogenic variants in the 75 affected individuals from the 61 *IFT140*-affected families.
Table S2. Rare variants identified in individuals with pLoF *IFT140* variants in other genes associated with the ADPKD spectrum.
Table S3. Monoallelic loss-of -function variants of *IFT140* identified in the GnomAD v.4.0 database.
Table S4. Large deletions of *IFT140* identified in the GnomAD v.4.0 database.
Figure S1. Pedigrees of 14 families with loss-of-function variants of *IFT140* including more than one single affected member. Black squares or circles indicate affected male of female subjects respectively, with kidney cysts and/or renal failure. Grey symbols indicate case subjects where clinical information is unavailable. Red asterixis indicate patients who underwent genetic test. Pointed symbol represents index patient.
Figure S2. CKD-EPI estimated glomerular filtration rate (eGFR) values are plotted against age in 75 individuals with ADPKD-IFT140 from 61 families. The age-adjusted eGFR in individuals with the recurrent variant c.2399+1G>T (n=11) was comparable to that observed in the remaining IFT140 individuals (P=0.843).
Figure S3. Hypertension-free survival estimation (using Kaplan-Meier analysis) in cohort of ADPKD-IFT140 (N=62). Median age at diagnosis of arterial hypertension was 59 years [range: 29-73].
Figure S4. Additional representative abdominal imaging of eight individuals. Detailed clinical information available in Table S1.

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Table 1. Characteristic of the 75 individuals with ADPKD-*IFT140*

Characteristic	Number	Value (%)
Age (years)*	75	56 [1 – 86]
Males	75	35 (46.7%)
eGFR (ml/min/1.73m^2)	75	80 (7.5-133)
CKD stage	75	100%
- 1	34	45.3%
- 2	20	26 .7%
- 3a	11	14.7%
- 3b	8	10.7%
- 4	1	1.3%
- 5	1	1.3%
Arterial hypertension (HTN)	75	38 (50.7%)
Age at diagnosis of HTN	62	59 [29–73]
Positive family history in probands	61	22 (36%)
Liver cysts	75	10 (13.3%)
Context of diagnosis	68	
- Incidental		35 (51.5%)
- Abdominal pain		10 (14.7%)
- Kidney failure		2 (2.9%)
- Familial history		21 (30.9%)
TKV (ml, median with range)	39	688 [211–4139]
Right kidney length (cm)	54**	11.9 [8.5–25]
Left kidney length (cm)	55	12 [7.5–28]
ADPKD Mayo Classification	51	
- 1A		3 (5.9%)
- 1B		1 (2%)
- 1C		1 (2%)
- 2A		46 (90.2%)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; CKD, chronic kidney disease; HT, hypertension; TKV, total kidney volume; RK, right kidney; LK, left kidney; *categorical variables are expressed as number and percentage and numerical as median with a range **one individual underwent a right nephrectomy.

Figure legends

Figure 1. Study workflow. A) On the left, the recruitment process of the ADPKD-IFT140 individuals from observational ADPKD cohorts and genetic laboratory cohorts is shown. B) On the right, the estimation of the genetic prevalence of pLoF IFT140 carriers within the 100kG and GnomAD is displayed, along with the CyKD penetrance analysis within the 100kG database.
1 – Initial cohorts from which patients were recruited, with the number of probands provided in brackets; 2 – type of genetic testing employed; 3 – final number of individuals and families included in analysis. **cystic kidney panel including 25 genes; **kidney disease panel including 316 genes; [+]no phenotype metadata available; samples are derived from large biobanks which can include individuals with disease (details available: https://gnomad.broadinstitute.org/stats); ADPKD, autosomal dominant polycystic kidney disease; WGS, whole genome sequencing; WES, whole exome sequencing; tNGS, targeted next-generation sequencing; CyKD, cystic kidney disease; pLoF, predicted loss-of-function.*

Figure 2. Gene structure of *IFT140* and pLoF variant distribution. IFT140 variants identified in GnomAD v4.0, our cohort of patients and the 100k Genome Project database (red and blue dots representing variants in individuals with cystic kidney phenotype and without kidney cysts, respectively, and black dots variants in individuals of unknown phenotype – those from GnomAD). Green marker indicates the WD40 domain.

Figure 3. Kidney function in *IFT140*-affected individuals. A) CKD-EPI estimated glomerular filtration rate (eGFR) values are plotted against age in 75 individuals with ADPKD-*IFT140* from 61 families from our case series. Adjusted for age, males exhibited significantly lower renal function (linear regression, P<0.001). B) Plotting eGFR against age demonstrates that individuals with ADPKD-*IFT140* (N=75) have a slower decline in renal function compared to ADPKD-*PKD2* (N=549 individuals from Genkyst cohort) and ADPKD-*PKD1* (N=1826 individuals from Genkyst cohort).

Figure 4. Representative abdominal imaging of twelve individuals. Magnetic resonance imaging (MRI) views are displayed for six individuals, T1-weighted in one (B) and T2-weighted in five (A, C-F). Contrast-enhanced computed tomography (CT) is displayed for six individuals, G - L. Detailed clinical information available in Table S1. Legend: **A.** T2-weighted coronal MRI view of male individual (I.1, Family 1) who has an eGFR of 74 ml/min/1.73m^2 at the age of 60 years. **B.** Dynamic T1-weighted coronal MRI view, in the corticomedullary phase, of female individual (II.2, Family 6) who has an eGFR of 80 ml/min/1.73m^2 at the age of 56 years. **C.** T2-weighted (with fat saturation) coronal MRI view of male individual (II.1, Family 28) who has an eGFR of 57 ml/min/1.73m^2 at the age of 65 years. **D.** T2-weighted coronal MRI view of female individual (I.1, Family 19) who has an eGFR of 90 ml/min/1.73m^2 at the age of 20 years. **E.** T2-weighted (with fat saturation) coronal MRI view of female individual (III.2, Family 17) who has an eGFR of 60 ml/min/1.73m^2 at the age of 60 years and before a precise genetic diagnosis, was treated with tolvaptan. **F.** T2-weighted (with fat saturation) coronal MRI view of female individual (I.1, Family 26) who has an eGFR of 70 ml/min/1.73m^2 at the age of 58 years. **G.** Contrast-enhanced coronal computed tomography (CT) view of female individual (I.1, Family 11) who has an eGFR of 90 ml/min/1.73m^2 at the age of 67 years. **H.** Contrast-enhanced coronal CT view of female individual (I.1, Family 30) who has an eGFR of 57 ml/min/1.73m^2 at the age of 75 years. **I.** Contrast-enhanced coronal CT view of female individual (I.1, Family 8) who has an eGFR of 91 ml/min/1.73m^2 at the age of 30 years. **J.** Contrast-enhanced coronal CT view of male individual (II.1, Family 10) who has an eGFR of 83 ml/min/1.73m^2 at the age of 40 years. **K.** Contrast-enhanced coronal CT view of female individual (I.1, Family 13) who has an eGFR of 97 ml/min/1.73m^2 at the age of 35 years. **L.** Contrast-enhanced coronal CT view of male individual (III.4, Family 20) who has an eGFR of 67 ml/min/1.73m^2 at the age of 65 years.

Figure 5. Percentage of carriers of predicted loss-of-function *IFT140* variants (LoF and INDELS) identified in the 100kG Project database (total of 180), with a diagnosis of kidney cysts or polycystic kidneys, categorized by different age groups. The prevalence of diagnosed cystic kidney disease in individuals with *IFT140* variants of interest increases with age.

Figure 1

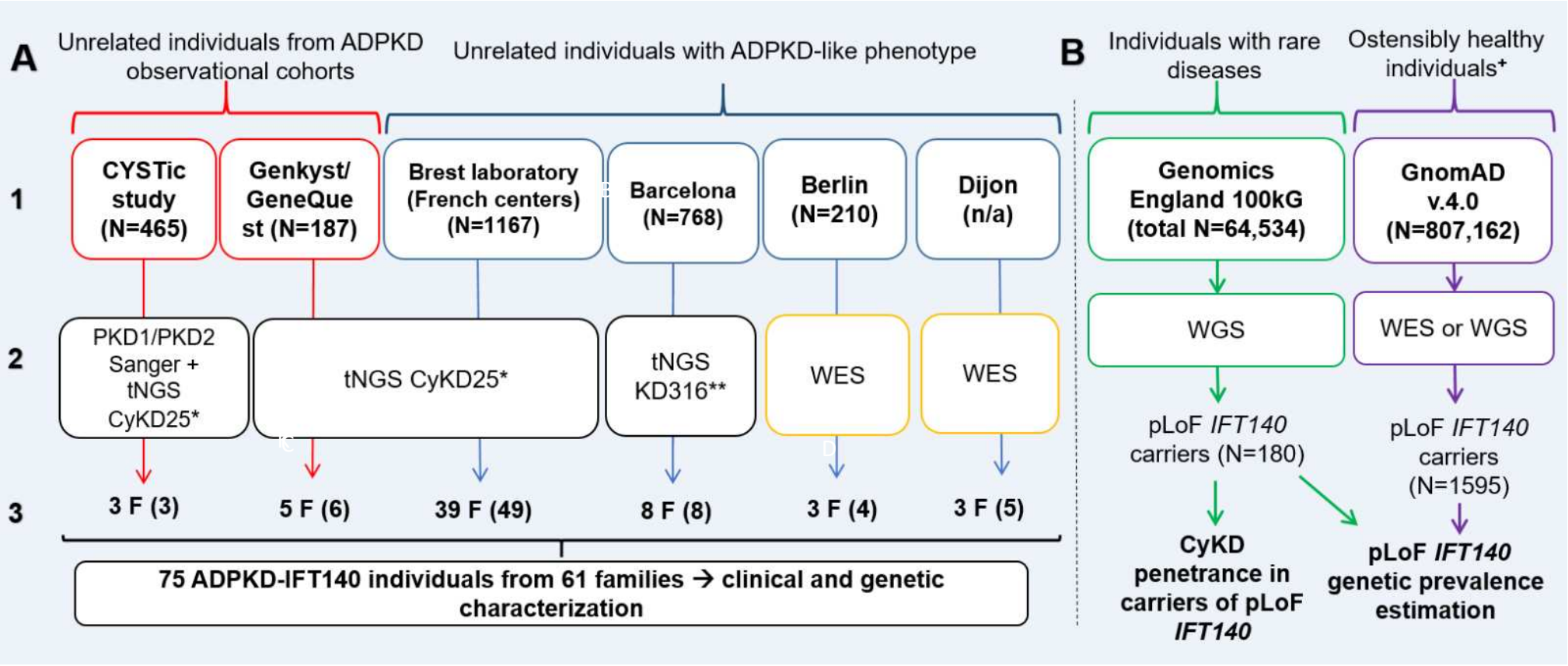
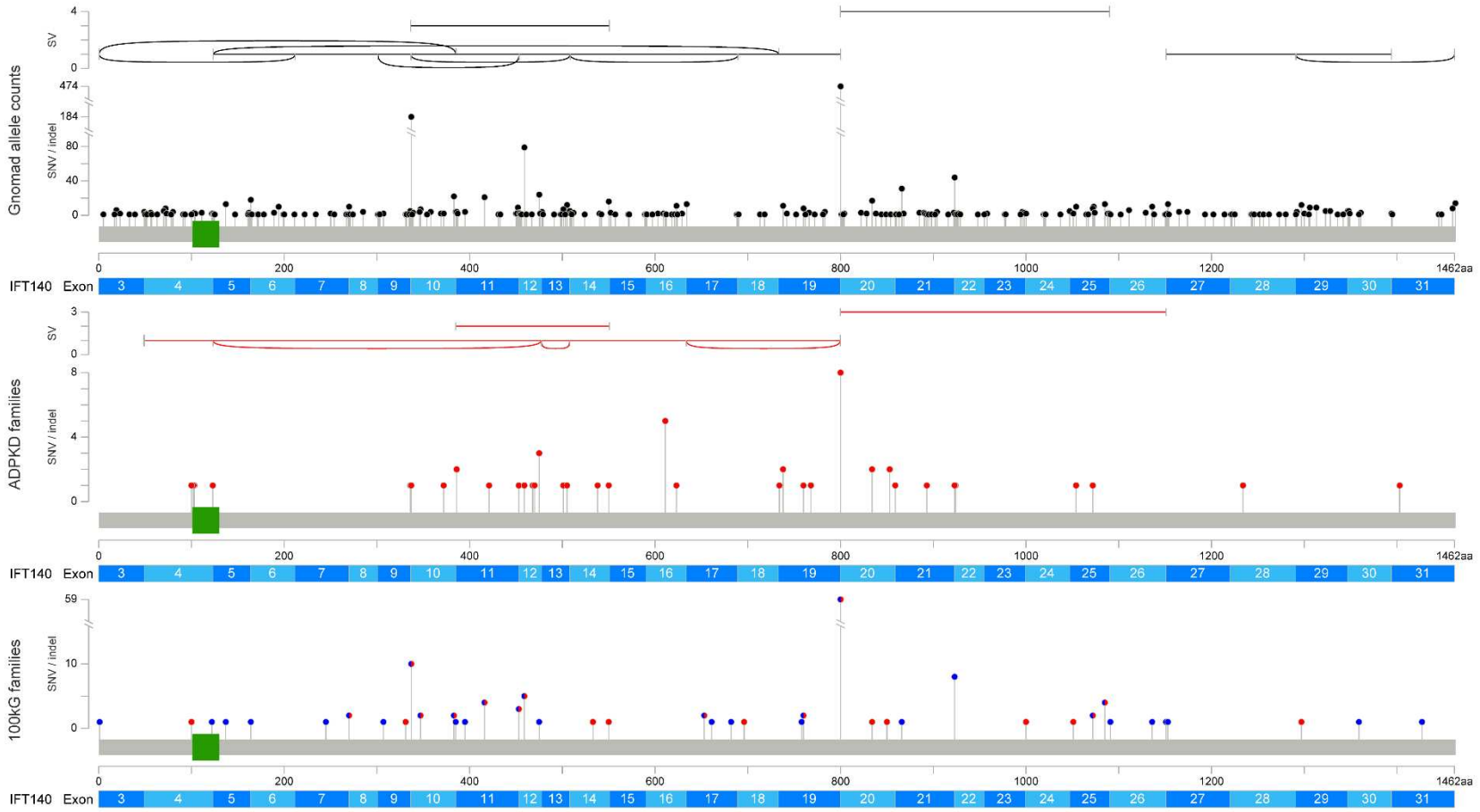

A
Unrelated individuals from ADPKD observational cohorts
Unrelated individuals with ADPKD-like phenotype
B
Individuals with rare diseases
Ostensibly healthy individuals+
1
CYSTic study (N=465)
Genkyst/ GeneQuest (N=187)
Brest laboratory (French centers) (N=1167)
Barcelona (N=768)
Berlin (N=210)
Dijon (n/a)
Genomics England 100kG (total N=64,534)
GnomAD v.4.0 (N=807,162)
2
PKD1/PKD2 Sanger + tNGS CyKD25*
tNGS CyKD25*
tNGS KD316**
WES
WES
WGS
WES or WGS
pLoF IFT140 carriers (N=180)
pLoF IFT140 carriers (N=1595)
3
3 F (3)
5 F (6)
39 F (49)
8 F (8)
3 F (4)
3 F (5)
CyKD penetrance in carriers of pLoF IFT140
pLoF IFT140 genetic prevalence estimation
75 ADPKD-IFT140 individuals from 61 families → clinical and genetic characterization

Figure 2


Gnomad allele counts
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SNV / indel
ADPKD families
100kG families
IFT140
Exon
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400
600
800
1000
1200
1462aa

Figure 3

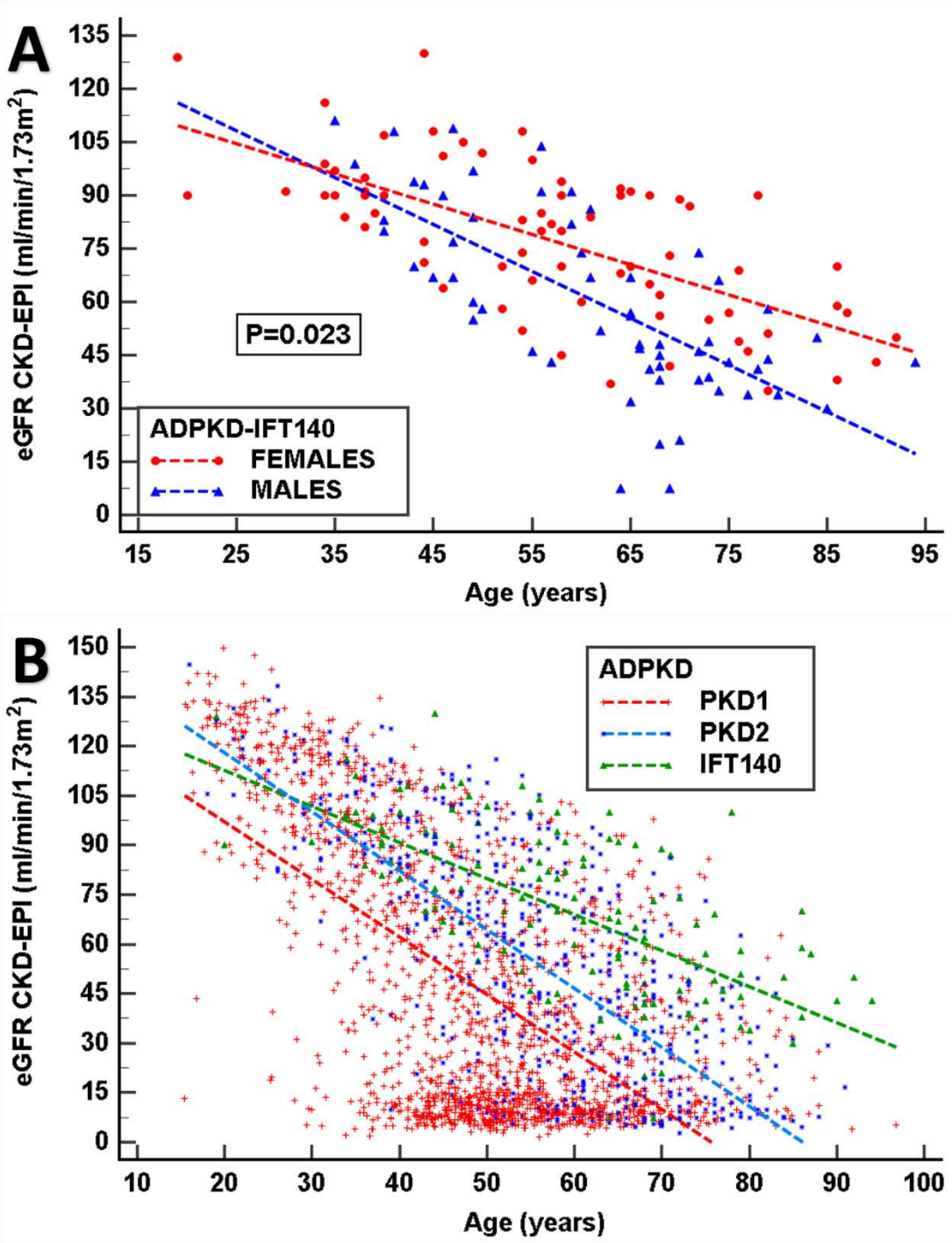

A
eGFR CKD-EPI (ml/min/1.73m²)
135
120
105
90
75
60
45
30
15
0
P=0.023
ADPKD-IFT140
FEMALES
MALES
15
25
35
45
55
65
75
85
95
Age (years)
B
eGFR CKD-EPI (ml/min/1.73m²)
150
135
120
105
90
75
60
45
30
15
0
ADPKD
PKD1
PKD2
IFT140
10
20
30
40
50
60
70
80
90
100
Age (years)

Figure 4

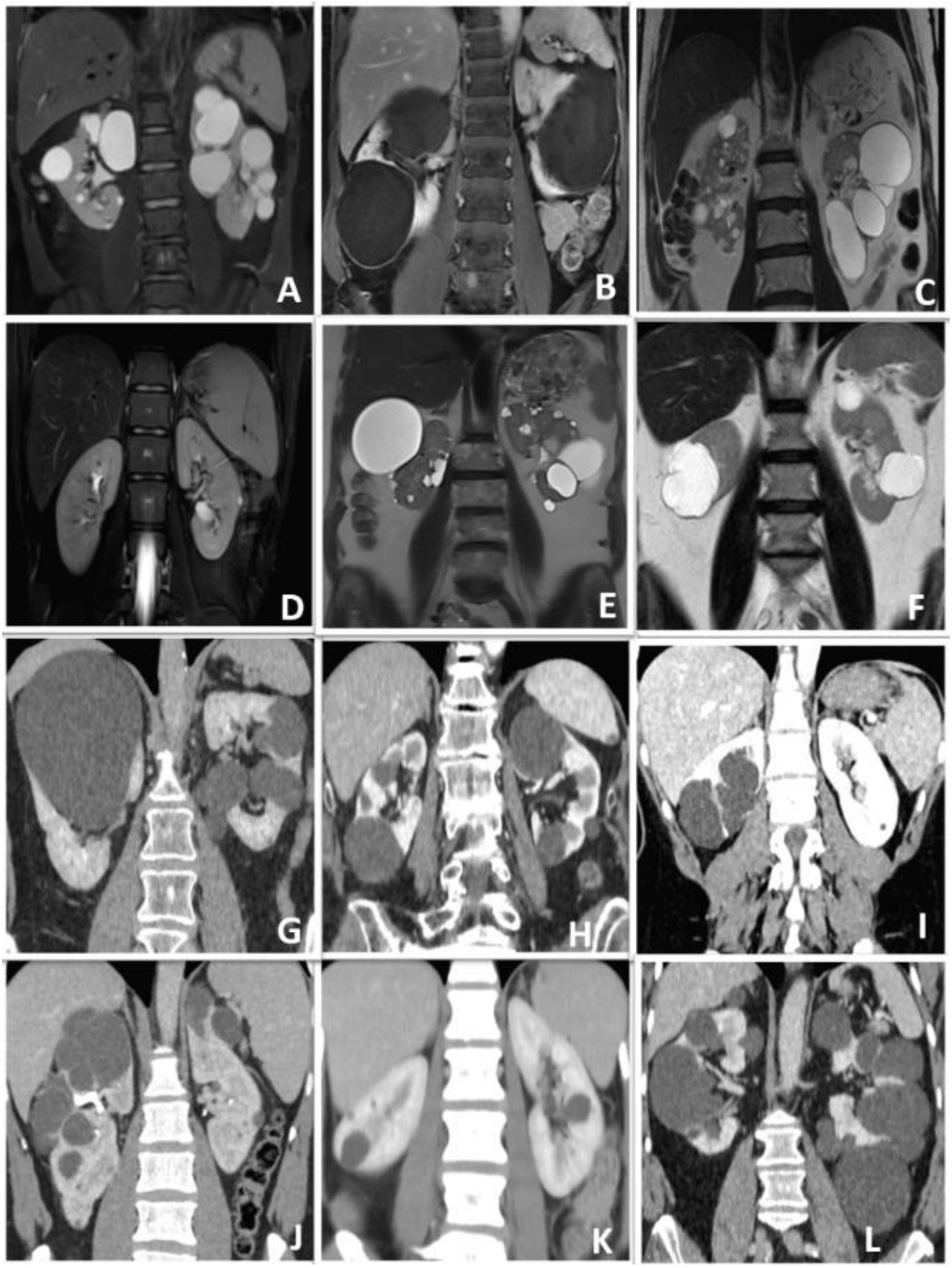
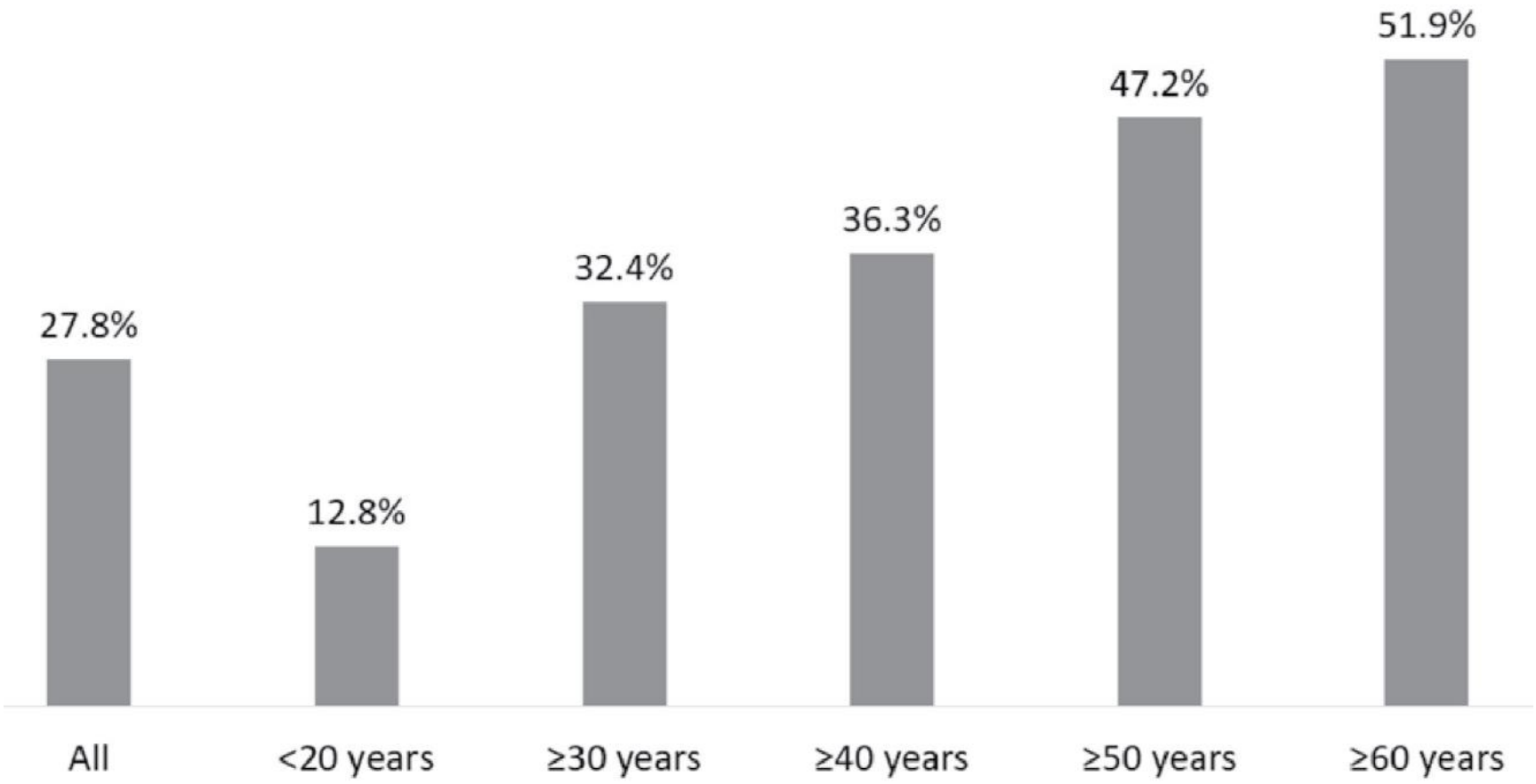


Figure 5


27.8%
12.8%
32.4%
36.3%
47.2%
51.9%
All
<20 years
≥30 years
≥40 years
≥50 years
≥60 years

SUPPLEMENTAL MATERIALS

List of Supplemental Material:

Table S1. Clinical presentation and pathogenic variants in the 75 affected individuals from the 61 ADPKD-IFT140 families.
Table S2. Rare variants identified in other genes associated with the ADPKD spectrum.
Table S3. Monoallelic loss-of -function variants of *IFT140* identified in the GnomAD v.4.0 database.
Supplemental Table S4. Large deletions of IFT140 identified in the GnomAD v.4.0 database.
Figure S1. Pedigrees of 14 families with loss-of-function *IFT140* variant including more than one single affected member. Black squares or circles indicate affected male of female subjects, respectively, with kidney cysts and/or kidney failure. Grey symbols indicate case subjects where clinical information are unavailable. Red asterixis indicate patients who underwent genetic test. Pointed symbol represents index patient.
Figure S2. CKD-EPI estimated glomerular filtration rate (eGFR) values are plotted against age in 75 individuals with ADPKD-IFT140 from 61 families. The age-adjusted eGFR in ADPKD-IFT140 individuals with the recurrent variant c.2399+1G>T (n=11) was comparable to that observed in the remaining IFT140 individuals (P=0.843).
Figure S3. Hypertension-free survival estimation (using Kaplan-Meier analysis) in a series of ADPKD-IFT140 (N=62). Median age at diagnosis of arterial hypertension was 59 years [range: 29-73].
Figure S4. Additional representative abdominal imaging of eight individuals. Detailed clinical information available in Table S1. Legend: **A.** Contrast-enhanced coronal CT view of female individual (I.1, Family 3) who has an eGFR of 95 ml/min/1.73m^2 at the age of 38 years. **B.** Contrast-enhanced coronal CT view of female individual (III.2, Family 5) who has an eGFR of 116 ml/min/1.73m^2 at the age of 34 years. **C.** T2-weighted coronal MRI view of female individual (III.1, Family 7) who has an eGFR of 129 ml/min/1.73m^2 at the age of 19 years. **D.** Contrast-enhanced coronal CT view of female individual (II.8, Family 15) who has an eGFR of 91 ml/min/1.73m^2 at the age of 65 years. **E.** T2-weighted coronal MRI view of male individual carrying pLoF variant in *IFT140* (p.Arg834*) and missense variant in *PKD1* (p.Cys232Gly) in trans (son of individual II.3, Family 16) who has an eGFR of 98 ml/min/1.73m^2 at the age of 8 years. **F1.** T2-weighted coronal MRI view of male individual (I.1, Family 38) who has an eGFR of 93 ml/min/1.73m^2 at the age of 44 years with additional LoF variant in *PKHD1* (Suppl Table 2). **F2.** T2-weighted coronal MRI view of the same male individual (I.1, Family 38) showing large kidney cyst and small-sized liver cysts. **G.** Non-enhanced coronal CT view of male individual (II.4, Family 25) who has an eGFR of 59 ml/min/1.73m^2 at the age of 79 years and has no liver cysts. He harbors additional class IV variant in *PKHD1* c.664A>G. **H.** T1-weighted coronal MRI view of male individual (III.1, Family 61) who has an eGFR of 34 ml/min/1.73m^2 at the age of 80 years (MRI performed at age of 64 years). He harbors additional class III variant in *PKD1* c.7373_7375del.

Table S1. Clinical presentation and pathogenic variants in the 75 affected individuals from the 61 ADPKD-IFT140 families.

Family	Pedigree Variant	Subject	Sex	eGFR (age) or KF (age)	Morphology of the kidneys				High blood pressure (age)	Context of diagnosis	Liver cysts (nb)	Mayo ADPKD Classification	Other personal or familial significant conditions (age), and if deceased, cause of death
					Type (Figure)	Age	Description of the cysts	Kidney length (cm), (TKV mL)					
1 PK14352	c.1611delG p.Thr538Glnfs*72	I.1	M	74 (60)	MRI (Fig.4A)	61	MBC Asymmetric kidneys	R: 11.5, L: 14 (1018)	Yes (59)	Incidental	No	2A	Prostatic adenoma (59) Cerebral MRI: no ICA
2 PK14391	c.1377G>A p.Trp459*	II.1	M	48 (66)	MRI	67	MBC, largest 10cm	NA	Yes (35)	Familial history	No	2A	T2DM (35) Father and brother with kidney cysts and T2DM
3 PK14390	c.1359+1G>C	I.1	F	95 (38)	CT (Fig. S4A)	38	MBC	R: 9.7, L: 10.5 (322)	No (38)	Abdominal pain	No	2A	Gestational HBP (28) Thyroid cancer (NA)
4 PK14424	Del exons 11 to 14	I.1	F	66 (55)	CT	55	MBC	NA	Yes (55)	Familial history	No	2A	Father with kidney cysts, COD complication of aortic valve replacement
5 PK14393	c.1501C>T p.Arg501Ter	II.4	F	89 (70)	CT	70	MBC, largest 2.7cm	R: 9.5, L: 7.5 (211)	Yes (60)	Familial history	Yes (6)	2A	Hepatic steatosis kidney stones
		III.2[2]	F	116 (34)	CT (Fig. S4B)	34	UC in LK, largest 4 cm, kidney stones in RK	R: 10.5, L: 12 (302)	No (34)	Incidental	No	2A	Symptomatic nephrolithiasis (33)
		III.3[1]	F	71 (44)	US	44	UC in RK, kidney stones	R: 11, L: 11 -	Yes (44)	Familial history	Yes (1)	2A	Gestational HBP
6 PK14423	Del exons 20 to 26	I.1[1]	F	38 (86)	US	85	MBC	R: 20, L: 20 -	Yes (NA)	Incidental	Yes	2A	COD peritonitis with ruptured colon diverticulitis (86)
		II.2[2]	F	80 (56)	MRI (Fig.4B)	56	MBC, largest 16cm	R: 25, L: 13 (2596)	No (56)	Familial history	No	2A	Glaucoma (NA); Hepatic angioma ; Cerebral MRI : no ICA; 2 Children with renal cysts (US)
7 PK14392	c.1513C>T p.Arg505*	II.3[1]	M	55 (49)	CT	49	MBC, largest 6 cm	R: 13.8, L: 12.5 (819)	No (49)	Incidental	No	2A	COD: pulmonary adenocarcinoma (49)
		III.1[2]	F	129 (19)	MRI (Fig. S4C)	17	MBC	R: 12.5, L :12 (413)	No (19)	Incidental	No	1C	Sus-ependymoma floor of 4th ventricule; Ovary cyst
8 PK14395	c.2399+1G>T	I.1	F	91 (30)	CT (Fig.4I)	29	MBC, largest 7.5cm, microcysts in the LK	R: 9.8, L: 10 (484)	No (24)	Abdominal pain	No	1B	Juvenile myoclonic epilepsy (26); Cerebral MRI: no ICA

9 PK14397	c.2500C>T p.Arg834*	I.1	M	48 (68)	CT	68	MBC largest 10cm	R: 17.5, L: 12.5 (1748)	Yes (NA)	Incidental	No	2A	Atrial fibrillation
10 PK14508	c.2577+1G>A	I.1[1]	M	KF (69)	US	69	MBC	NA	Yes (NA)	Incidental	No	NA	T2DM, COD heart failure (83)
		II.1	M	83 (40)	CT (Fig.4J)	40	MBC, largest 9cm	R: 17, L: 15 (1385)	No (40)	Incidental	No	2A	Abdominal traumatism with partial fracture of the RK
11 PK14443	c.1422_1423insAA p.(Arg475Asnfs*14)	I.1	F	90 (67)	CT (Fig.4G)	67	MBC, largest 10cm	R: 12.8, L: 9.5 (903)	No (67)	Incidental	No	2A	Treated hepatitis C Appendectomy
		II.1	M	111 (35)	MRI	34	MBC	ND	No (35)	Familial history	No	NA	None
12 PK14389	c.299del p.Leu100Argfs*45	I.1	F	108 (45)	US	45	MBC, largest 8 cm	Normal sized kidneys	Yes (30)	Abdominal pain	No	2A	None
13 PK14442	c.1114C>T p.Gln372*	I.1	F	97 (35)	CT (Fig.4K)	34	MBC, largest 3.2cm	R: 9 , L: 12 (309)	No (34)	Incidental	No	1A	Uncle and grand-father with ESKD
14 PK14396	c.2214_2217delCAGA p.Asp738Glufs*47	II.7[2]	M	32 (65)	CT	65	MBC, largest in left 5.6cm	R: 13.6, L: 12.7 (1523)	Yes (57)	Familial history	No	2A	SAH caused by ruptured ICA (50); Hyperuricemia ; Mother with PKD
		II.6[1]	M	56 (65)	US	65	MBC	Normal sized kidneys	Yes (38)	Incidental	No	NA	Bilateral inguinal hernia (55)
15 PK14447	Del exons 4 to 19	II.8[1,2]	F	91 (65)	CT (Fig. SD)	65	MBC, largest 10cm	R: 11, L: 14.5 (917)	Yes (65)	Incidental	No	2A	Hypercholesterolemi; 4 siblings with kidney cysts
16 PK14398	c.2500C>T p.Arg834*	I.1	F	>90 (38)	US	36	MBC	R :10.5, L :12	No (38)	Family history	No	NA	None
17 PK14394	c.1830_1832deinsTTTGA p.Val611Leufs*34	III.2[1,2]	F	60 (60)	MRI (Fig. 4E)	60	MBC, largest 8cm	R: 10.6, L: 11.5 (740)	No (60)	Familial history	Yes (1)	2A	Cerebral MRI: no ICA;Mother and daughter with kidney cysts
18 PK14422	c.1422_1423insAA p.(Arg475Asnfs*14)	I.1	F	100 (55)	MRI	55	MBC, largest 5 cm	R: 9, L: 10.5 (539)	No (55)	Abdominal pain	Yes (6)	2A	Gingival cysts; Cerebral MRI: no ICA ; Sclerosis of 1 cyst in the LK (55) ; Liver cyst fenestration (49)
19 PK14455	Del exons 20 to 26	I.1	F	90 (20)	MRI (Fig.4D)	19	MBC	R: 9.3, L: 9.5 (213)	No (19)	Abdominal pain	No	1A	UTI Ovary cyst
20 PK14444	c.2399+1G>T	III.4[2]	M	67 (65)	CT (Fig.4L)	64	MBC, largest 13.4cm	R: 16.5, L: 21.5 (2406)	Yes (35)	Familial history	No	2A	Hyperuricemia; Inguinal hernia ; Appendicectomia ;Mother and grandmother with kidney cysts
		III.1[1]	F	92 (64)	CT	64	MBC, largest 5.5 cm	R: 8.5, L: 12 (472)	No (64)	Familial history	No	2A	None reported
21 PK14445	c.3160C>T p.Gln1054Ter61	I.1	M	70 (43)	CT	45	MBC, largest 9.8 cm	R: 12, L: 14.5 (992)	Yes (43)	Incidental	No	2A	None reported
22 PK14465	c.2200-1G>A	II.4	M	>90 (39)	US	39	MBC largest 2 cm	Normal sized kidney	No (39)	Familial history	No	NA	Father with kidney and pancreatic cysts; Sister with kidney cysts
		III.1[2]	F	133 (13)	US	6	UC largest 1.5cm	R: 10, L: 11	No (14)	Incidental	No	NA	GERD

								-					
23 PK14506	c.1402G>T p.Glu468*	II.1	F	84 (61)	US	61	MBC	Normal-sized kidneys	No (61)	Familial history	No	NA	GERD
		II.2[2]	F	101 (46)	MRI	43	MBC	R: 9.6, L: 11.3	No (46)	Familial history	No	2A	Mother with kidney cysts
24 PK14626	c.2767_2768+2delTAGT	I.1	M	91 (59)	CT	59	MBC, largest 9cm	NA	No (59)	Incidental	No	2A	Appendectomy
25 PK14504	c.2399+1G>T	II.4[1,2]	M	58 (79)	CT (Fig. S4G)	79	MBC, largest 12cm	R: 24.7, L: 13 (4139)	Yes (NA)	Incidental	No	2A	T2DM Deafness; Rectum cancer (79) ; Inguinal hernia ; Daughter and grandson with kidney cysts
26 PK14660	Del exons 20 to 26	I.1	F	70 (58)	MRI (Fig.4F)	58	MBC, largest 4cm	R: 9.5, L: 8 (413)	Yes (58)	Incidental	No	2A	Migraine (15); Hypothyroidism (53)
27 PK14082	c.1010-1G>A	I.1	F	77 (44)	CT	44	MBC, largest 6 cm	R: 9.5, L: 10 (453)	No (44)	Abdominal pain	No	2A	UTI
28 PK14083	c.3696del p.Ile1234Serfs*33	II.1[2]	M	57 (65)	MRI (Fig.4C)	62	MBC, largest 7cm	R: 14.7, L: 14.3 (1523)	Yes (55)	Familial history	No	2A	Mother with renal cysts
		II.2	F	37 (63)	MRI	62	MBC, largest 6.5cm	R: 11.7, L: 13.3 (686)	Yes (55)	Familial history	No	2A	None reported
29 PK14084	c.2542_2559del p.Arg848_Ala853del	I.1	F	105 (48)	MRI	48	MBC	R: 12, L: 13.8 (624)	No (48)	Incidental	No	2A	Renal lithiasis
30 PK14085	c.1648C>T p.Arg550*	I.1	F	57 (75)	CT (Fig.4H)	75	MBC, largest 7.8cm	R: 9.8, L: 10 (419)	No (75)	Incidental	No	2A	None reported
31 PK14633	c.2278C>T p.Arg760*	I.1	M	45 (68)	MRI	68	MBC, largest 8 cm	R :16, L: 19 (2052)	No	Incidental	No	NA	None reported
32 PK14634	c.2399+1G>T	I.1	M	77 (47)	MRI	47	MBC, largest 11 cm	R:19, L:18 (2439)	No(47)	Incidental	No	2A	Lynch syndrome, Renal lithiasis
33 PK14635	c.2214_2217delCAGA p.Asp738glufs*47	II.1	M	86 (61)	US	61	MBC, largest 12.1 cm	R :10.6, L12.5	Yes (56)	NK	No	NA	Thrombosis (60), steato hepatitis (60),Father with nephrectomy
34 PK14770	c.1830_1832delinsTTTGA p.Val611Leufs*34	I.4	M	67(47)	CT	46	MBC, largest 6 cm	Normal sized kidneys	No (47)	Kidney insufficiency	No	2A	Thrombosis(41), 3 episodes of gout attacks (41), pulmonary embolism (46); Mother with kidney cysts Father died of a stroke
35 PK14771	c.1830_1832delinsTTTGA p.Val611Leufs*34	II.1	F	42 (69)	MRI	69	MBC, largest 10.6 cm	R :9.9 cm , L :10.2 cm (1580 mL)	Yes (63)	Incidental	No	2A	Left internal carotid aneuvysm, colic diverticulosis; 2 strokes ADPKD Familial history (father (died aged 75 ESKD), 2 aunts,sister,2 brothers)

36 PK14772	c.1422_1423insAA p.Arg475Asnfs*14	I.1	M	49 (73)	MRI	74	MBC, largest 7 cm	R : 12, L : 10 (912)	Yes (NK)	Kidney insufficiency	No	NA	Hemorrhagic stroke (58)
37 PK14773	c.2542_2559del p.Arg848_Ala853del	I.1	M	97 (49)	MRI	50	MBC, largest 8.2 cm	R :16.3, L :12.9	Yes (50)	Abdominal mass palpation + Abdominal pain	No	2A	None reported
38 PK14774	c.2768+4_2768+7del	I.1	M	93 (44)	MRI (Fig.S4 F1&F2)	44	MBC, largest 4.7 cm	R :10, L :10.5 (518)	No (44)	Incidental	Yes (mm_sized, >10)	2A	7 years old daughter with kidney cysts (2 cysts LK, 1 cyst RK)
39 PK14781	Deletion exons 17 to 19	II.1	F	73 (1)	US	1	UC, largest 3 mm	NA	No (1)	Familial history	No	NA	Father with kidney cysts
40 PK14817	c.1408del p.Ser470Leufs*18	I.1	M	20 (68)	US	68	MBC	R :14cm, L :21.9cm	Yes	Incidental	No	NA	Colic diverticulosis
41 PK14830	c.2399+1G>T	I.1	M	74 (72)	CT	72	MBC, largest 5.6cm	R :11.6, L :12 (688)	Yes (NK)	NK	Yes	NA	2 episodes of Acute coronary syndrome; thrombosis; Hepatitis E
42 PK14831	c.1009+1G>T	I.1	F	90 (58)	CT	58	MBC, largest 8 cm	Normal sized kidneys	Yes (43)	Incidental	Yes (2)	NA	Diabetes T2 (43)
43 PK14832	c.302_306dup p.Thr103Hisfs*44	II.1	M	34 (77)	MRI	73	MBC, largest 7.3 cm	R :8.6 ;L :9.8 (431)	Yes (NK)	Incidental	No	1A	None reported
44 PK14833	c.1830_1832delinsTTTGA p.Val611Leufs*34	II.1	M	58(50)	CT	59	UC, largest 4.4 cm	R :nephrectomy L :12.4 cm	Yes (29)	NK	No	NA	Right nephrectomy aged 35 Father died of a stroke aged 46
45 PED4094	c.2677G>T p.Glu893*	I.1	F	70 (86)	CT	81	MBC	Normal sized kidneys	NA	Familial history	No	2A	Kidney cyst aspiration (55) ; 2 unruptured ICA (82) ; Colon adenocarcinoma (81); Pulmonary adenocarcinoma (84)
		II.2[2]	M	104 (56)	CT	55	MBC, largest 6 cm	R: 13.5, L: 11 (652)	No (57)	Incidental	No	2A	ICA (51)
		II.3	M	91(56)	US	57	MBC, largest 12 cm	NA	Yes (NK)	Familial history	No	2A	Atrial fibrillation
46 PED6393	c.1261C>T p.Gln421*	I.1	M	42 (68)	US	74	MBC, largest 9 cm	R: 15, L: 13 -	Yes (73)	Incidental	No	2A	Arachnoid cyst Hyperuricemia
47 PED8286	c.2399+1G>T	I.1	F	108 (54)	CT	54	MBC, largest 12.8 cm	R: 10, L20 (1582)	NA	Incidental	No	2A	Mild deafness for low frequency sounds (48)
48 SHE-046	c.2399+1G>T	I.1	M	43 (75)	MRI	75	NA	(652)	Yes (NA)	NA	No	2A	None reported
49 BER-007	c.1158G>A p.Trp386Ter	I.1	F	64 (46)	MRI	46	NA	(1852)	No	NA	No	2A	None reported
50 BRU-063	c.1158G>A p.Trp386Ter	I.1	M	60 (49)	MRI	49	NA	(2722)	Yes (NA)	NA	No	2A	None reported

51 ALP-0516 20-0107	c.4207del p.Arg1403GlyfsTer13	I.1	F	>90 (64)	US	64	Few simple cysts	R: 11.9, L: 11.1 -	Yes (64)	Incidental	No	NA	None reported
52 CAKUT-0082 19-0255	c.2304C>A p.Cys768Ter	II.2	F	>90 (34)	US	34	MBC, largest 4.5cm	R: 15, L: 12 -	No	Incidental	No	2A	None reported
53 PQRAD-0619 21-0555	Del exon 5 to 12	I.1	M	67 (61)	MRI	61	MBC, asymmetrical enlarged kidneys	R: 17, L: 28 -	Yes (30)	Incidental	No	2A	Hyperuricemia; kidney stones
54 PQRAD-0517 18-0449	Del exon 13	I.1	M	>90 (46)	US	46	MBC	R: 14.5, L: 17.4	No	Incidental	Yes (few)	NA	Left seminal vesicle agenesis
55 PQRAD-0956 22-0481	Del exon 11 to 14	I.1	F	>90 (40)	US	40	MBC	R: 9.2, L: 10.6 -	No	Abdominal pain	Yes (<10)	NA	Kidney stones
56 PQRAD-0370 17-0162	c.369+1G>C	II.1	F	>90 (35)	US	35	MBC	Normal sized kidneys	No	Familial history	No	NA	Mother with kidney cysts
57 PKD-0021 20-0321	c.306_309del p.His102GlnsTer42	II.1	F	>90 (34)	US	34	MBC	Normal sized kidneys	No	Familial history	No	NA	Father with kidney cysts
58 PQRAD-0943 22-0336	c.3214C>T p.Arg1072Ter	I.1	F	>90 (78)	US	78	MBC, largest 10cm	NA	Yes (63)	Incidental	No	2A	Large hepatic angioma (8 cm); Chronic lymphoproliferative syndrome ; Cholecystectomy
59 GER01	c.2399+1G>T	BELE II.1	M	108 (41)	CT	36	Few large bilateral cysts	R: 11.8, L:13.0	Yes (39)	Incidental finding when he suffered from hepatitis (26)	No	NA	None reported
		BELE II.3	F	91 (38)	CT	37	Few large bilateral cysts	R:12.6, L:10.8	Yes (37)	Abdominal pain	No	NA	Anemia, Suspected Nephrolithiasis (confirmed concrements left on CT scan)
60 GER02	c.2399+1G>T	BELE II.1	F	52 (54)	MRI	53	Few large bilateral cysts	R:13.2, L15.2	Yes (50)	Abdominal pain	No	NA	Mitral valve regurgitation, Osteoporosis, Hashimoto

61 GER03	c.1867_1870del, p.Glu623Argfs*20	BELE III.1	M	34 (80)	MRI (Fig. S4H)	80	Few large bilateral cysts	R:22, L:16	Yes (65)	NA	No	NA	Gout, Splenomegaly, Benign prostatic hyperplasia (BPH), inguinal hernia

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CT, computed tomography; COD, cause of death; F, female; GERD, gastroesophageal reflux disease; HBP, high blood pressure; TKV, total kidney volume; ICA, intracranial aneurysm; KF, kidney failure; LK, left kidney; M, male; MBC, multiple bilateral cysts; MRI: magnetic resonance imaging; NA, not available; NK, not known; RK, right kidney; T2DM, Type 2 diabetes mellitus; UC, unilateral cysts; US, ultrasound; UTI, urinary tract infection; [1]No blood sample available, the presence of the familial variant was not confirmed; [2]Propositus.

Table S2. Rare variants identified in other genes associated with the ADPKD spectrum.

Pedigree/proband IFT140 variant	Other variant of interest						
	Gene	**cDNA variant**	**Protein variant**	**CADD score**	**ACMG class**	**Variant allele frequency in GnomAD (exome + genome)**	**ClinVar interpretation**
3 / PK14390 c.1359+1G>C	*PKD1*	c.8938A>T	p.Ile2980Phe	23.80	Class III	Absent	No
12 / PK14389 c.299del p.Leu100Argfs*45	*PKD1*	c.10397C>T	p.Ser3466Leu	23.00	Class I/II	E: 0.0001 G: 0.0002	1*Benign 2*Likely benign
14 / PK14396 c.2214_2217delCAGA p.Asp738Glufs*47	*PKD1*	c.4210G>A	p.Ala1404Thr	11.76	Class II	Absent	No
15 / PK14447 Del exons 4 to 19	*PKD1*	c.9990C>T	p.Ser3330=	1.45	Class II	E: 7.376 x 10^{-5} G: 4.599 x 10^{-5}	2*Likely benign
20 / PK14444 c.2399+1G>T p.Ser800?	*PKD1*	c.3077C>T	p.Thr1026Ile	18.23	Class II	E: 3.505x10^{-5} G: 9.845x10^{-5}	No
22 / PK14465 c.2200-1G>A	*PKD1*	c.9668C>T	p.Thr3223Met	18.35	Class III or II	E: 0.0002 G: 0.0002	1*VUS 1*Likely benign
61 / GER03 c.1867_1870del, p.Glu623Argfs*20	*PKD1*	c.7373_7375del	p.Glu2458del	-	Class III	E: 8.319 x 10^{-6} G: absent	2*VUS
7 / PK14392 c.1513C>T p.Arg505*	*PKHD1*	c.131G>A	p.Gly44Asp	5.66	Class III	E: 6.157 x 10^{-6} G: absent	No
17 / PK14394 c.1830_1832deinsTTTGA p.Val611Leufs*34	*PKHD1*	c.11400G>A	p.Gly3800=	0.1	Class III or II	E: 0.0002 G: 0.0002	1*VUS; 1*Likely benign; 1*Benign; 1*Conflicting
25 / PK14504 c.2399+1G>T p.Ser800?	*PKHD1*	c.664A>G	p.Ile222Val	18.22	Class IV	E: 0.0001 G: 7.235 x 10^{-5}	Likely pathogenic/ Pathogenic
31 / PK14633 c.2278C>T p.Arg760*	*PKHD1*	c.3703C>T	p.Arg1235Trp	23.30	Class III	E: 8.000x 10^{-5} G: 7.884x10^{-5}	1*Likely benign 2*VUS
38 / PK14774 c.2768+4_2768+7del	*PKHD1*	c.4330C>T	p.Gln1444*	35	Class V	E: 1.2x10^{-6} G: absent	2*Likely pathogenic 1*Pathogenic

Abbreviations: ADPKD, autosomal-dominant polycystic kidney disease; ACMG, American College of Medical Genetics; CADD, Combined Annotation Depandent Depletio; PKHD1, GenBank: NM_138694.4; PKD1, polycystic kidney disease 1, GenBank: NM_001009944.3; VUS, variant of undetermined significance (class III ACMG).

Table S3. Monoallelic loss-of -function variants (280) of *IFT140* identified in the GnomAD database (v4.0).

Chromosome	Position	Source	HGVS Consequence	Transcript Consequence	VEP Annotation	Allele Count	Allele Number
16	1510945	gnomAD Exomes, gnomAD Genomes	p.Ter1463GlufsTer75	c.4387del	frameshift_variant	14	1610568
16	1510955	gnomAD Exomes, gnomAD Genomes	p.Asp1460ArgfsTer60	c.4377_4378insA	frameshift_variant	8	1611612
16	1510991	gnomAD Exomes	p.Arg1448GlyfsTer90	c.4341del	frameshift_variant	1	626346
16	1511000	gnomAD Exomes	p.Glu1445Ter	c.4333G>T	stop_gained	1	625762
16	1511152	gnomAD Exomes	c.4183-2A>G	c.4183-2A>G	splice_acceptor_variant	1	1449234
16	1518141	gnomAD Exomes	p.Asn125LysfsTer?	c.374dup	frameshift_variant	1	1330460
16	1518145	gnomAD Exomes, gnomAD Genomes	p.Asn122LysfsTer?	c.363_370del	frameshift_variant	8	1499354
16	1518145	gnomAD Exomes	p.Ser124Ter	c.371C>A	stop_gained	1	1347126
16	1518154	gnomAD Exomes	p.Asn122ThrfsTer14	c.361del	frameshift_variant	2	1409206
16	1518161	gnomAD Exomes	p.Arg119Ter	c.355C>T	stop_gained	23	1429144
16	1518173	gnomAD Genomes	p.Thr114LysfsTer8	c.341_342del	frameshift_variant	1	152258
16	1518181	gnomAD Exomes	p.Arg112ProfsTer7	c.333_334dup	frameshift_variant	3	1423094
16	1518215	gnomAD Exomes, gnomAD Genomes	c.4182+1G>A	c.4182+1G>A	splice_donor_variant	2	777856
16	1518317	gnomAD Exomes	p.Glu1361Ter	c.4081G>T	stop_gained	3	1461796
16	1518323	gnomAD Exomes	p.Gln1359Ter	c.4075C>T	stop_gained	1	833110
16	1518351	gnomAD Exomes	p.Tyr1349Ter	c.4047C>G	stop_gained	1	628282
16	1518358	gnomAD Exomes	c.4041-1G>A	c.4041-1G>A	splice_acceptor_variant	1	627520
16	1518359	gnomAD Exomes	c.4041-2A>G	c.4041-2A>G	splice_acceptor_variant	5	627362
16	1519880	gnomAD Exomes	c.4040+1G>A	c.4040+1G>A	splice_donor_variant	5	1382156
16	1519887	gnomAD Exomes	p.Phe1342ProfsTer71	c.4024_4033del	frameshift_variant	1	1392862
16	1519913	gnomAD Exomes	p.Met1336ArgfsTer4	c.4007del	frameshift_variant	1	1431762
16	1519939	gnomAD Exomes, gnomAD Genomes	p.Arg1328GlyfsTer12	c.3981del	frameshift_variant	5	770998
16	1519953	gnomAD Exomes	p.Leu1323TrpfsTer17	c.3967del	frameshift_variant	4	621166
16	1519953	gnomAD Exomes	p.Leu1323ProfsTer39	c.3967dup	frameshift_variant	1	621198
16	1519982	gnomAD Exomes, gnomAD Genomes	p.Cys1313Ter	c.3939C>A	stop_gained	9	773436
16	1520004	gnomAD Exomes, gnomAD Genomes	p.Ala1306GlyfsTer56	c.3916dup	frameshift_variant	9	1602386
16	1520007	gnomAD Exomes	p.Gly1305AlafsTer58	c.3910_3913dup	frameshift_variant	1	617738

16	1520021	gnomAD Exomes	p.Tyr1300Ter	c.3900C>A	stop_gained	2	1448206
16	1520030	gnomAD Exomes, gnomAD Genomes	p.Tyr1297Ter	c.3891C>A	stop_gained	12	1601048
16	1520048	gnomAD Exomes, gnomAD Genomes	c.3874-1G>A	c.3874-1G>A	splice_acceptor_variant	4	771596
16	1520049	gnomAD Exomes	c.3874-2A>G	c.3874-2A>G	splice_acceptor_variant	1	1451694
16	1520049	gnomAD Exomes	c.3874-2A>C	c.3874-2A>C	splice_acceptor_variant	1	1451694
16	1520165	gnomAD Exomes	p.Asp1280ThrfsTer28	c.3838del	frameshift_variant	1	1461854
16	1520185	gnomAD Exomes	p.Tyr1273Ter	c.3819C>A	stop_gained	1	1461874
16	1520217	gnomAD Exomes	p.Glu1262AspfsTer5	c.3786del	frameshift_variant	1	1461888
16	1520237	gnomAD Genomes	p.Ser1256ProfsTer11	c.3766del	frameshift_variant	1	152248
16	1520245	gnomAD Genomes	p.Asn1252ThrfsTer14	c.3755_3758del	frameshift_variant	1	152236
16	1520267	gnomAD Exomes	p.Ile1246AsnfsTer7	c.3736dup	frameshift_variant	1	833110
16	1520274	gnomAD Exomes	p.Lys1244Ter	c.3730A>T	stop_gained	1	1461884
16	1520277	gnomAD Exomes	p.Gln1243Ter	c.3727C>T	stop_gained	1	628778
16	1520330	gnomAD Exomes	p.Leu1225AlafsTer27	c.3672_3673del	frameshift_variant	1	1461788
16	1520345	gnomAD Exomes	c.3661-2A>G	c.3661-2A>G	splice_acceptor_variant	1	628444
16	1520622	gnomAD Exomes	p.Gln1214Ter	c.3640C>T	stop_gained	1	607980
16	1520635	gnomAD Exomes	p.Ser1204GlnfsTer43	c.3610_3626del	frameshift_variant	1	612796
16	1520658	gnomAD Exomes	p.Gln1202Ter	c.3604C>T	stop_gained	1	619336
16	1520685	gnomAD Exomes	p.Glu1193Ter	c.3577G>T	stop_gained	1	623676
16	1520740	gnomAD Exomes, gnomAD Genomes	p.Met1174ArgfsTer22	c.3521del	frameshift_variant	4	1610908
16	1520768	gnomAD Exomes	p.Ser1165AlafsTer10	c.3493del	frameshift_variant	4	622268
16	1520801	gnomAD Exomes	p.Glu1154LysfsTer11	c.3460del	frameshift_variant	1	617494
16	1520802	gnomAD Exomes	p.Gln1153ArgfsTer32	c.3458_3459del	frameshift_variant	1	617158
16	1520805	gnomAD Exomes	p.Gln1153Ter	c.3457C>T	stop_gained	10	1449954
16	1520806	gnomAD Genomes	p.Tyr1152Ter	c.3456T>A	stop_gained	1	152136
16	1520809	gnomAD Exomes	c.3454-1G>A	c.3454-1G>A	splice_acceptor_variant	2	1449364
16	1520810	gnomAD Exomes	c.3454-2A>G	c.3454-2A>G	splice_acceptor_variant	1	1448832
16	1523517	gnomAD Exomes	c.3453+1G>A	c.3453+1G>A	splice_donor_variant	1	624384
16	1523517	gnomAD Exomes	c.3453+1G>C	c.3453+1G>C	splice_donor_variant	1	624384

16	1523559	gnomAD Exomes	p.Gln1138SerfsTer48	c.3411dup	frameshift_variant	1	627958
16	1523561	gnomAD Exomes, gnomAD Genomes	p.His1136GlnfsTer49	c.3408_3409del	frameshift_variant	10	1613370
16	1523586	gnomAD Exomes, gnomAD Genomes	p.Cys1129SerfsTer58	c.3384_3385insAGTG	frameshift_variant	3	1613720
16	1523640	gnomAD Exomes	p.Gln1111Ter	c.3331C>T	stop_gained	6	1461602
16	1523664	gnomAD Exomes	p.Phe1102LeufsTer12	c.3306del	frameshift_variant	1	628420
16	1523826	gnomAD Exomes	c.3270+2T>C	c.3270+2T>C	splice_donor_variant	1	627170
16	1523827	gnomAD Exomes	c.3270+1G>C	c.3270+1G>C	splice_donor_variant	1	1460388
16	1523827	gnomAD Exomes	c.3270+1G>A	c.3270+1G>A	splice_donor_variant	2	1460388
16	1523834	gnomAD Exomes	p.Tyr1088Ter	c.3264C>A	stop_gained	1	627468
16	1523837	gnomAD Genomes	p.Tyr1088ValfsTer32	c.3260dup	frameshift_variant	1	152238
16	1523844	gnomAD Exomes, gnomAD Genomes	p.Val1085GlyfsTer36	c.3250_3253dup	frameshift_variant	13	1613098
16	1523876	gnomAD Exomes	p.Tyr1074Ter	c.3222C>A	stop_gained	3	1461168
16	1523879	gnomAD Exomes, gnomAD Genomes	p.Tyr1073Ter	c.3219C>A	stop_gained	10	1613436
16	1523884	gnomAD Exomes, gnomAD Genomes	p.Arg1072Ter	c.3214C>T	stop_gained	8	1613366
16	1523897	gnomAD Exomes	p.Met1067IlefsTer2	c.3199_3200dup	frameshift_variant	1	1461230
16	1523905	gnomAD Exomes	p.Glu1065ArgfsTer3	c.3192del	frameshift_variant	1	1461132
16	1523938	gnomAD Exomes	p.Gln1054Ter	c.3160C>T	stop_gained	10	1460308
16	1523948	gnomAD Exomes	p.Leu1051ProfsTer69	c.3149dup	frameshift_variant	2	1459708
16	1524551	gnomAD Exomes	c.3141+1G>T	c.3141+1G>T	splice_donor_variant	5	1459722
16	1524584	gnomAD Exomes	p.Gln1037Ter	c.3109C>T	stop_gained	1	1459070
16	1524632	gnomAD Exomes	p.Glu1021Ter	c.3061G>T	stop_gained	1	1448030
16	1524633	gnomAD Genomes	p.Tyr1020Ter	c.3060C>A	stop_gained	1	152212
16	1524638	gnomAD Exomes	p.Gln1019Ter	c.3055C>T	stop_gained	1	610210
16	1524696	gnomAD Exomes	c.2998-2del	c.2998-2del	splice_acceptor_variant	2	1423030
16	1524788	gnomAD Exomes	p.Gln998ArgfsTer6	c.2992del	frameshift_variant	2	621288
16	1524789	gnomAD Exomes	p.Gln998Ter	c.2992C>T	stop_gained	1	833110
16	1524793	gnomAD Exomes	p.Asn996MetfsTer8	c.2987del	frameshift_variant	4	1455940
16	1524801	gnomAD Exomes	p.Gln994Ter	c.2980C>T	stop_gained	1	624886
16	1524847	gnomAD Exomes	p.Tyr978Ter	c.2934C>G	stop_gained	1	1460874

16	1524850	gnomAD Exomes	p.Tyr977Ter	c.2931C>G	stop_gained	1	627824
16	1524907	gnomAD Genomes	p.Trp958AlafsTer161	c.2872_2873del	frameshift_variant	1	152188
16	1524907	gnomAD Exomes	p.Trp958Ter	c.2874G>A	stop_gained	1	833110
16	1525230	gnomAD Exomes	c.2864+1G>C	c.2864+1G>C	splice_donor_variant	1	626976
16	1525251	gnomAD Exomes	p.Tyr948Ter	c.2844C>A	stop_gained	1	1459988
16	1525308	gnomAD Exomes	p.Thr929SerfsTer21	c.2786del	frameshift_variant	1	1459798
16	1525315	gnomAD Exomes	p.Ser927Ter	c.2780C>A	stop_gained	2	1459174
16	1525319	gnomAD Exomes	p.Lys926Ter	c.2776A>T	stop_gained	1	1459210
16	1525326	gnomAD Exomes	c.2769-1del	c.2769-1del	splice_acceptor_variant	2	626008
16	1525327	gnomAD Exomes	c.2769-1G>T	c.2769-1G>T	splice_acceptor_variant	1	1457288
16	1525884	gnomAD Exomes, gnomAD Genomes	c.2767_2768+2del	c.2767_2768+2del	splice_donor_variant	44	1537352
16	1525885	gnomAD Genomes	c.2768+1dup	c.2768+1dup	splice_donor_variant	3	152242
16	1525909	gnomAD Exomes	p.Asp916ThrfsTer34	c.2745del	frameshift_variant	1	1402420
16	1525943	gnomAD Exomes	p.Tyr904Ter	c.2712C>A	stop_gained	2	592270
16	1525944	gnomAD Exomes	p.Tyr904LeufsTer48	c.2710dup	frameshift_variant	2	592130
16	1525951	gnomAD Exomes	p.Ser902AlafsTer49	c.2702_2703dup	frameshift_variant	1	1427556
16	1525962	gnomAD Exomes	p.Val898CysfsTer52	c.2692del	frameshift_variant	1	598944
16	1525972	gnomAD Exomes	p.His895ThrfsTer57	c.2682_2683insA	frameshift_variant	1	1438418
16	1525974	gnomAD Exomes	p.Gln890ThrfsTer56	c.2668_2680del	frameshift_variant	1	1439098
16	1525978	gnomAD Exomes	p.Glu893Ter	c.2677G>T	stop_gained	1	1440058
16	1525983	gnomAD Exomes	p.Val891Ter	c.2671del	frameshift_variant	2	1442276
16	1525986	gnomAD Exomes	p.Gln890ArgfsTer2	c.2668del	frameshift_variant	1	610556
16	1525999	gnomAD Exomes	p.Trp885CysfsTer7	c.2655del	frameshift_variant	2	1447526
16	1526001	gnomAD Exomes	p.Trp885Ter	c.2654G>A	stop_gained	1	614570
16	1526052	gnomAD Exomes	p.Lys868ArgfsTer89	c.2587_2602dup	frameshift_variant	1	1444780
16	1526053	gnomAD Exomes	p.Lys868SerfsTer8	c.2601del	frameshift_variant	1	611332
16	1526057	gnomAD Exomes, gnomAD Genomes	p.Tyr866Ter	c.2598C>G	stop_gained	31	1594394
16	1526068	gnomAD Exomes	p.Glu863Ter	c.2587G>T	stop_gained	1	1434098
16	1526077	gnomAD Exomes	p.Glu860Ter	c.2578G>T	stop_gained	1	595366

16	1526617	gnomAD Exomes	c.2558_2577+1del	c.2558_2577+1del	splice_donor_variant	1	1358574
16	1526617	gnomAD Exomes	c.2577+2T>C	c.2577+2T>C	splice_donor_variant	1	1358574
16	1526628	gnomAD Exomes	p.Met858HisfsTer94	c.2567dup	frameshift_variant	3	1410934
16	1526632	gnomAD Exomes	p.Thr854AlafsTer96	c.2559_2563del	frameshift_variant	1	1389322
16	1526641	gnomAD Exomes	p.Val849GlyfsTer99	c.2544_2554del	frameshift_variant	1	1416840
16	1526666	gnomAD Exomes	p.Glu844Ter	c.2530G>T	stop_gained	1	1445072
16	1526684	gnomAD Exomes	p.Glu838Ter	c.2512G>T	stop_gained	2	1449682
16	1526696	gnomAD Exomes, gnomAD Genomes	p.Arg834Ter	c.2500C>T	stop_gained	17	1603360
16	1526712	gnomAD Exomes	p.Gly828AlafsTer18	c.2483del	frameshift_variant	2	622286
16	1526731	gnomAD Exomes	p.Val822CysfsTer24	c.2464del	frameshift_variant	3	623994
16	1526785	gnomAD Exomes	p.Trp804Ter	c.2411G>A	stop_gained	2	623616
16	1526796	gnomAD Genomes	c.2400-13_2400-1del	c.2400-13_2400-1del	splice_acceptor_variant	1	152202
16	1526797	gnomAD Exomes	c.2400-1G>A	c.2400-1G>A	splice_acceptor_variant	1	1454628
16	1526798	gnomAD Genomes	c.2400-2A>T	c.2400-2A>T	splice_acceptor_variant	1	152226
16	1557934	gnomAD Exomes, gnomAD Genomes	c.2399+1G>T	c.2399+1G>T	splice_donor_variant	474	1613066
16	1557935	gnomAD Exomes	p.Ser800ValfsTer13	c.2398del	frameshift_variant	1	833076
16	1557985	gnomAD Exomes	p.Val783HisfsTer18	c.2347_2348del	frameshift_variant	4	1461638
16	1557987	gnomAD Genomes	p.Phe781LeufsTer4	c.2343_2346del	frameshift_variant	1	152182
16	1558020	gnomAD Exomes	p.Thr772ProfsTer14	c.2313del	frameshift_variant	1	833104
16	1558038	gnomAD Exomes	p.Glu766Ter	c.2296G>T	stop_gained	3	628630
16	1558047	gnomAD Exomes	p.Phe762CysfsTer39	c.2285_2286del	frameshift_variant	1	1461740
16	1558056	gnomAD Exomes	p.Arg760Ter	c.2278C>T	stop_gained	8	1461738
16	1558059	gnomAD Exomes	p.Gln752CysfsTer27	c.2253_2274del	frameshift_variant	1	628682
16	1558109	gnomAD Exomes, gnomAD Genomes	p.Glu742AlafsTer45	c.2223_2224dup	frameshift_variant	2	985322
16	1558116	gnomAD Exomes, gnomAD Genomes	p.Asp738GlufsTer47	c.2214_2217del	frameshift_variant	11	1614064
16	1562028	gnomAD Genomes	p.His718GlnfsTer83	c.2154_2155del	frameshift_variant	1	152118
16	1562046	gnomAD Exomes	p.Arg713GlyfsTer73	c.2137del	frameshift_variant	1	1459486
16	1562118	gnomAD Exomes	c.2068-2A>G	c.2068-2A>G	splice_acceptor_variant	1	595958
16	1563996	gnomAD Exomes	c.2067+1G>A	c.2067+1G>A	splice_donor_variant	1	1420864

16	1566160	gnomAD Exomes, gnomAD Genomes	c.1901+1G>T	c.1901+1G>T	splice_donor_variant	13	1612190
16	1566177	gnomAD Exomes, gnomAD Genomes	p.Glu629Ter	c.1885G>T	stop_gained	2	780480
16	1566190	gnomAD Exomes	p.Thr624SerfsTer20	c.1871del	frameshift_variant	1	1461384
16	1566191	gnomAD Exomes, gnomAD Genomes	p.Glu623ArgfsTer20	c.1867_1870del	frameshift_variant	11	1613614
16	1566192	gnomAD Exomes	p.Arg621HisfsTer5	c.1862_1869del	frameshift_variant	1	1461554
16	1566210	gnomAD Genomes	p.Gln618Ter	c.1852C>T	stop_gained	1	152184
16	1566229	gnomAD Exomes	p.Phe612Ter	c.1832_1833insTTGA	stop_gained	1	1461604
16	1566230	gnomAD Exomes	p.Val611LeufsTer2	c.1830_1831del	frameshift_variant	1	1461606
16	1566237	gnomAD Exomes	p.Val609Ter	c.1824del	frameshift_variant	2	1461570
16	1566253	gnomAD Exomes	p.Asp603ValfsTer7	c.1808del	frameshift_variant	2	1461518
16	1566272	gnomAD Exomes	p.Ser597PhefsTer9	c.1789dup	frameshift_variant	1	833102
16	1566292	gnomAD Genomes	c.1771-1G>A	c.1771-1G>A	splice_acceptor_variant	1	152094
16	1568215	gnomAD Exomes	c.1770+2T>C	c.1770+2T>C	splice_donor_variant	1	1438022
16	1568216	gnomAD Exomes	c.1770+1G>A	c.1770+1G>A	splice_donor_variant	1	1441512
16	1568274	gnomAD Exomes	p.Gly571AlafsTer39	c.1712del	frameshift_variant	1	628042
16	1568274	gnomAD Exomes	p.Ile572HisfsTer21	c.1712dup	frameshift_variant	1	628044
16	1568316	gnomAD Genomes	p.Cys557Ter	c.1671T>A	stop_gained	1	152210
16	1568330	gnomAD Exomes	p.Glu552GlyfsTer6	c.1655_1656del	frameshift_variant	1	1461008
16	1568336	gnomAD Exomes	c.1653-2A>G	c.1653-2A>G	splice_acceptor_variant	2	832266
16	1571411	gnomAD Exomes	p.Arg550Ter	c.1648C>T	stop_gained	16	1456902
16	1571433	gnomAD Exomes	p.His542ProfsTer68	c.1625del	frameshift_variant	1	1461206
16	1571439	gnomAD Exomes	p.Leu540PhefsTer5	c.1619dup	frameshift_variant	1	628658
16	1571440	gnomAD Exomes	p.Leu540Ter	c.1619T>A	stop_gained	1	628708
16	1571486	gnomAD Exomes	p.Pro524LeufsTer20	c.1571_1572del	frameshift_variant	1	628770
16	1571519	gnomAD Exomes	p.Lys512AsnfsTer24	c.1536_1539del	frameshift_variant	1	1459740
16	1571523	gnomAD Exomes	p.Lys512AsnfsTer23	c.1525-29_1535dup	frameshift_variant	1	626500
16	1571525	gnomAD Exomes	p.Lys512Ter	c.1534A>T	stop_gained	1	832954
16	1571534	gnomAD Exomes	c.1525-2_1525-1del	c.1525-2_1525-1del	splice_acceptor_variant	1	624376
16	1571535	gnomAD Exomes	c.1525-1G>A	c.1525-1G>A	splice_acceptor_variant	2	832816

16	1580758	gnomAD Exomes	c.1524+1G>A	c.1524+1G>A	splice_donor_variant	5	1457774
16	1580770	gnomAD Exomes, gnomAD Genomes	p.Arg505Ter	c.1513C>T	stop_gained	12	1612920
16	1580776	gnomAD Exomes	p.Gln503Ter	c.1507C>T	stop_gained	1	1461272
16	1580782	gnomAD Exomes, gnomAD Genomes	p.Arg501Ter	c.1501C>T	stop_gained	7	1613644
16	1580787	gnomAD Exomes	p.Ser499Ter	c.1496C>G	stop_gained	1	1461580
16	1580791	gnomAD Exomes	p.Glu498Ter	c.1492G>T	stop_gained	1	1461642
16	1580812	gnomAD Exomes	p.Glu491Ter	c.1471G>T	stop_gained	1	628646
16	1580851	gnomAD Exomes	c.1433-1G>A	c.1433-1G>A	splice_acceptor_variant	1	1458188
16	1583313	gnomAD Exomes, gnomAD Genomes	c.1432+1G>A	c.1432+1G>A	splice_donor_variant	4	1613830
16	1583320	gnomAD Exomes	p.Ser476ValfsTer12	c.1425del	frameshift_variant	2	1461796
16	1583323	gnomAD Exomes	p.Arg475AsnfsTer14	c.1422_1423insAA	frameshift_variant	24	1461728
16	1583347	gnomAD Exomes	p.Phe467SerfsTer21	c.1398del	frameshift_variant	1	1461872
16	1583365	gnomAD Genomes	p.Gly461Ter	c.1381G>T	stop_gained	1	152188
16	1583369	gnomAD Exomes, gnomAD Genomes	p.Trp459Ter	c.1377G>A	stop_gained	79	1614018
16	1583387	gnomAD Exomes	c.1360-1G>C	c.1360-1G>C	splice_acceptor_variant	1	1461724
16	1583387	gnomAD Exomes	c.1360-1G>A	c.1360-1G>A	splice_acceptor_variant	1	1461724
16	1583388	gnomAD Exomes	c.1360-2A>G	c.1360-2A>G	splice_acceptor_variant	1	628688
16	1584213	gnomAD Exomes, gnomAD Genomes	c.1359_1359+3del	c.1359_1359+3del	splice_donor_variant	2	779010
16	1584216	gnomAD Exomes	c.1359+1G>A	c.1359+1G>A	splice_donor_variant	9	1460506
16	1584216	gnomAD Exomes	c.1359+1G>C	c.1359+1G>C	splice_donor_variant	3	1460508
16	1584217	gnomAD Genomes	p.Asp454ArgfsTer35	c.1358_1359insAC	frameshift_variant	1	152202
16	1584228	gnomAD Exomes	p.Phe450GlufsTer40	c.1343_1347dup	frameshift_variant	2	833106
16	1584278	gnomAD Exomes, gnomAD Genomes	p.Ser433ProfsTer55	c.1297del	frameshift_variant	2	780674
16	1584286	gnomAD Exomes	p.Phe431AlafsTer58	c.1288_1289dup	frameshift_variant	1	1461618
16	1584330	gnomAD Exomes, gnomAD Genomes	p.Gln416Ter	c.1246C>T	stop_gained	21	1613610
16	1584393	gnomAD Exomes	p.Val395Ter	c.1182del	frameshift_variant	4	1458566
16	1584418	gnomAD Exomes	p.Trp386Ter	c.1158G>A	stop_gained	1	1450414
16	1584419	gnomAD Exomes	p.Trp386Ter	c.1157G>A	stop_gained	1	616358
16	1584421	gnomAD Genomes	c.1156-5_1156-2del	c.1156-5_1156-2del	splice_acceptor_variant	2	152190

16	1584422	gnomAD Exomes	c.1156-2A>G	c.1156-2A>G	splice_acceptor_variant	2	615254
16	1586129	gnomAD Exomes, gnomAD Genomes	c.1155+1G>A	c.1155+1G>A	splice_donor_variant	4	1612254
16	1586138	gnomAD Exomes, gnomAD Genomes	p.Gln383Ter	c.1147C>T	stop_gained	22	1612816
16	1586170	gnomAD Exomes	p.Gln372ArgfsTer24	c.1114del	frameshift_variant	1	1461700
16	1586171	gnomAD Exomes	p.Gln372Ter	c.1114C>T	stop_gained	1	1461676
16	1586178	gnomAD Genomes	p.Trp369Ter	c.1107G>A	stop_gained	1	152168
16	1586179	gnomAD Exomes	p.Trp369Ter	c.1106G>A	stop_gained	1	1461756
16	1586212	gnomAD Exomes, gnomAD Genomes	p.Leu358TrpfsTer38	c.1072del	frameshift_variant	4	780568
16	1586225	gnomAD Exomes	p.Val354TyrfsTer42	c.1059del	frameshift_variant	1	628710
16	1586246	gnomAD Exomes	p.Arg347Ter	c.1039C>T	stop_gained	7	1461566
16	1586248	gnomAD Exomes	p.Gly346AlafsTer137	c.1035_1036del	frameshift_variant	4	1461644
16	1586276	gnomAD Exomes, gnomAD Genomes	c.1010-1G>A	c.1010-1G>A	splice_acceptor_variant	184	1610716
16	1586277	gnomAD Exomes	c.1010-2A>G	c.1010-2A>G	splice_acceptor_variant	1	1458736
16	1586277	gnomAD Exomes, gnomAD Genomes	c.1010-2A>C	c.1010-2A>C	splice_acceptor_variant	3	1610810
16	1587197	gnomAD Exomes	c.1009+1G>C	c.1009+1G>C	splice_donor_variant	1	1442078
16	1587197	gnomAD Exomes, gnomAD Genomes	c.1009+1G>T	c.1009+1G>T	splice_donor_variant	5	1594270
16	1587211	gnomAD Exomes	p.Tyr332Ter	c.996C>G	stop_gained	1	1454960
16	1587213	gnomAD Exomes	p.Cys331LeufsTer3	c.992_993del	frameshift_variant	1	827332
16	1587288	gnomAD Exomes	p.Arg307Ter	c.919C>T	stop_gained	2	1458020
16	1587299	gnomAD Exomes	p.Trp303Ter	c.908G>A	stop_gained	1	628588
16	1587931	gnomAD Exomes	c.902+2T>G	c.902+2T>G	splice_donor_variant	1	1456010
16	1587932	gnomAD Exomes	c.902+1G>A	c.902+1G>A	splice_donor_variant	1	832724
16	1587980	gnomAD Exomes	p.Leu285Ter	c.854del	frameshift_variant	4	1461510
16	1588013	gnomAD Exomes	p.Ser274ThrfsTer12	c.821del	frameshift_variant	1	1461318
16	1588025	gnomAD Exomes	c.811-1G>A	c.811-1G>A	splice_acceptor_variant	1	628078
16	1589603	gnomAD Exomes	c.810+2T>G	c.810+2T>G	splice_donor_variant	1	1460458
16	1589603	gnomAD Exomes	c.810+2T>C	c.810+2T>C	splice_donor_variant	1	1460458
16	1589604	gnomAD Exomes	c.810+1G>A	c.810+1G>A	splice_donor_variant	10	1460966
16	1589616	gnomAD Exomes	p.Glu267Ter	c.799G>T	stop_gained	1	833110

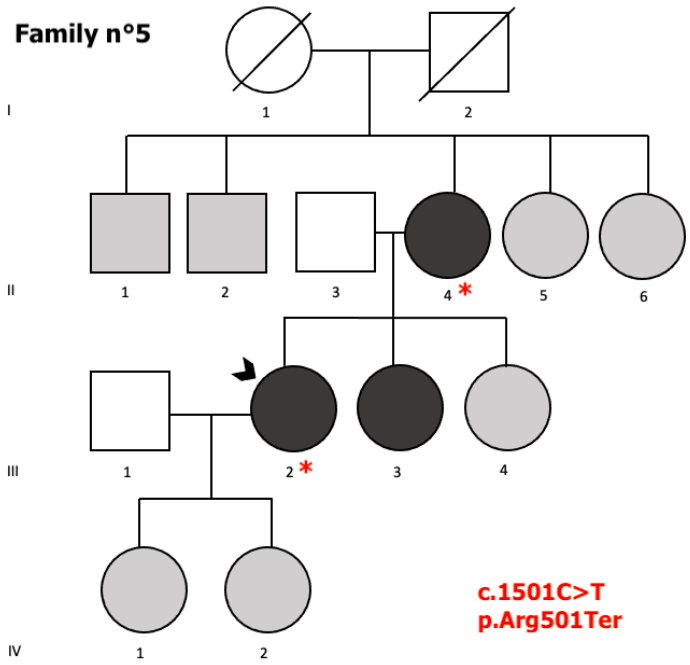
16	1589655	gnomAD Exomes	p.Leu254CysfsTer15	c.759del	frameshift_variant	1	1461874
16	1589667	gnomAD Exomes	p.Glu250ArgfsTer13	c.747dup	frameshift_variant	2	1461884
16	1589715	gnomAD Exomes	p.Gln234SerfsTer29	c.699dup	frameshift_variant	1	1461834
16	1589751	gnomAD Exomes	p.Lys222ArgfsTer47	c.663del	frameshift_variant	1	628760
16	1592179	gnomAD Exomes	p.Asp211GlnfsTer59	c.630_631insCA	frameshift_variant	1	833110
16	1592209	gnomAD Exomes	p.His200GlnfsTer10	c.600del	frameshift_variant	1	1461854
16	1592215	gnomAD Exomes	p.Ser199ValfsTer21	c.594dup	frameshift_variant	1	628748
16	1592228	gnomAD Exomes, gnomAD Genomes	p.Leu194CysfsTer2	c.581del	frameshift_variant	10	985344
16	1592244	gnomAD Genomes	p.Ser189AlafsTer7	c.565del	frameshift_variant	2	152240
16	1592245	gnomAD Exomes	p.Ser189GlufsTer31	c.564dup	frameshift_variant	1	833108
16	1592274	gnomAD Exomes	p.Glu178LysfsTer17	c.532_535del	frameshift_variant	1	628770
16	1592287	gnomAD Exomes	p.Ala172GlufsTer3	c.515_522del	frameshift_variant	1	628766
16	1592297	gnomAD Exomes	p.Lys171GlyfsTer6	c.511_512del	frameshift_variant	1	628766
16	1592320	gnomAD Exomes	c.492-2A>G	c.492-2A>G	splice_acceptor_variant	1	628728
16	1592463	gnomAD Exomes	c.485_491+3del	c.485_491+3del	splice_donor_variant	1	628612
16	1592465	gnomAD Exomes	c.491+2T>C	c.491+2T>C	splice_donor_variant	1	628592
16	1592468	gnomAD Exomes	p.Glu164Ter	c.490G>T	stop_gained	16	1461678
16	1592468	gnomAD Exomes	p.Glu164ArgfsTer11	c.489del	frameshift_variant	1	1461680
16	1592470	gnomAD Exomes	p.Pro162ArgfsTer14	c.483_487del	frameshift_variant	1	1461734
16	1592475	gnomAD Exomes	p.Pro161LeufsTer14	c.482del	frameshift_variant	1	628706
16	1592475	gnomAD Genomes	p.Pro162SerfsTer16	c.482dup	frameshift_variant	2	152176
16	1592519	gnomAD Exomes	p.Glu147Ter	c.439G>T	stop_gained	1	1461870
16	1592549	gnomAD Exomes, gnomAD Genomes	p.Arg137Ter	c.409C>T	stop_gained	13	1614094
16	1602368	gnomAD Exomes	c.369+2T>C	c.369+2T>C	splice_donor_variant	1	628658
16	1602369	gnomAD Exomes	c.369+1G>A	c.369+1G>A	splice_donor_variant	1	832814
16	1602369	gnomAD Exomes	c.369+1G>T	c.369+1G>T	splice_donor_variant	2	832814
16	1602374	gnomAD Exomes	p.Asp122ThrfsTer23	c.364del	frameshift_variant	2	1461602
16	1602407	gnomAD Exomes, gnomAD Genomes	p.Trp111Ter	c.332G>A	stop_gained	3	780988
16	1602429	gnomAD Exomes	p.Thr103SerfsTer74	c.308_309del	frameshift_variant	3	1461888

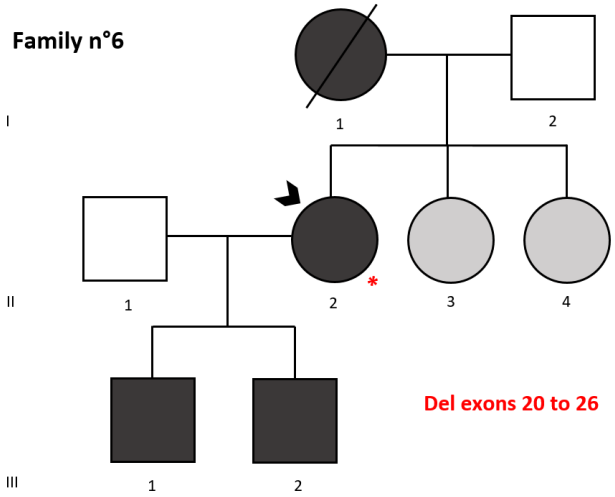
16	1602430	gnomAD Exomes	p.Ala104SerfsTer74	c.308_309insG	frameshift_variant	2	628776
16	1602439	gnomAD Exomes	p.Leu100ArgfsTer45	c.299del	frameshift_variant	1	833110
16	1602462	gnomAD Exomes	p.Lys93Ter	c.277A>T	stop_gained	1	628782
16	1602468	gnomAD Genomes	p.Gln91Ter	c.271C>T	stop_gained	1	152300
16	1602499	gnomAD Exomes, gnomAD Genomes	p.Trp80Ter	c.240G>A	stop_gained	4	1614068
16	1602508	gnomAD Exomes	p.Val78ProfsTer19	c.209_230dup	frameshift_variant	1	1461868
16	1602508	gnomAD Exomes	p.His70LeufsTer9	c.209_230del	frameshift_variant	5	1461868
16	1602520	gnomAD Exomes	p.Arg73AlafsTer16	c.217_218del	frameshift_variant	2	1461816
16	1602526	gnomAD Exomes	p.Thr72ValfsTer22	c.200_212dup	frameshift_variant	8	1461800
16	1602551	gnomAD Exomes	p.Arg63GlyfsTer23	c.187del	frameshift_variant	1	1461516
16	1602567	gnomAD Exomes	p.His57SerfsTer28	c.168_171del	frameshift_variant	1	1460850
16	1602572	gnomAD Exomes, gnomAD Genomes	p.Thr56AsnfsTer34	c.166dup	frameshift_variant	3	1612578
16	1602583	gnomAD Exomes	p.Cys52Ter	c.156C>A	stop_gained	1	1459106
16	1602593	gnomAD Exomes	c.148-2A>G	c.148-2A>G	splice_acceptor_variant	1	624602
16	1607117	gnomAD Exomes	c.146_147+2del	c.146_147+2del	splice_donor_variant	4	1461458
16	1607151	gnomAD Exomes	p.Ser39Ter	c.116C>G	stop_gained	1	833098
16	1607169	gnomAD Exomes	p.Ala33LeufsTer53	c.97del	frameshift_variant	1	628780
16	1607198	gnomAD Exomes	p.Trp23Ter	c.69G>A	stop_gained	2	628780
16	1607212	gnomAD Exomes	p.Ser19LeufsTer71	c.54dup	frameshift_variant	6	1461880
16	1607217	gnomAD Exomes	p.Ser17Ter	c.50C>A	stop_gained	1	628772
16	1607253	gnomAD Exomes	p.Tyr5MetfsTer5	c.13del	frameshift_variant	1	1461762

Table S4. Large deletions of *IFT140* identified in the GnomAD database (v4.0).

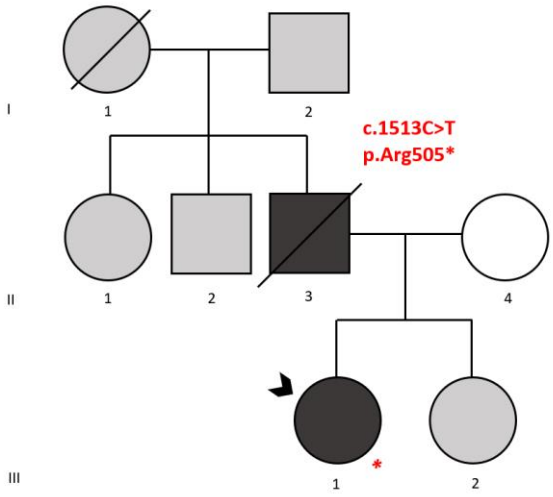
Variant ID	Class	Position	Size (kB)	Site Count	Site Number
187330__DEL	deletion	1505042-1520088	15046	1	464297
187338__DEL	deletion	1533582-1592686	59104	1	464297
187400__DEL	deletion	1518005-1520906	2901	1	464297
187411__DEL	deletion	1523766-1527122	3356	4	464297
187430__DEL	deletion	1561888-1592686	30798	1	464297
187442__DEL	deletion	1563900-1571632	7732	1	464297
187446__DEL	deletion	1571310-1586320	15010	3	464296
187460__DEL	deletion	1580430-1586373	5943	1	464297
187463__DEL	deletion	1592079-1607395	15316	1	464297
187475__DEL	deletion	1584120-1587402	3282	1	464297
187479__DEL	deletion	1586033-1655398	69365	1	464297

Figure S1. Pedigrees of 14 families with loss-of-function *IFT140* variant including more than one single affected member. Black squares or circles indicate affected male of female subjects, respectively, with kidney cysts and/or kidney failure. Grey symbols indicate case subjects where clinical information are unavailable. Red asterixis indicate patients who underwent genetic test. Pointed symbol represents index patient.

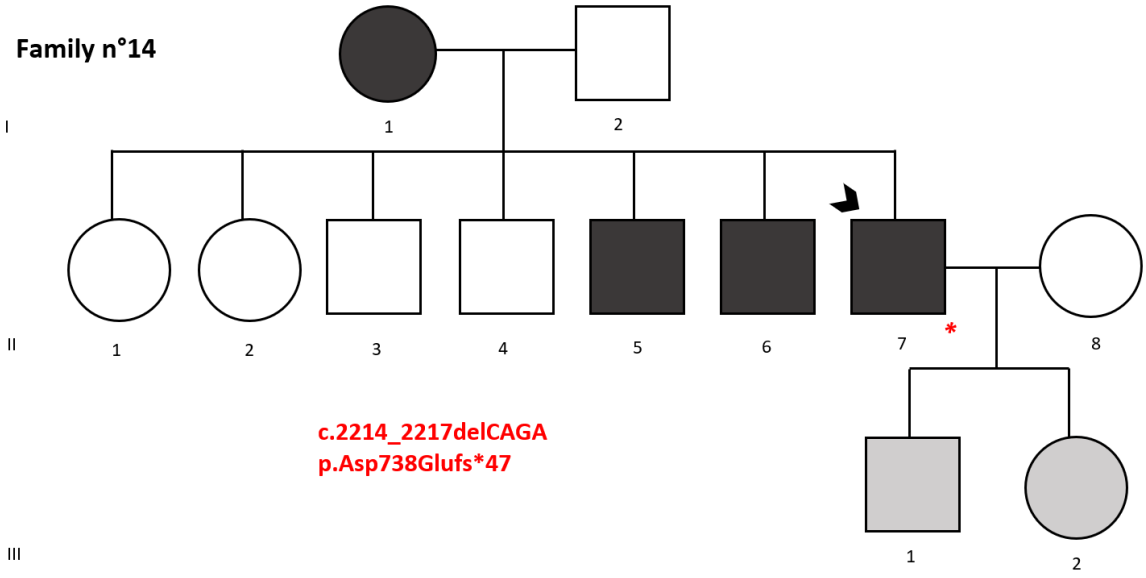




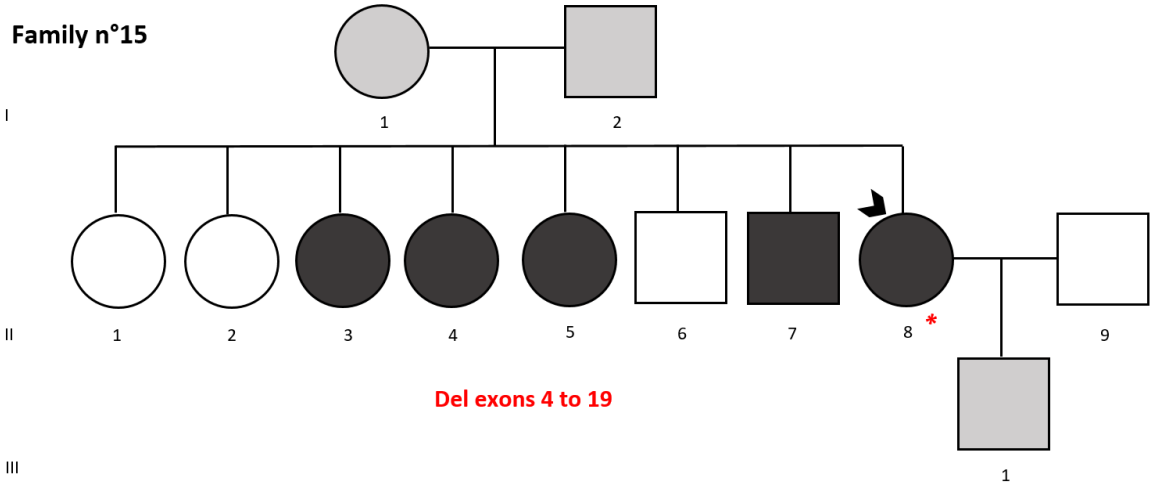
Family n°7



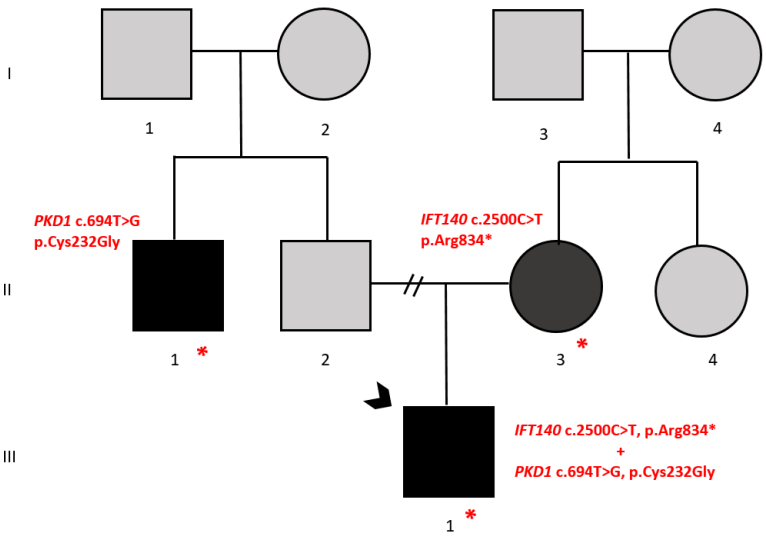
Family n°14



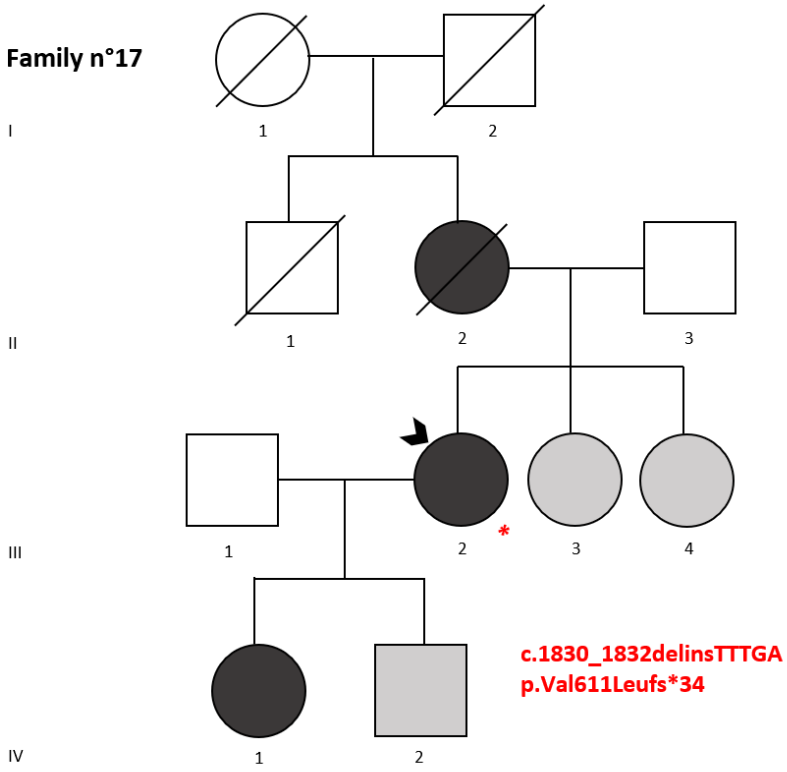
Family n°15



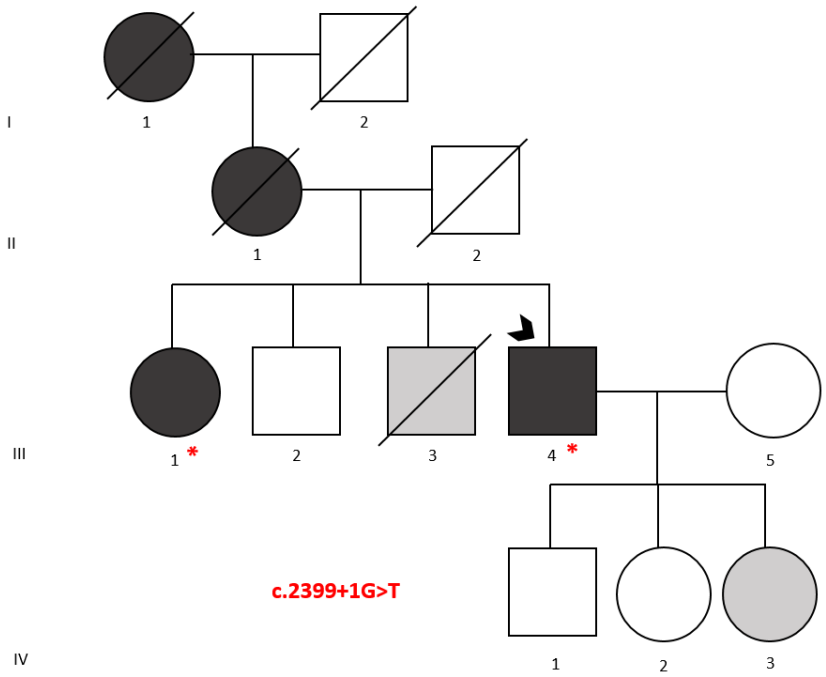
Family n°16



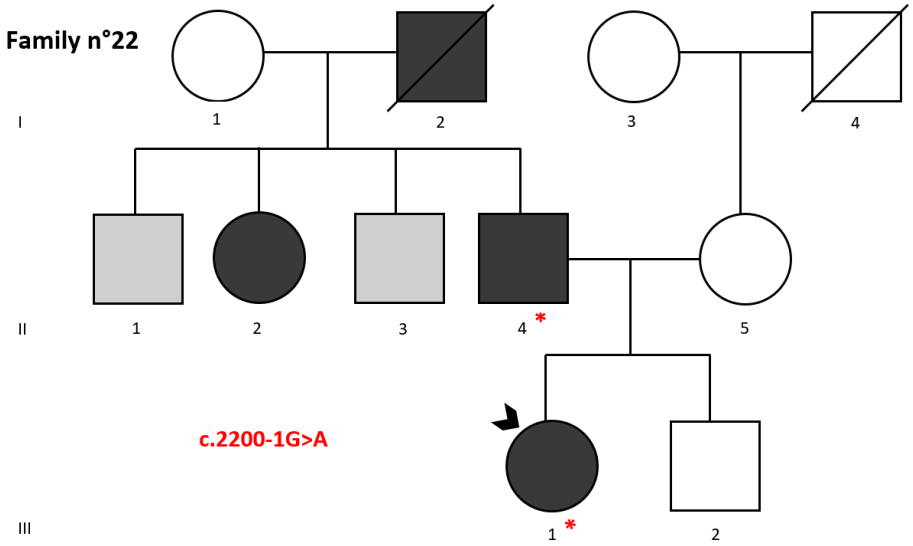
Family n°17



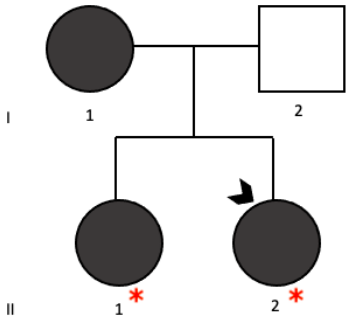
Family n°20



Family n°22

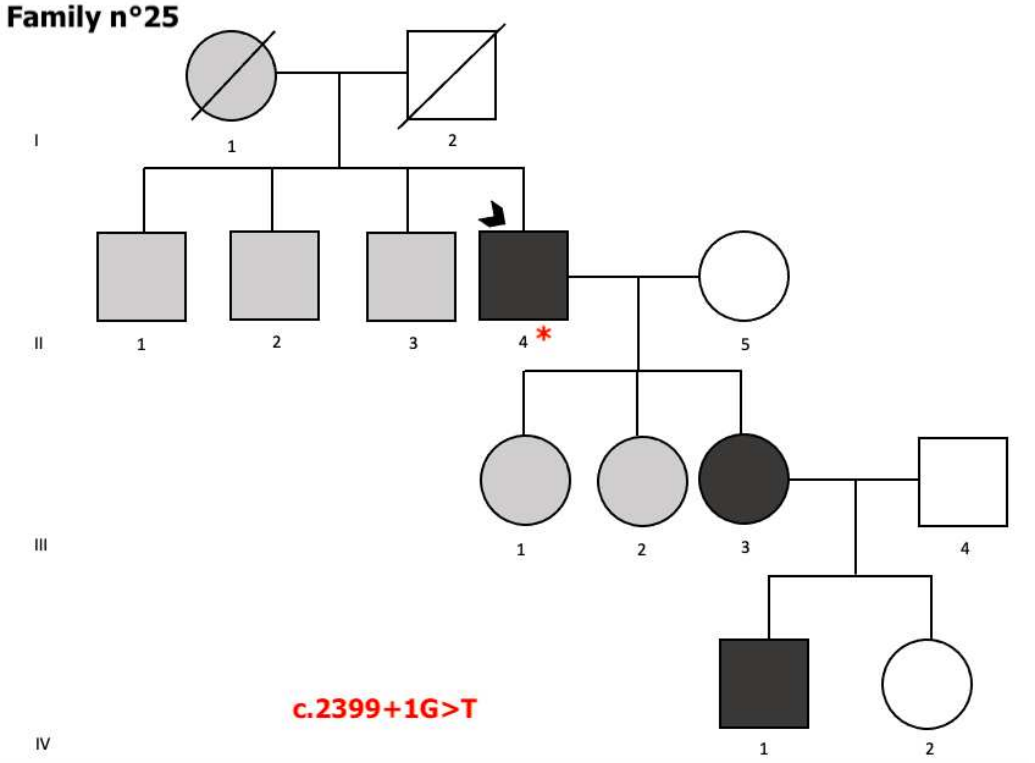


Family n°23

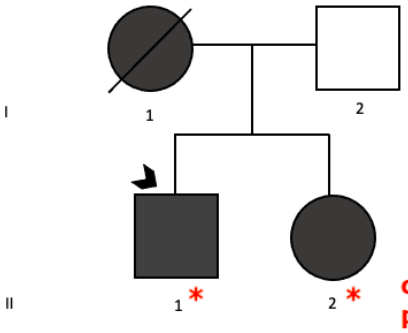


c.1402G>T
p.Glu468*

Family n°25

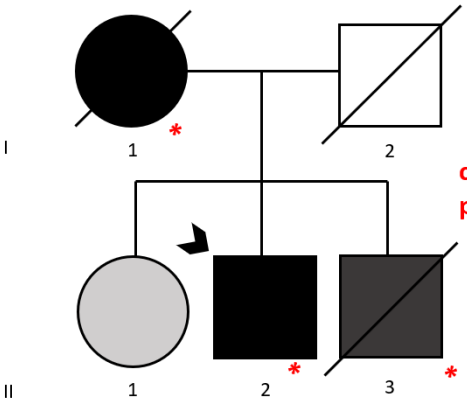


Family n°28



c.3696del
p.Ile1234Serfs*33

Family n°45



c.2677G>T
p.Glu893*

Family n°59

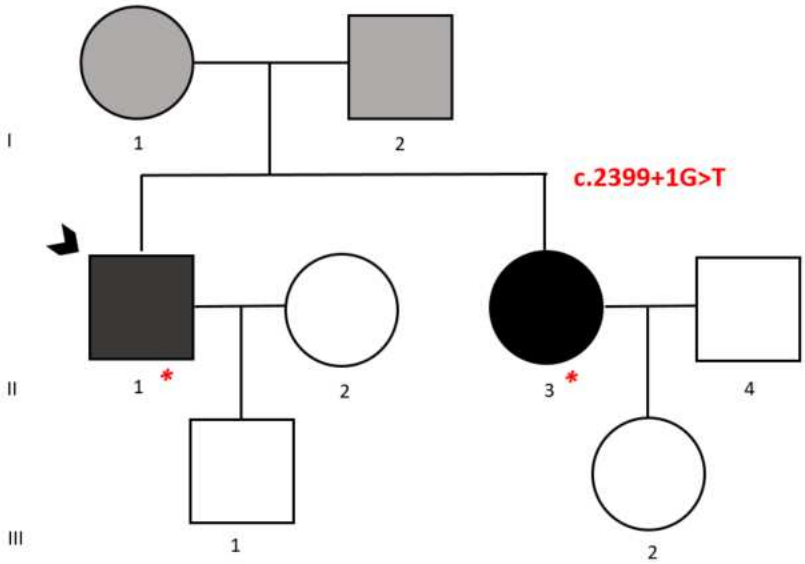


Figure S2. CKD-EPI estimated glomerular filtration rate (eGFR) values are plotted against age in series of 75 individuals with ADPKD-IFT140 from 61 families. The age-adjusted eGFR in ADPKD-IFT140 individuals with the recurrent variant c.2399+1G>T (n=11) was comparable to that observed in the remaining *IFT140* individuals (P=0.843).

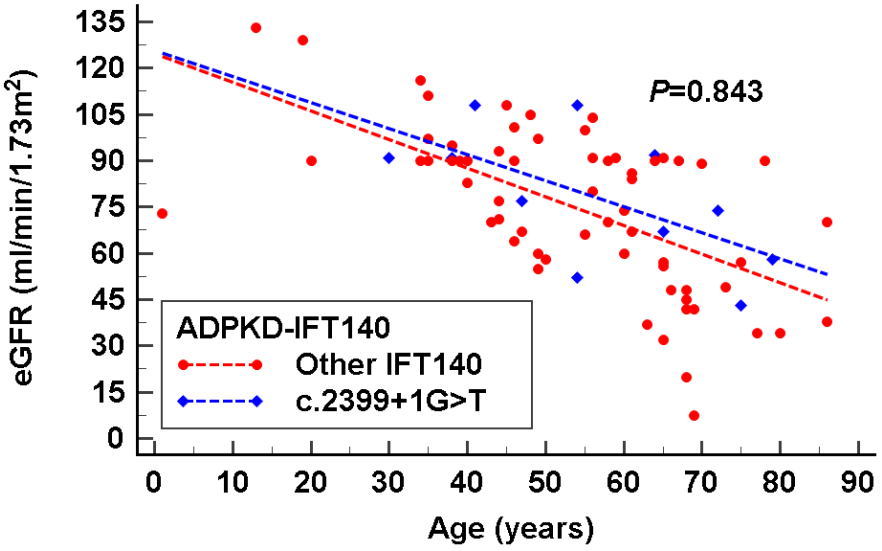
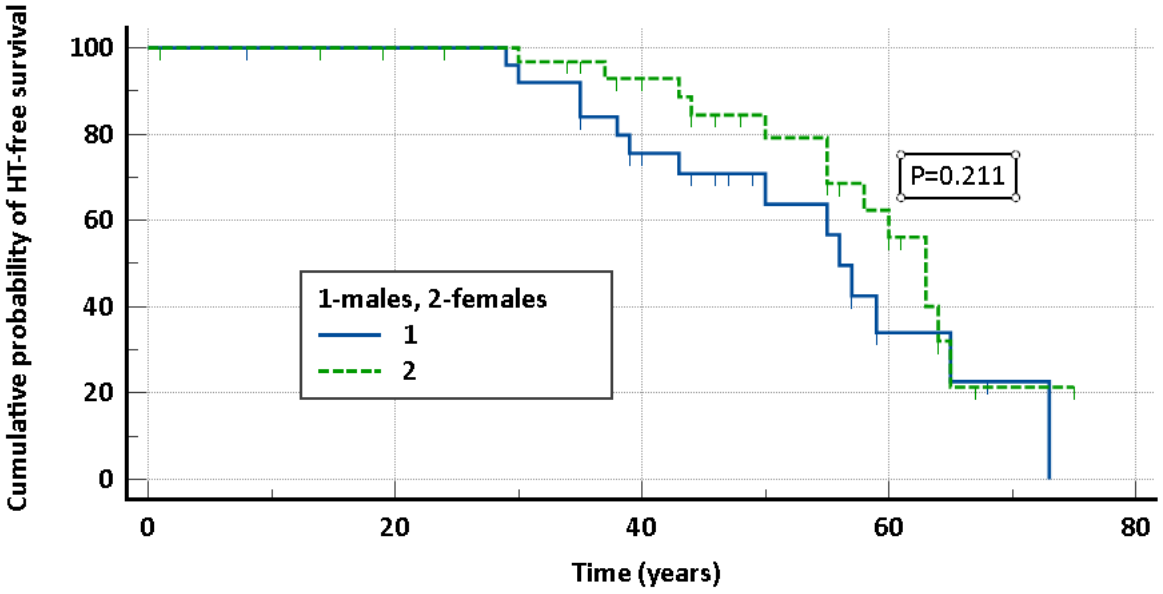


Figure S3. Hypertension-free survival estimation (using Kaplan-Meier analysis) in series of ADPKD-IFT140 patients (N=62). Median age at diagnosis of arterial hypertension was 59 years [range: 29-73].



Number at risk					
Group: 1					
	26	25	16	3	0
Group: 2					
	36	32	22	8	0

Figure S4. Additional representative abdominal imaging of eight ADPKD-IFT140 individuals. Detailed clinical information available in Table S1. Legend: **A.** Contrast-enhanced coronal CT view of female individual (I.1, Family 3) who has an eGFR of 95 ml/min/1.73m^2 at the age of 38 years. **B.** Contrast-enhanced coronal CT view of female individual (III.2, Family 5) who has an eGFR of 116 ml/min/1.73m^2 at the age of 34 years. **C.** T2-weighted coronal MRI view of female individual (III.1, Family 7) who has an eGFR of 129 ml/min/1.73m^2 at the age of 19 years. **D.** Contrast-enhanced coronal CT view of female individual (II.8, Family 15) who has an eGFR of 91 ml/min/1.73m^2 at the age of 65 years. **E.** T2-weighted coronal MRI view of male individual carrying pLoF variant in *IFT140* (p.Arg834*) and missense variant in *PKD1* (p.Cys232Gly) in trans (son of individual II.3, Family 16) who has an eGFR of 98 ml/min/1.73m^2 at the age of 8 years. **F1.** T2-weighted coronal MRI view of male individual (I.1, Family 38) who has an eGFR of 93 ml/min/1.73m^2 at the age of 44 years with additional LoF variant in *PKHD1* (Suppl Table 2). **F2.** T2-weighted coronal MRI view of the same male individual (I.1, Family 38) showing large kidney cyst and small-sized liver cysts. **G.** Nonenhanced coronal CT view of male individual (II.4, Family 25) who has an eGFR of 59 ml/min/1.73m^2 at the age of 79 years and has no liver cysts. He harbors additional class IV variant in *PKHD1* c.664A>G. **H.** T1-weighted coronal MRI view of male individual (III.1, Family 61) who has an eGFR of 34 ml/min/1.73m^2 at the age of 80 years (MRI performed at age of 64 years). He harbors additional class III variant in *PKD1* c.7373_7375del.