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DNAJB11-nephropathy: clinical spectrum, prognosis and estimated prevalence

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Abstract (250 words)

Monoallelic mutations of *DNAJB11* were recently described in seven pedigrees with atypical clinical presentations of autosomal dominant polycystic kidney disease (ADPKD). *DNAJB11* encodes one of the main cofactors of the endoplasmic reticulum chaperon BiP, a heat-shock protein required for efficient protein folding and trafficking. Here we conducted an international collaborative study to better characterize the *DNAJB11*-associated phenotype. Thirteen different loss-of-function variants were identified in twenty new pedigrees (54 affected individuals) by targeted next-generation sequencing, whole-exome sequencing or whole-genome sequencing. Amongst the 77 patients (27 pedigrees) now in total reported, 32 reached ESRD (range, 55-89y), with a median age of 75 years (0.95 CI, 72.5-77.5 years), and without a significant difference between males and females. While a majority of patients presented with non-enlarged polycystic kidneys, renal cysts were inconsistently identified in patients <45y. Vascular phenotypes, including intracranial aneurysms, dilatation of the thoracic aorta and dissection of a carotid artery were present in four pedigrees. We accessed Genomics England 100,000 genomes project data, and identified pathogenic variants of *DNAJB11* in 9/3934 probands with various renal and urinary tracts disorders. The clinical diagnosis was cystic kidney disease for eight probands and nephrocalcinosis for one proband; no additional pathogenic variants likely explaining the renal disease were identified. Using the publicly available GnomAD database, *DNAJB11* genetic prevalence was calculated at 0.85/10.000 individuals (0.95 CI, 0.34-2.02). Establishing a precise diagnosis in atypical cystic or interstitial nephropathies is crucial, with important implications in terms of follow-up, genetic counseling, prognostic evaluation, therapeutic management, and for the selection of living kidney donors.

Introduction

The two major genes causing autosomal dominant polycystic kidney disease (ADPKD) are *PKD1* (MIM: 601313), encoding polycystin 1 (PC1), and *PKD2* (MIM: 173910) encoding polycystin 2 (PC2), identified in 72%–78% and 15%–18% of families, respectively.[1] Three additional genes have been recently identified in pedigrees with an atypical ADPKD presentation: *GANAB* (OMIM: 104160), *DNAJB11* (OMIM: 618061) and *ALG9* (OMIM: 606941); all three genes encoding proteins involved in the maturation and processing of membrane and secreted proteins.[1-6] Other genes might occasionally phenocopy ADPKD clinical presentation, including notably *HNF1B,* with dominantly inherited mutations associated with a highly heterogeneous phenotypic spectrum, including maturity onset diabetes of the young, a personal or familial history of urogenital malformations, early onset gout, the presence of elevated liver enzymes or hypomagnesaemia and/or bilateral renal cysts.[7] Monoallelic mutations of *PRKCSH*, *SEC63*, *ALG8*, *SEC61B* and *LRP5* are associated with autosomal dominant polycystic liver disease (ADPLD), characterized by the development of hepatic cysts, with occasional renal cysts.[1,3,8] While the expansion of the ADPKD genetic landscape allows a better understanding of its clinical variability, the phenotypic and prognostic characterization of these newly identified disorders is still limited to a small number of pedigrees.

Monoallelic pathogenic variants to *DNAJB11* have recently been reported in 23 patients from seven ADPKD-like pedigrees, who presented with non-enlarged or atrophic cystic kidneys, and late-onset end-stage renal disease (ESRD).[4] *DNAJB11,* located on chromosome 3q27.3, encodes a soluble glycoprotein of the endoplasmic reticulum (ER), DNAJB11, which acts as one of the main cofactor of the chaperone BiP (for binding immunological protein, alias GRP78).[9] BiP regulates protein folding and assembly, targets misfolded proteins to ER degradation, and acts as a master regulator of the unfolded protein response (UPR), an adaptive cellular response to ER stress.[10] *DNAJB11* loss is associated with impaired polycystin 1 (PC1) maturation.[4] However, kidney function decline in *DNAJB11* individuals seems also the result of the development of extensive interstitial fibrosis, reminiscent of autosomal dominant tubulo-interstitial kidney disease (ADTKD).[4,11] Interestingly,

defective proteostasis caused by *DNAJB11* variants might also affect the trafficking of uromodulin, mimicking the ADTKD-*UMOD* phenotype.[4]

This study presents the clinical, radiological and genetic characterization of 54 *DNAJB11*-affected individuals from 20 pedigrees identified in France, the United Kingdom, the Netherlands, United States and Australia. We also describe the renal survival in a cohort of 77 individuals, combining the 20 newly identified (54 individuals) and the seven reported pedigrees (23 individuals). Last, we explore the prevalence of *DNAJB11* variants in a large cohort of patients affected by various possibly inherited kidney diseases, and in the publicly available population-sequencing database GnomAD.

RESULTS

Patient characteristics and description of the mutation spectrum

Twenty *DNAJB11* pedigrees were identified in the six referral-centers performing molecular diagnostics of cystic kidney diseases involved in the study (Supplemental Figure 1). In the 20 probands, the median age at referral for genetic diagnosis was 63.5 years (range 45-80), and the presumptive clinical diagnosis, or primary reasons for referral for genetic testing was ADPKD in 17 pedigrees, ADTKD in two pedigrees and nephropathy of unknown etiology in one pedigree. Familial studies led to the identification of 54 affected individuals in total (35 female patients). The thirteen different pathogenic variants identified in the 20 newly reported pedigrees were all predicted loss-of-function variants, including four short frameshifting deletions or insertions (six pedigrees), seven nonsense variants (11 pedigrees), one start-codon mutation (two pedigrees) and one substitution of the last nucleotide of exon 6, predicted to weaken the splicing donor site (one pedigree) (Table 1 and Figure 1).

Diagnosis and clinical features in *DNAJB11* patients

Kidney function and renal survival

To provide a better description of the *DNAJB11*-associated renal outcome, we combined the 23 previously identified and the 54 newly reported *DNAJB11*-affected individuals. The distribution of patients according to Chronic Kidney Disease (CKD) stage at last follow-up is reported in Table 2.No significant proteinuria was reported in any of the patients identified. Before or at age 55, a high majority of the patients were classified at CKD stages 1 or 2 (94%, n=17/18), while after age 55, 73% of the patients were classified at CKD stages 4 or 5 (n=44/59). Renal function at a given age did not differ between males and females (P=0.428, Figure 2A). In total, 32 individuals reached ESRD, at ages ranging from 55 to 89y. Median age at ESRD obtained by Kaplan-Meier curve analysis was 75 years (0.95 CI, 72.5-77.5 years), and renal survival did not differ according to sex (Figure 2B). At ages 60, 70, and 80 years, probabilities of having reached ESRD were 4.4% (standard error [SE] =3%), 37.4%

(SE=7.6), and 82.2% (SE=7.6). Renal histology was available for three patients, Individual II.1 from Family A, II.1 from Family C, and III.1 from Family R, showing for the two first cases diffuse interstitial fibrosis and tubular dilatations (Supplemental Figure 2), while the third patient had minimal interstitial fibrosis and tubular dilatations at an early stage of the disease (CKD stage 1, 43 years). No specific glomerular lesions in the non-sclerotic glomeruli were present in any of these three cases.

Radiological presentation

Details regarding morphology of the kidneys in the 54 *DNAJB11* individuals, when available, are reported in Table 1, illustrative imaging are displayed on Figure 3 and Supplemental figure 3. Multiple bilateral small cysts were reported in a vast majority of the patients, and mean kidney length (calculated as the mean of the average length of both kidneys) was 11.6 cm [range 7.6-19.25 cm, n=36]. Mayo Imaging Classification was applied in 39 individuals: 8 (20.5%) were classified as 1A, 2 (5.1%) 1B, 1 (2.6%) 2A, and 28 (71.8%) were classified as 2B. In younger patients, renal cysts were inconsistently identified. Indeed, in pedigree A, no cysts were identified by renal ultrasound examination in individual IV.4 at age 34, and the patient was initially considered unaffected. Following the identification of the familial mutation, an MRI was performed and confirmed the presence of small millimeter-sized renal and liver cysts. In pedigree R, the 43 years-old female individual III.1, who was a candidate as a living kidney donor for her mother II.1, was initially considered unaffected based on imaging. The subsequent identification of the familial *DNAJB11* mutation in her prompted her physicians to review the contrast-enhanced CT imaging, which showed a small number of millimeter-sized kidney cysts, and one liver cyst. In some affected individuals, no or few renal cysts were identified at an advanced stage of the nephropathy. In participant II.2 of the pedigree G, who had reached CKD stage 5 at age 74, only a small number of renal cysts were identified by MRI (Figure 3F). In the subject II.3 from pedigree L, who had an eGFR of 30ml/min/1.73m² at age 62, a non-contrast enhanced CT scan examination did not show any renal or liver cysts. Only one patient in this cohort, individual II.2 from pedigree I, had enlarged kidneys when

he reached ESRD, with left and right kidney lengths of 19 and 19.5 cm, and a total kidney volume (TKV) of 1445 ml (Figure 3H). No other likely pathogenic variants were identified in *PKD1*, *PKD2*, or any other cystogenes.

Extra-renal phenotypes

Information regarding the presence of liver cysts was available in 39 subjects, and at least one liver cyst was reported in 19 patients (48.7%) (e.g. Figure 3N and 3O), but most of the patients did not have clinically significant polycystic liver disease. In female individual II.1 from pedigree A, abdominal pain and jaundice led to the aspiration of a 10cm liver cyst compressing the common bile duct (Supplemental Figure 3A). Female subject II.2 from family K had multiple large liver cysts at age 74 (Supplemental Figure 3F). Gout was only reported in individual II.3 from pedigree I, a 79 year-old male approaching ESRD, and in a 64-year-old male participant of the 100,000-genome project, at CKD stage 3.

Vascular phenotypes were reported in four pedigrees. Subject I.1 from Family F underwent a cerebral MRI at the age of 57 years because of chronic headache. This led to the detection of a saccular aneurysm of the anterior circulation, measuring 6 mm of diameter. As most of her family members lived in different countries, to date, no affected relative has been identified and screened for ICA. In subject II.4 from Family L, systematic screening at age 66 led to the incidental diagnosis of a 3mm-sized ICA of the posterior circulation, for which simple imaging monitoring was recommended. No other case was identified in the family, his mother died of ischemic cerebral vascular accident at age 68. In family O, a spontaneous dissection of the left carotid was reported in individual I.1. Last, in family P, aneurysms of the ascending thoracic aorta were diagnosed at age 45 and 50 in two siblings. The proband had surgical replacement of the ascending aorta at the age of 46 years.

DNAJB11 prevalence in patients with genetically unresolved nephropathies

The Genomics England 100,000 Genomes Project data was analyzed for rare and likely pathogenic variants in *DNAJB11*. As of September 2019, whole genome sequencing (WGS) was performed in

35042 probands affected by rare diseases, including 3934 probands with various renal and urinary tracts disorders (see details in Table S1). Pathogenic variants (truncating or otherwise described) of *DNAJB11* were searched for in the participants with renal disorders, and identified in eight probands (nine individuals) in the cystic kidney disease subgroup, and one proband in the wider renal and urinary tract disease cohort. Details on the variants identified and the clinical information available for these nine probands are listed in Table 3. No other pathogenic variants likely to explain the renal disorder were identified in any of the ten individuals, and variants of unknown significance in other cystogenes are reported in the footnotes of Table 3. While incomplete phenotypic data was available for these patients, multiple bilateral renal cysts were reported in eight individuals out of nine, and liver cysts were reported in two individuals. Two unrelated individuals had abdominal wall hernias.

DNAJB11-nephropathy genetic prevalence

Eleven *DNAJB11* likely pathogenic variants were identified in twelve subjects from the GnomAD database (Table S2). Thus, DNAJB11 genetic prevalence is estimated at 0.85 (95% CI, 0.44-1.48)/10,000 in the whole GnomAD population (n=141456). As the GnomAD database comprises patients with different ethnicities, we also considered separately the European population (n=64603), in which 6 individuals were found to have a *DNAJB11* pathogenic variant, corresponding to a prevalence of 0.93 (95% CI, 0.34-2.02)/10,000.

Discussion

The tremendous progress in genomics in the past 10 years has translated into an acceleration in gene discoveries. The newly identified inherited disorders are generally rare diseases, described in a handful of pedigrees; solved "diagnosis odysseys". The possibility to offer early screening to at-risk relatives is a major advantage of obtaining a genetic diagnosis, however, the paucity of clinical/phenotypic data for solved rare diseases can be a limitation to provide adequate clinical and prognosis information. In this study, the collaboration of six expert inherited kidney disease centers across three continents has provided a description of the phenotype in a much larger *DNAJB11*-nephropathy population, only two years after the first identification of the gene.

In the 27 *DNAJB11* families clinically characterized to date, renal insufficiency and/or cystic disease were present in all the mutations carriers, including relatives identified through family studies, suggesting that monoallelic *DNAJB11* pathogenic variants are highly penetrant. No additional variants, in *PKD1*, *PKD2*, or other cystogenes, were identified in any of the family probands, despite careful analysis by WES, WGS or by targeted next generation sequencing (NGS). In the additional 10 individuals (9 pedigrees) identified through the Genomes England 100,000 Genomes Project, no other pathogenic variant likely to explain the renal disorders (renal cystic disease in 9 individuals, and unexplained CKD stage 3 with nephrocalcinosis in one individual) were identified; further supporting high penetrance of *DNAJB11* variants. Hence, the genetic prevalence of *DNAJB11* loss-of-function variants in the GnomAD population-sequencing database, of 0.85 in 10000 individuals, appears as a good lower estimate of the lifetime-risk of developing *DNAJB11*-nephropathy. Some rare missense variants of *DNAJB11* identified in GnomAD, not included in our analysis, may actually be pathogenic, resulting in a possible underestimation of this genetic prevalence. However, a large majority (~88%) of the mutations identified in affected individuals are loss-of-function variants, and thus we have presently limited knowledge of *DNAJB11* missense variants functional consequences. A similar approach was previously employed that resulted in an estimated ADPKD genetic prevalence (*PKD1* and *PKD2*) of 9.3 in 10.000 individuals.[12] While these figures suggest that *DNAJB11* disease is only

~11 times less common than *PKD1/PKD2* associated ADPKD, the contribution of *DNAJB11* in ADPKD patients cohort appears significantly lower. Indeed, as of September 2019, *DNAJB11* pathogenic variants were identified in 2.6% of the 228 *PKD1/PKD2* negative pedigrees of the Genkyst cohort (6 pedigrees including one previously reported family), and 1.3% of the 457 *PKD1/PKD2* negative pedigrees analyzed at Mayo Clinic (6 pedigrees including three previously reported families).[4] However, the median age at diagnosis of 63.5 years in the probands suggest that a majority of *DNAJB11* patients remain currently under the radar, due to lack of a clinical phenotype in younger individuals. In addition, one has to keep in mind the important variability in terms of clinical presentation; with occasionally, no or few renal cysts detected despite advanced kidney disease. For this reason, we suggest using the term *DNAJB11*-nephropathy rather than ADPKD.

Several younger individuals of this cohort were initially considered unaffected when imaging-based diagnosis was employed. One of these individuals was even considered as a living-related kidney donor. One of the key message of this study is that imaging-based diagnosis criteria developed in PKD1 and PKD2 patient cohorts should not be employed in cases of atypical polycystic kidney disease, where only genetic diagnosis can be used to rule out the diagnosis in at-risk individuals.[13,14] Similarly, prognostic tools based on TKV, such as the Mayo Imaging Classification, or the height-adjusted TKV, should not be employed in DNAJB11 patients, as, unlike in *PKD1* or *PKD2*-associated ADPKD, kidney function decline is not driven mainly by cystogenesis, and hence, kidney enlargement does not precede eGFR decline.[15-17]

Both ADTKD-*UMOD* and ADTKD-*MUC1* are marked by strong variability in terms of progression to ESRD, with ages at ESRD onset ranging from less than 20 years to more than 80 years, and respective median ages at ESRD of 56 and 51 years.[18-20] In contrast, the DNAJB11 disease course appears more consistent amongst individuals and families, with ESRD onset ranging from 55 to 89 years and median age at ESRD of 75 years. Moreover, the low prevalence of gout in DNAJB11 patients (4 in 77 individuals identified to date, ~5.2%) contrasts with the respective estimates of 25-

70% and 7-24% in ADTKD-*UMOD* and -*MUC1* affected individuals, respectively.[18-21] The pathogenesis of *DNAJB11*- nephropathy remains incompletely understood. While mature PC1 deficiency likely account for the cystic component of the phenotype, kidney function decline seems mainly driven by the development of extensive interstitial fibrosis, apparently independent from evident cystic expansion. DNAJB11 plays a central role in the maintenance of ER protein homeostasis (or proteostasis). Proteostasis requires precise control of protein synthesis, folding, conformational maintenance, and degradation. Aging is associated with a declining cellular capacity to maintain proteostasis.[22,23] Indeed, the proteostasis network is increasingly burdened by misfolded proteins, and proteins impaired by oxidative stress. The role of age-related defective proteostasis is regarded as a major driver of neurodegenerative disorders, with heavy loads of misfolded proteins gradually accumulating in neurons.[24] Tubular epithelial cells are likely to be prone to similar sensitivity to aging. This could explain the accelerated decline of kidney function after the fifth to sixth decade observed consistently in *DNAJB11* patients. Comorbidities increasing the misfolded protein load, such as obesity, dyslipidemia, diabetes, and chronic inflammation,[25] could also play an aggravating role on *DNAJB11*-nephropathy's course. Larger patients' cohort, and functional /tissue analyses will be needed to better understand DNAJB11 pathogenesis. While no specific treatment is currently available to slow the kidney function decline in *DNAJB11*-associated disease, emerging therapies in ADTKD, improving cellular proteostasis, might be of interest in the future. Indeed, a recent study demonstrated that toxic accumulation of *MUC1* mutant proteins could be rescued by a small molecule, rerouting the mutant protein for lysosomal degradation, a therapeutic strategy that might be applicable to other proteostasis related disorders.[26]

Of interest, different vascular phenotypes were reported in this cohort, notably ICA in two pedigrees, carotid dissection in one individual and dilatation of the thoracic aorta in two siblings. Interestingly, data generated by the International Mouse Phenotyping Consortium (IPMC) indicates that mice with heterozygous inactivation of *Dnajb11* exhibit aortic dilatation.[27] Abdominal wall hernias (AWH) segregated with the disease in two siblings and were reported in two out nine

pedigrees identified in the Genomes England 100,000 dataset. AWH have been noted more frequently in patients with ADPKD as compared to ESRD patients without ADPKD.[28] It has been hypothesized that AWH result from the combination of altered matrix integrity and increased abdominal pressure from cyst burden.[29,30] While the latter seems unlikely in DNAJB11 patients, who generally present with non-enlarged polycystic kidneys and mild liver involvement, reduced mature PC1 might cause altered extracellular matrix organization. Interestingly, AWH and arterial phenotypes are also described in hereditary connective tissue disorders such as vascular Ehlers-Danlos syndrome (vEDS), an autosomal dominant disorder due to mutations of *COL3A1* gene.[31] A recent transcriptome analysis of skin fibroblasts of vEDS patients has highlighted, amongst different pathways, significant changes in the expression levels of genes involved in ER-related homeostasis, including *DNAJB11*.[32]

In conclusion, our study shows that *DNAJB11*-disease is a rare but probably underestimated cause of CKD, combining clinical features of ADPKD and ADTKD. The association of normal-sized/atrophic kidneys with millimeter-sized renal and liver cysts should prompt the physicians to consider this diagnosis, with important implications in term of follow-up, prognostic evaluation, therapeutic management and for the selection of living kidney donors. DNAJB11-nephropathy and classical ADPKD (i.e. caused by mutations of *PKD1* or *PKD2*) have distinct disease courses, different pathogeneses, and will likely necessitate different therapeutic strategies. Although *DNAJB11*-nephropathy can present, in some patients, as a phenocopy of ADPKD, it should not be considered, to our opinion, as a subtype of ADPKD, but as a distinct disorder. In the future, increased awareness amongst nephrologists, combined with better access to genetic testing, will likely translate in a better recognition of the disease, earlier diagnoses in at-risk individuals and, hopefully, into the development of specific therapeutic strategies.

PATIENTS AND METHODS

Study participants and clinical analyses

We collected newly identified *DNAJB11* pedigrees in six genetic laboratories of expertise in inherited kidney diseases. The identified pedigrees originate from France (Families A to J), the US (Families K to M), United Kingdom (Families N to P), Netherlands (Family Q) and Australia (Families R, S and T). Families came from various study cohorts: GeneQuest (NCT02112136) (Families A, B, G, I, J), Brest University Hospital, France (C, D, E, F, H), the Mayo PKD Center (Families K to M), The National Registry of Rare Kidney Diseases (RaDaR) cohort (Family P), the Sheffield Kidney Institute (Families N and O), and the KidGen collaborative cohort (Families R to T). 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. Affected relatives' kidney function was calculated from clinical serum creatinine measurements with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Blood or saliva samples for standard DNA isolation were collected from the probands and all available family members.

Molecular analyses

Different NGS strategies were employed in the different centers: targeted NGS (TNGS) panels of 9, 15 and 137 cystogenes in Brest, Sheffield and in Mayo Clinic, respectively, cystogene panel filtered from whole exome sequencing in Utrecht, Netherlands, whole genome sequencing for the pedigree from Newcastle as part of the 100,000-genome project and in Australia. The TNGS panel employed in Brest (Nimblegen) includes the following genes: *PKD1, PKD2, GANAB, DNAJB11, HNF1β, PKHD1, UMOD, SEC63, PRKCSH*; the TNGS panel employed in Sheffield (SureSelect) includes, in addition to the aforementioned genes, the following genes: *REN*, *SEC61A1*, *TSC1*, *TSC2*, *LRP5*, *AGT*. Details about the TNGS panel employed in Mayo have been published recently.[33] All changes were confirmed by Sanger sequencing. When family samples were available, segregation analysis of the variant of interest was performed.

Imaging classification

Available abdominal CT, MRI and ultrasound images, or/and reports were retrieved from medical records. In patients with bilateral renal cysts, Mayo imaging classification was applied.[17] Patients were classified as typical (Class 1) or atypical (Class 2). Class 1 ADPKD patients were further stratified into five subclasses based on height-adjusted TKV and age, whenever available, as previously described.[17] Individuals with asymmetrical, unilateral, segmental, or lopsided imaging presentations were classified as 2A. Individuals with impaired renal function (serum creatinine≥1.5 mg/dl) without significant enlargement of the kidneys, defined by an average length <14.5 cm, were classified as 2B.[17]

Statistical analysis

All statistical analyses were performed using SPSS software, version 20 (IBM Corp), and GraphPad Prism, 5.00 for Windows (GraphPad Software, La Jolla California US). Renal survival (time from birth to ESRD) was analyzed using the Kaplan-Meier method. Differences between survival curves in male and female patients were assessed using a log rank test with a 0.05 significance level.

Genetic prevalence estimate

The Genome Aggregation Database (GnomAD, Cambridge, MA) is a collection of 125,748 exome and 15,708 genome data of unrelated individuals from different origins.[34] GnomAD v2.1 data were downloaded from http://gnomad.broadinstitute.org. Truncating variants (nonsense, splice, and frameshift mutations) and missense variants known to be fully penetrant were inventoried, with their respective allele counts, and entered in the calculation of the genetic prevalence. The 95% confidence intervals (CIs) for prevalence rates were computed assuming that the observed number of cases follows a binomial distribution.

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Table 1. Pathogenic variants, clinical and radiological features in the 54 affected individuals from 20 DNAJB11 pedigrees

Family	Mutation	Subject	Sex	eGFR (age) or ESRD (age)	Morphology of the kidneys					High blood pressure	Liver cysts (number of cysts)	ADPKD Classification	Other significant conditions (age), and if deceased cause of death
					Type	Age	Description of the cysts	Kidney length (cm), (TKV ml)	Fig				
A PK12819	c.532delA p.T178fs	I.1[a]	M	ESRD (80)	NA	NA	NA	NA	NA	NA	NA	NA	COD uremia at age 80
		II.1[a]	F	ESRD (63)	CT	74	MBSC	NA	S3A	Yes	Yes (~20, largest 100mm)	2B	Gastric adenocarcinoma (80)
		III.2	M	ESRD (67)	CT	66	MBSC	R:12.7, L:12.9 (1169)	3A	Yes	Yes	2B	Pancreatic cysts
		III.4[b]	F	58 (64)	CT	66	MBSC	R:9.5, L:9.3 (443)	S3B	No	No	1A	Pancreatic cysts T2DM
		IV.3	M	92 (41)	US	38	4 small cysts LK, 2 small cysts RK	R:13, L:13	NA	No	No	NA	None
		IV.4	F	91 (39)	MRI	36	2 small cysts LK, 5 small cysts RK	R:12, L:12 (380)	3B	No	Yes (4)	1A	None
B PK12850	c.70_85del p.R24Sfs	I.1[b]	F	ESRD (61)	CT	63	MBSC	R:14.3, L:14 (1322)	S3C	Yes	Yes (3)	2B	T2DM (68)
C PK13222	c.100C>T p.R34*	II.1	M	18 (69)	MRI	66	MBSC	R: 6.2, L: 9 (206)	S3D	Yes (49)	Yes (multiple)	2B	T2DM (50) Chronic pancreatitis and hepatitis (63)
		II.2[b]	F	37 (66)	MRI	64	MBSC	R:9.8, L:9.8 (325)	3C	Yes	No	2B	Graves Basedow's disease T2DM (65)
		III.2	F	107 (43)	MRI	43	MBSC	R:12, L:13	NA	No	No	1A	None
D PK13224	c.616C>T p.R206*	II.2	F	ESRD (85)	CT	85	MBSC	R: 8.5, L:10.9 (713)	3D	Yes	Yes	2B	None
		III.6[b]	F	30 (61)	US	61	MBSC	R:9.4, L:7.6	NA	Yes (58)	No	2B	None
		III.7	F	32 (63)	US	63	MBSC, micro calcifications	R 8.5, L 8.8	NA	Yes	No	2B	None
E PK13223	c.100C>T p.R34*	III.2	F	ESRD (64)	CT	66	MBSC	R:12, L:10 (381)	S3E	Yes	Yes	2B	Obesity
		III.6[b]	F	24 (78)	MRI	74	MBSC, micro calcifications	R: 9, L:10	NA	Yes	Yes	2B	Acute rheumatic fever in childhood,

													Meniere's disease
F PK13318	c.831_849dup p.K284Yfs*	II.1 [b]	F	38 (58)	CT	58	MBSC largest 12.6 mm	R:11.3, L:13.2 (446)	3E	Yes (58)	No	2B	ICA (anterior, 6mm, 57y), SLE
G PKD13331	c.724C>T p.R242*	II.2[b]	F	12 (74)	MRI	74	Few kidney cysts, one kidney stone and micro calcifications	R 9.5, L 10.2 (223)	3F	Yes (74)	No	2B	None
		II.4	F	22 (64)	CT	60	MBSC and micro calcifications	Normal-sized	NA	Yes	NA	2B	None
H PK13332	c.3G >A	I.1 [a]	M	ESRD (70)	NA	NA	Polycystic kidneys	Normal-sized	NA	NA	NA	NA	COD prostate cancer
		II.3 [b]	F	44 (60)	US	61	MBSC (largest 34mm)	Normal-sized	NA	Yes	No	2B	Multiple sclerosis
I PK13429	c.3G >A	I.1[a]	F	ESRD (80)	NA	NA	Polycystic kidneys	NA	NA	NA	NA	NA	COD uremia (80)
		I.2[a]	M	ESRD (80)	NA	NA	Polycystic kidneys	NA	NA	NA	NA	NA	COD PD-related peritonitis
		II.2[b]	M	ESRD (80)	CT	79	MBSC (largest 20mm)	R 14, L 14.5 (954)	3G	Yes	No	1B	None
		II.3	M	ESRD (80)	MRI	80	MSBC	R 19, L 19.5 (1449)	3H	Yes (60)	No	1B	Gout (79)
J PK13325	c.100C>T p.R34*	II.3 [a]	M	12 (52)	US	51	MBSC	Atrophic kidneys	NA	Yes	No	2B	Pre-emptive transplantation (52) BMI 31
		III.2[b]	F	99 (45)	MRI	45	8 small cysts LK, 12 RK, largest 1.4cm	R: 13, L:12 (458)	3I	Yes (39)	No	1A	None
K M1092	c.425T>A p.L142*	I.2 [a]	F	ESRD (69)	Auto-psy	69	MBSC	Autopsy: Atrophy total weight 95g	NA	Yes	No	2B	T2DM (68)
		II.2[b]	F	ESRD (71)	MRI	74	MBSC, 1 very large cyst RK	R:16.9, L:12.3, (1326)	3J, S3F	Yes	Yes (Multiple)	2A	None
		II.3 [a]	M	ESRD (68)	US	71	MBSC	R:11.3, L:12.0	NA	Yes	Yes (Multiple)	2B	Meningioma, COD CVA (72)
		III.2	F	68 (61)	US	61	MBSC, largest 27mm	R:13.1, L:14.1	S3G	Yes	Yes (Multiple)	NA	None
		III.4	F	25 (60)	CT	57	MBSC	Normal-sized	NA	Yes	Yes (Multiple)	2B	None

L M1260	c.616C>T p.R206*	I.2 [a]	F	ESRD (69)	NA	NA	NA	NA	NA	NA	NA	NA	COD ESRD and CVA
		II.1 [a]	F	ESRD (68)	NA	NA	MBSC	NA	NA	NA	NA	NA	COD CVA (68)
		II.2	F	22 (71)	MRI	71	MBSC	R:10.5, L:11.2 (314)	3K	Yes	Yes (Multiple)	2B	Meningioma
		II.3	F	30 (70)	CT	62	None observed	Small-sized (283)	NA	NA	No	NA[c]	None
		II.4[b]	M	25 (67)	CT	65	MBSC	R:10.9, L:9.9 (542)	3L	Yes (64)	No	2B	ICA (posterior, 3mm), kidney stones, colon cancer
M M555	c.682G>T[d] p.G228C	I.1	F	24 (66)	NA	NA	MBSC	NA	NA	Yes	NA	NA	None
		II.1[b]	M	90 (53)	CTw	43	9 small cysts	R:12.8, L:11.9 (489)	3M	No	No	1A	None
N S256	c.400delA p.I134fs	II.1[a]	M	ESRD (76)	NA	NA	NA	NA	NA	NA	NA	NA	None
		II.3[b]	M	29 (72)	CT	67	MBSC, a few larger cysts	R:11.3, L:11.7	S3H	No	Yes (2)	2B	Chronic pancreatitis; T2DM (62)
O S375	c.70C>T p.R24*	I.1[b]	M	ESRD (68)	MRI	68	MBSC	R:12.1, L:11.7	3N	Yes	Yes (30-50)	2B	Left carotid dissection (49), prostate cancer
		II.1	F	100 (44)	ceCT	44	8 cysts RK, 6 cysts LK	R: 11, L: 11	S3I	No	No	1A	Left unguinal hernia repair (25)
		II.2	F	102 (40)	ceCT	40	2 cysts RK, 8 cysts LK	R:12.5, L: 12.3	S3J	No	No	1A	Umbilical hernia in childhood
P Newcastle	c.730A>T p.K244*	II.1[a]	M	ESRD (68)	US	68	MBSC	Non-enlarged	NA	NA	NA	2B	None
		III.1[b]	F	74 (50)	MRI	50	MBSC	R 10.4, L 10.8 (360)	3O	No	Yes (Multiple)	1A	Thoracic aortic aneurysm (45)
		III.2 [a]	F	ESRD (60)	CT	60	MBSC	Non-enlarged	NA	NA	NA	2B	Thoracic aortic aneurysm (50)
Q Utrecht	c.532delA p.T178fs	II.5	F	55(56)[e]	US	56	MBSC (largest 11mm)	R:11.3, L:10.3	NA	No	No	NA	Poliomyelitis
R AUS1	c.430G>T p.E144*	I.1 [a]	F	ESRD (75)	NA	NA	NA	NA	NA	Yes	NA	NA	COD uremia (75)
		II.1[b]	F	ESRD (69)	US	69	MBSC	R:13.0, L:10.6	NA	Yes	No	2B	Melanoma
		III.1	F	95 (43)	ceCT	39	Small number of millimeter-sized cysts	R:11.1, L:10.3	NA	Yes	Yes (1)	2B	Recurrent UTI

S AUS2	c.616C>T p.R206*	I.1[a]	M	ESRD (75)	NA	NA	NA	NA	NA	NA	NA	NA	COD uremia (75)
		II.1[b]	F	58 (58)	US	56	MBSC	R:10.9, L:11.8	NA	No	Yes	2B	Meniere's Disease
T AUS3	c.400delA p.I134fs	I.1	M	ESRD (73)	US	75	MBSC	R:13.6,L:13.1	NA	NA	Yes (1)	2B	COD: Metastatic prostate cancer
		II.1[b]	M	67 (55)	US	54	At least seven small cortical cyst LK and RK	R:12.5,L:11.6	NA	Yes (39)	No	NA	None

[a] No blood sample available, the presence of the familial variant was not confirmed. [b]Proband. [c]Despite being affected, non-enhanced CT scan did not reveal any renal cyst, the Mayo Imaging Classification could not be applied. [d]Last nucleotide of exon 6, the substitution is predicted to weaken the donor site (BDGP, 0.06 to <0.01; HSF 83.39 to 72.52, and the motif entropy score for the donor site goes from +4.51 to -4.94). [e]24-hours-creatinine clearance is reported instead of CKD-EPI eGFR because the patient is wheelchair bound since childhood and has severe sarcopenia

BMI body-mass index, CVA cerebral vascular accident, COD cause of death, CT computed tomography, ceCT contrast-enhanced CT, ESRD end-stage renal disease, MBSC multiple bilateral small cysts, MRI magnetic resonance imaging, NA non available, PD peritoneal dialysis, SLE systemic lupus erythematosus,T2DM Type 2 diabetes mellitus, UTI urinary tract infections

Table 2. Distribution of the 77 *DNAJB11*-affected individuals according to Chronic Kidney Disease (CKD) stage

CKD stage	Number of subjects (%)
1	14 (18.2%)
2	9 (11.7%)
3a	5 (6.5%)
3b	4 (5.2%)
4	12 (15.6%)
5	33 (42.9%)

Table 3. Unrelated *DNAJB11*-affected individuals identified in the Genomics England 100,000-genome database

	Pathogenic variant	Sex	Age	Normalized specific disease group	Phenotypes
1	c.724C>T p.Arg242*	M	76	Cystic Kidney disease	Multiple renal cysts (cortical and medullary), HBP, inguinal and umbilical hernias
2	c.161C>G p.Pro54Arg	F	81	Cystic Kidney disease	Multiple renal cysts, HBP, CKD[a], Stroke, Macular degeneration
3	c.296_297delAG	F	55	Cystic Kidney disease	Hypertension, Renal cortical cysts, cone dystrophy
4	c.100C>T[c] p.Arg34*	F	63	Cystic Kidney disease	Multiple renal cysts, HBP, CKD stage 4
5[b]	c.730A>T p.Lys244*	F	50	Cystic Kidney disease	Multiple renal cysts, liver cysts, ascending aortic aneurysm
6	c.724C>T p.Arg242*	F	66	Renal tract calcification (or nephrolithiasis or nephrocalcinosis)	Nephrocalcinosis, CKD stage 3
7	c.67delG[d]	F	64	Cystic Kidney disease	Multiple renal cysts, HBP
8	c.400delA	M	64	Cystic Kidney disease	Multiple renal cysts (cortical), liver cysts, CKD stage 3, gout, HBP, obesity, hernia of the abdominal wall
9	C.616C>T p.Arg206*	M	59	Cystic Kidney disease	Multiple renal cysts, HBP

CKD Chronic Kidney Disease; HBP High blood pressure

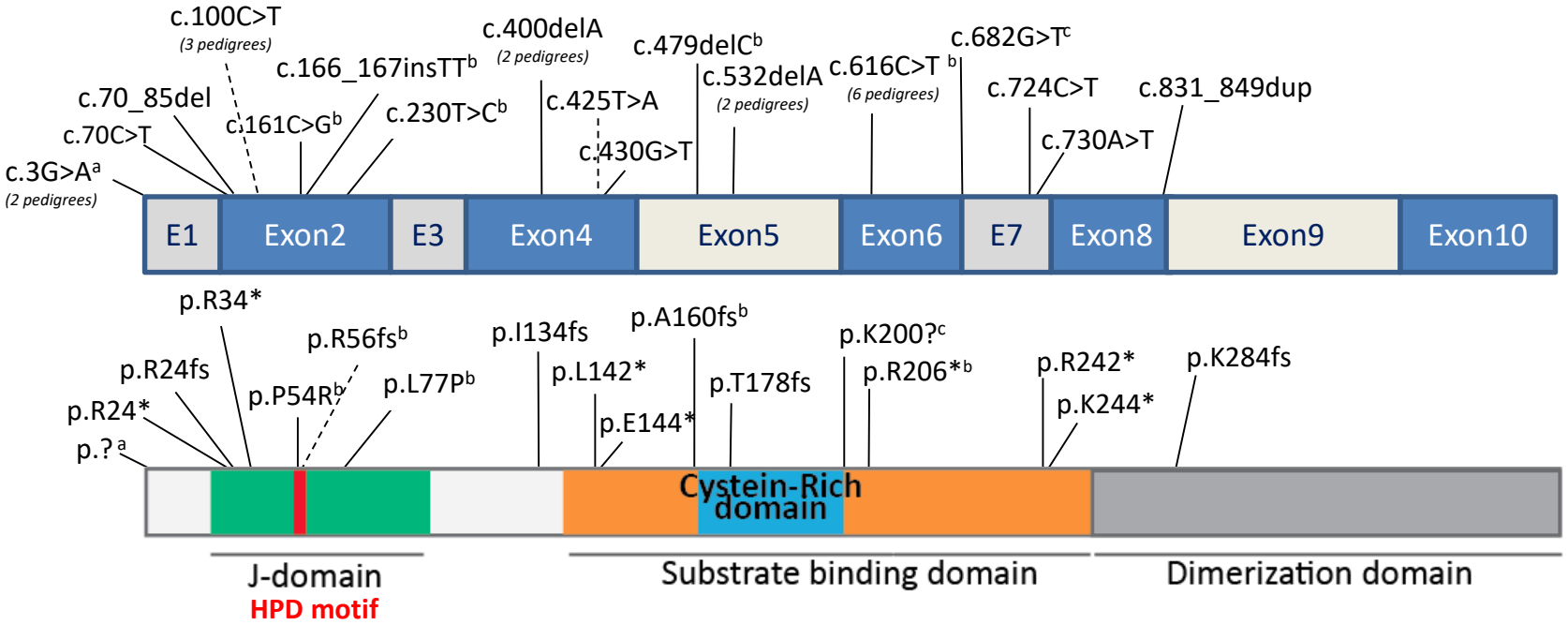
[a] CKD stage not reported in the database [b] This patient is also included in Table 1 (individual III.1 of the pedigree P) [c] Identification of a variant of unknown significance in *PKD2* c.2140A>G (p.Lys714Glu): conservative change affecting a moderately conserved residue, variant reported twice in GnomAD [d] Identification of a variant of unknown significance in *PKD1* c.4085C>T (p.Ser1362Phe): fairly conservative change affecting a residue conserved in orthologs but not in the protein domain (PKD repeats), variant reported once in GnomAD.

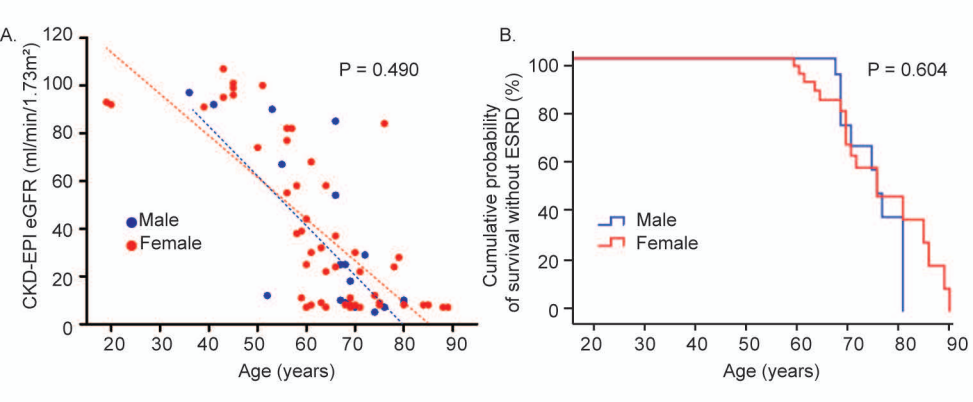
Figure legends

Figure 1- **Distribution of the 17 previously reported and newly described pathogenic variants identified in *DNAJB11* (27 pedigrees), and domain organization of DNAJB11**. DNAJB11 is a 358-amino-acid protein comprising a highly conserved J domain, with a characteristic His-Pro-Asp (HPD) motif through which it interacts with the chaperone BiP, a substrate-binding domain, and a dimerization domain. While most of the variants identified are loss of function variants, the only two pathogenic missense variants described occurred in the J domain.
*(*a) Nucleotide substitution causing a disruption of the initiation codon (b) pathogenic variants previously reported in *Am J Hum Genet. 2018 May 3;102(5):832-844* (c) Last nucleotide of exon 6, the substitution is predicted to weaken the donor site (BDGP, 0.06 to <0.01; HSF 83.39 to 72.52, and the motif entropy score for the donor site goes from +4.51 to -4.94)

Figure 2. Kidney functions and renal survival in DNAJB11-affected individuals. (A) CKD EPI eGFR values are plotted against age in 77 patients from 27 families (comprising the seven previously reported and the twenty newly described pedigrees). Renal function does not differ according to sex. (B) Kaplan-Meier curves show that renal survival does not differ in male and female subjects with a median age at ESRD of 75 years (0.95 CI, 72.5-77.5 years).

Figure 3. Representative abdominal imaging of fifteen individuals from twelve families. Computed tomography (CT) are displayed for six individuals (non-contrast-enhanced in A, E, G, L; contrast-enhanced in D and M), and magnetic resonance imaging (MRI) for 10 individuals, T2-weighted in B, C, F, H, I, K, N, O, T1-weighted in J. Detailed clinical information available in Table 2.


c.100C>T
(3 pedigrees)
c.166_167insTT[b]
c.400delA
(2 pedigrees)
c.479delC[b]
c.682G>T[c]
c.70_85del
c.532delA
(2 pedigrees)
c.616C>T [b]
(6 pedigrees)
c.724C>T
c.831_849dup
c.70C>T
c.161C>G[b]
c.230T>C[b]
c.425T>A
c.730A>T
c.3G>A[a]
(2 pedigrees)
c.430G>T
E1
Exon2
E3
Exon4
Exon5
Exon6
E7
Exon8
Exon9
Exon10
p.R34*
p.R56fs[b]
p.I134fs
p.A160fs[b]
p.K200?[c]
p.R242*
p.K284fs
p.R24fs
p.L142*
p.R206*[b]
p.R24*
p.P54R[b]
p.L77P[b]
p.T178fs
p.K244*
p.?[a]
p.E144*
Cystein-Rich domain
J-domain
HPD motif
Substrate binding domain
Dimerization domain


A.
CKD-EPI eGFR (ml/min/1.73m²)
120
100
80
60
40
20
0
P = 0.490
Male
Female
20
30
40
50
60
70
80
90
Age (years)
B.
Cumulative probability of survival without ESRD (%)
100
80
60
40
20
0
P = 0.604
Male
Female
20
30
40
50
60
70
80
90
Age (years)

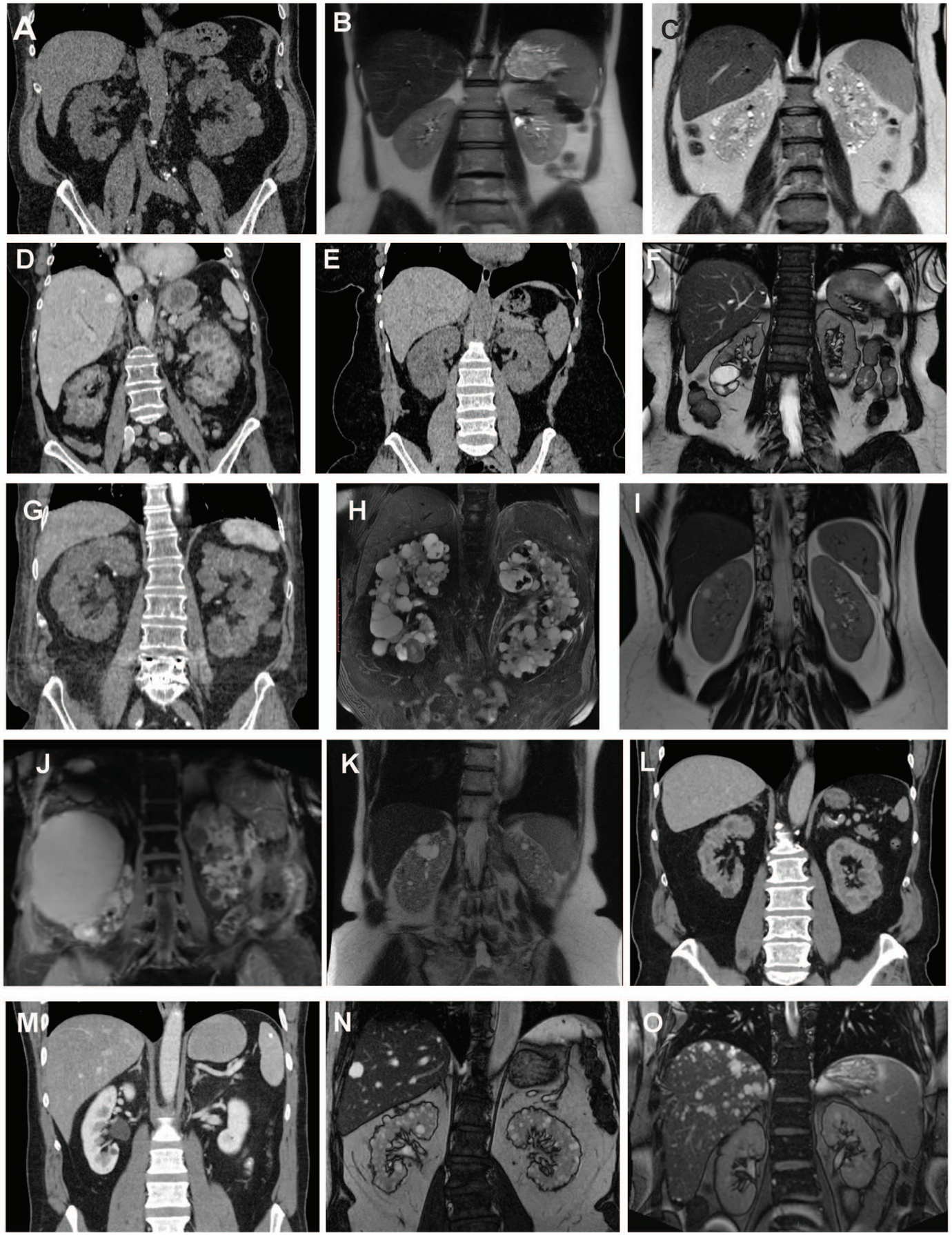
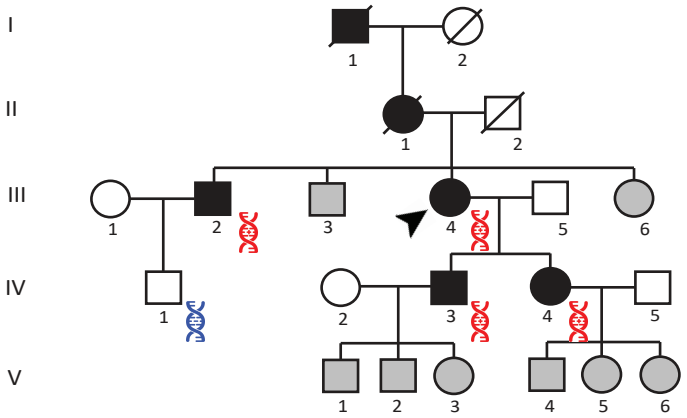

A
B
C
D
E
F
G
H
I
J
K
L
M
N
O

Table S1. Distribution of the probands recruited in the Genomes England 100,000 Project in the "renal and urinary tracts disorders" category

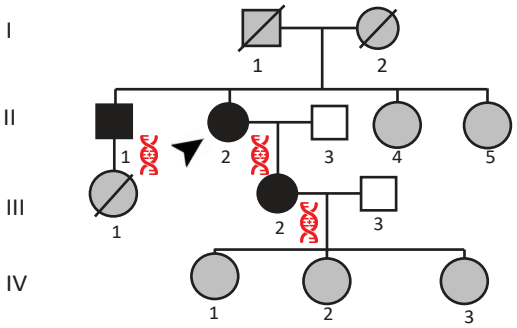
Disease category	Number of probands
aHUS	42
Amyloidosis	91
CAKUT	1083
Cystic kidney disease	1304
Severe Early-onset hypertension	234
Familial hematuria	246
Proteinuric renal disease	288
Renal tract calcification (or Nephrolithiasis/nephrocalcinosis)	290
Renal tubular acidosis and other electrolyte disorders	58
Unexplained kidney failure in young people	346
Rare multisystem ciliopathy disorders	24
Total	**3934**

Family A



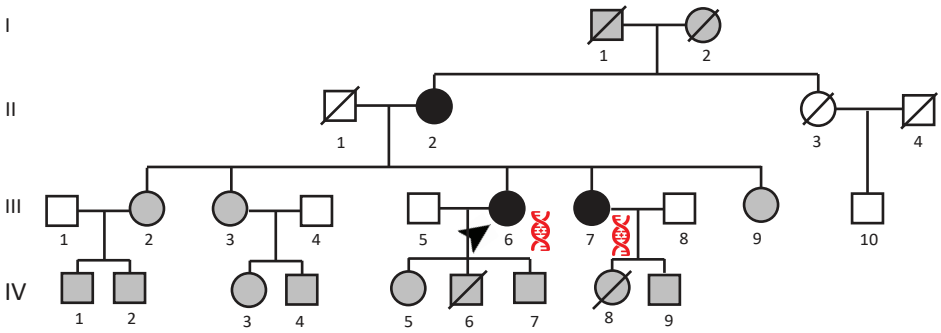
c.532delA ; p.T178Pfs

Family C



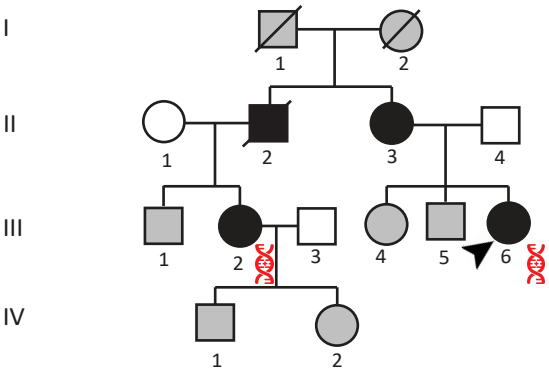
c.100C>T ; p.R34*

Family D



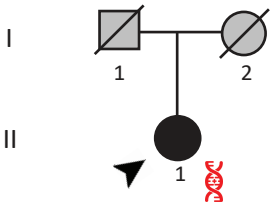
c.616CT ; p.R206*

Family E



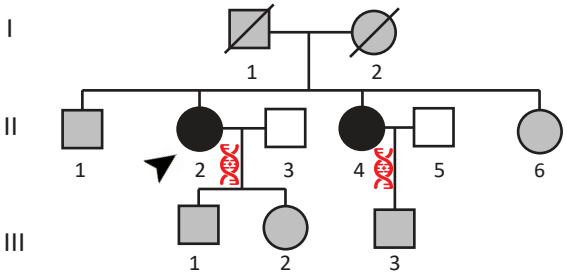
c.100C>T ; p.R34*

Family F



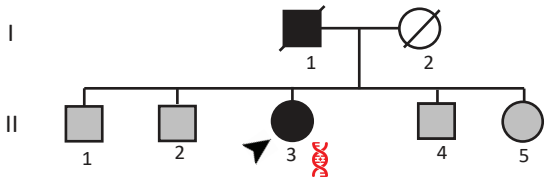
c.831_849dup ; p.K284Yfs

Family G



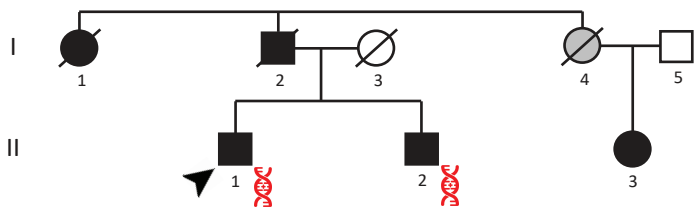
c.724C>T ; p.Arg242*

Family H



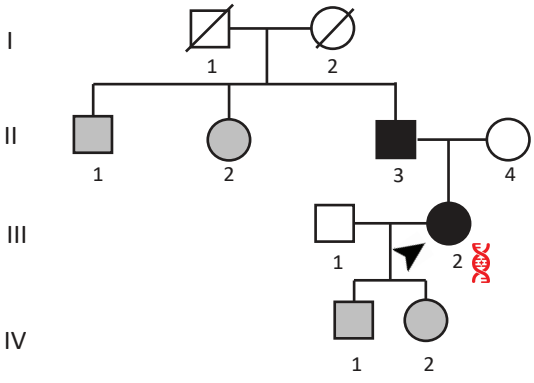
c.3G>A ; p.0

Family I

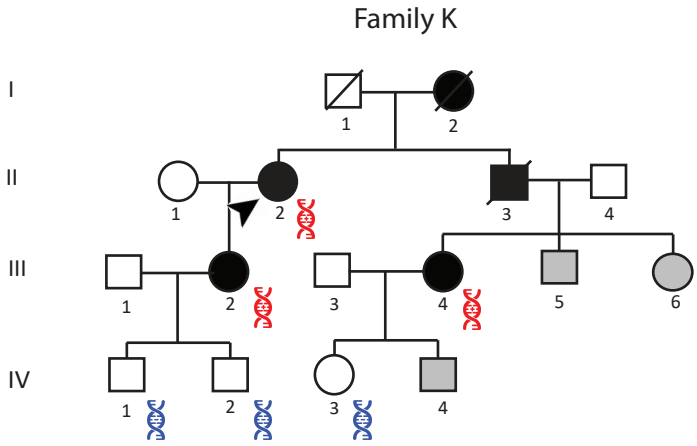


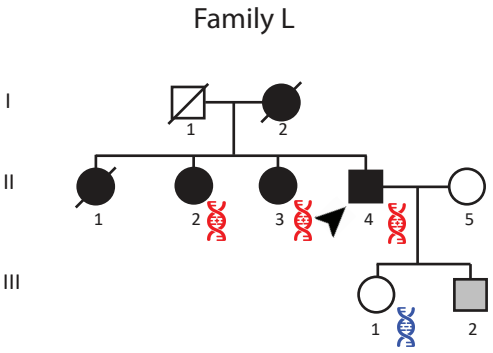
c.3G>A : p.0

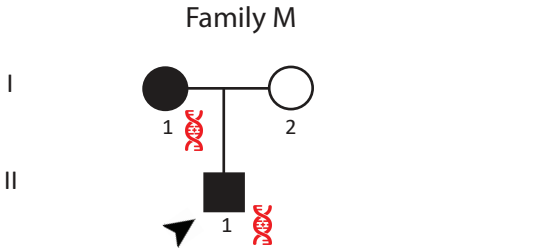
Family J

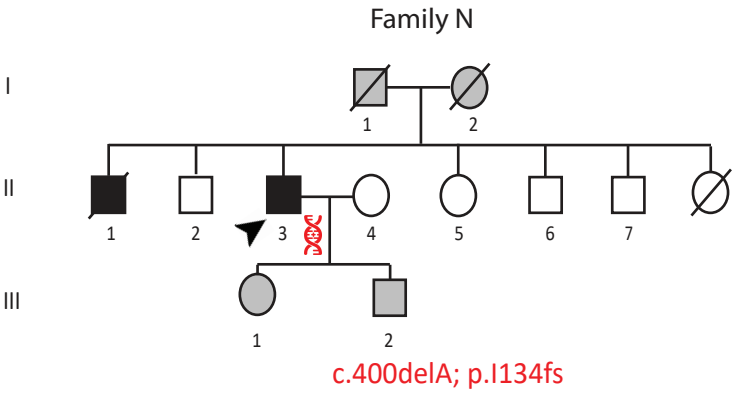


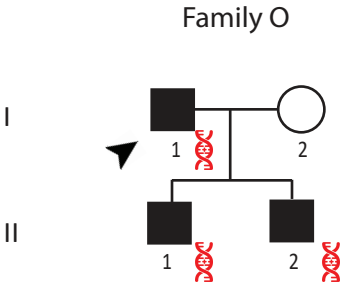
c.100C>T ; p.R34*

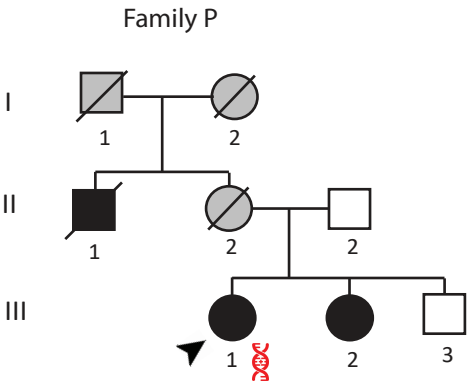


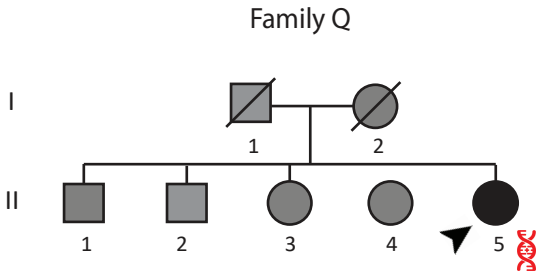


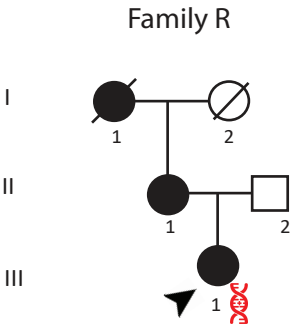


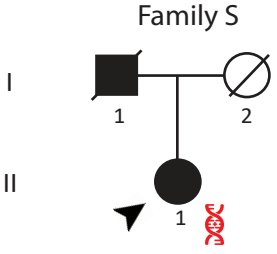


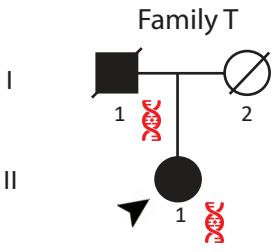




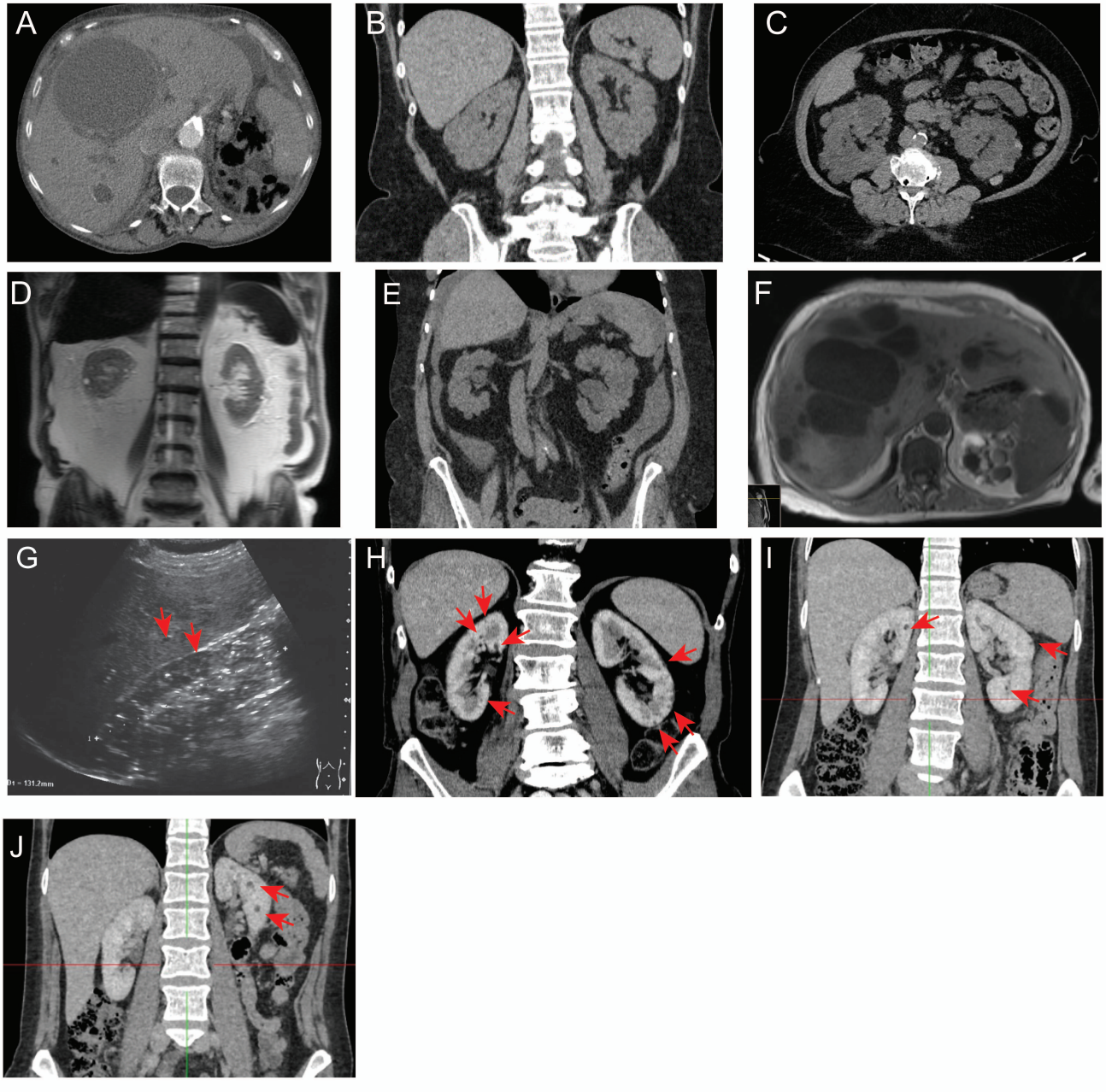








Supplemental Figure 1. Pedigrees of the 17 families including more than one single affected member. Black squares or circles indicate affected male or female subjects, respectively, presenting with bilateral renal cysts, liver cysts, renal failure, and/or genetically diagnosed and gray symbols indicate case subjects where clinical information is unavailable. Clinical characteristics are detailed in Table 1. The DNAJB11 pathogenic variants identified in each family are indicated below each pedigree, red DNA symbol denotes that DNA sequencing proved the mutation; blue DNA symbol denotes the absence of the pathogenic variant. Probands are indicated by a black arrow.



Supplementary Figure 2. Abdominal imaging of 10 affected individuals from 7 pedigrees.Seven have non contrast-enhanced computed tomography (A, B, C, E, H, I, J), 2 have magnetic resonnance imaging (D, F) and one has ultrasound imaging (G). Millimeter-sized cysts are indicated by red arrows. Clinical details are available in table 1.