HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2022 December 14.

Published in final edited form as:

Kidney Int. 2020 August ; 98(2): 476–487. doi:10.1016/j.kint.2020.02.022.

Clinical spectrum, prognosis and estimated prevalence of *DNAJB11*-kidney disease

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DISCLOSURE

JAS has received speaker’s fees and consultancy honoraria from Otsuka Pharmaceutical Industry; PCH has received research grants from Otsuka Pharmaceutical and consultancy honoraria from Mitobridge and Vertex Pharma; AJM has received research grant funding from Sanofi-Genzyme and is a Medical Advisory Board member for Otsuka Australia; and EC-LG has received speaker’s fees or consultancy honoraria from Otsuka Pharmaceutical Industry, Genzyme, and MedUpdate Europe. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

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Abstract

Monoallelic mutations of *DNAJB11* were recently described in seven pedigrees with atypical clinical presentations of autosomal dominant polycystic kidney disease. *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 20 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 end stage kidney disease (range, 55–89 years, median age 75); 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 under age 45. 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 nine of 3934 probands with various kidney and urinary tract disorders. The clinical diagnosis was cystic kidney disease for eight probands and nephrocalcinosis for one proband. No additional pathogenic variants likely explaining the kidney disease were identified. Using the publicly available GnomAD database, *DNAJB11* genetic prevalence was calculated at 0.85/10.000 individuals. Thus, establishing a precise diagnosis in atypical cystic or interstitial kidney disease is crucial, with important implications in terms of follow-up, genetic counseling, prognostic evaluation, therapeutic management, and for selection of living kidney donors.

Keywords

chronic kidney disease; *DNAJB11* ; genetics; polycystic kidney disease; prognosis

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The 2 major genes causing autosomal dominant polycystic kidney disease (ADPKD) are *PKD1* (MIM: 601313), encoding polycystin (PC)1, and *PKD2* (MIM: 173910), encoding PC2, identified in 72% to 78% and 15% to 18% of families, respectively.[1] Three additional genes recently were identified in pedigrees with an atypical ADPKD presentation: *GANAB* (OMIM: 104160), *DNAJB11* (OMIM: 618061), and *ALG9* (OMIM: 606941); all 3 genes encode proteins involved in the maturation and processing of membrane and secreted proteins.[1–6] Other genes occasionally might 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 increased liver enzyme levels or hypomagnesemia, and/or bilateral renal cysts.[7] Monoallelic mutations of *PRKCSH*, *SEC63*, *ALG8*, *SEC61B*, and *LRP5* are associated with autosomal dominant polycystic liver disease, characterized by the development of hepatic cysts, with occasional renal cysts.[1,3,8] Although 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 still is limited to a small number of pedigrees.

Monoallelic pathogenic variants to *DNAJB11* recently were reported in 23 patients from 7 ADPKD-like pedigrees, who presented with nonenlarged 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 binding immunological protein (alias GRP78).[9] Binding immunologic protein regulates protein folding and assembly, targets misfolded proteins to ER degradation, and acts as a master regulator of the unfolded protein response, an adaptive cellular response to ER stress.[10] *DNAJB11* loss is associated with impaired PC1 maturation.[4] However, kidney function decline in *DNAJB11* individuals also seems to be the result of the development of extensive interstitial fibrosis, reminiscent of autosomal dominant tubulointerstitial kidney disease (ADTKD).[4,11] Interestingly, defective proteostasis caused by *DNAJB11* variants also might affect the trafficking of uromodulin, mimicking the ADTKD-*UMOD* phenotype.[4]

This study presents the clinical, radiologic, and genetic characterization of 54 *DNAJB11*-affected individuals from 20 pedigrees identified in France, the United Kingdom, the Netherlands, the 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 7 reported pedigrees (23 individuals). Finally, 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 Genome Aggregation Database (GnomAD) (Cambridge, MA).

RESULTS

Patient characteristics and description of the mutation spectrum

Twenty *DNAJB11* pedigrees were identified in the 6 referral centers performing molecular diagnostics of cystic kidney diseases involved in the study (Supplementary Figure S1). In the 20 probands, the median age at referral for genetic diagnosis was 63.5 years (range, 45–80 years), and the presumptive clinical diagnosis, or primary reasons for referral for genetic testing, was ADPKD in 17 pedigrees, ADTKD in 2 pedigrees, and nephropathy of unknown etiology in 1 pedigree. Familial studies led to the identification of 54 affected individuals in total (35 female patients). The 13 different pathogenic variants identified in the 20 newly reported pedigrees were all predicted loss-of-function variants, including 4 short frameshifting deletions or insertions (6 pedigrees), 7 nonsense variants (11 pedigrees),

1 start-codon mutation (2 pedigrees), and 1 substitution of the last nucleotide of exon 6, predicted to weaken the splicing donor site (1 pedigree) (Table 1 and Figure 1[4]).

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 the last follow-up evaluation 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 of 18), whereas after age 55, 73% of the patients were classified at CKD stages 4 or 5 (n = 44 of 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 89 years. The median age at ESRD obtained by Kaplan-Meier curve analysis was 75 years (95% confidence interval, 72.5–77.5 years), and renal survival did not differ according to sex (Figure 2b). At ages 60, 70, and 80 years, the probabilities of having reached ESRD were 4.4% (SE, 3%), 37.4% (SE, 7.6), and 82.2% (SE, 7.6). Renal histology was available for 3 patients: individual II.1 from family A, II.1 from family C, and III.1 from family R, showing for the 2 first cases diffuse interstitial fibrosis and tubular dilatations (Supplementary Figure S2), while the third patient had minimal interstitial fibrosis and tubular dilatations at an early stage of the disease (CKD stage 1; age, 43 years). No specific glomerular lesions in the nonsclerotic glomeruli were present in any of these 3 cases.

Radiologic presentation.—Details regarding morphology of the kidneys in the 54 *DNAJB11* individuals, when available, are reported in Table 1, illustrative imaging is shown in Figure 3 and Supplementary Figure S3. 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%) were classified as 1B, 1 (2.6%) was classified as 2A, and 28 (71.8%) were classified as 2B. In younger patients, renal cysts were identified inconsistently. 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. After the identification of the familial mutation, magnetic resonance imaging (MRI) was performed and confirmed the presence of small millimeter-sized renal and liver cysts. In pedigree R, the 43-year-old woman (individual III.1), who was a candidate as a living kidney donor for her mother (individual 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 computed tomography imaging, which showed a small number of millimeter-sized kidney cysts, and 1 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 pedigree G, who reached CKD stage 5 at age 74, only a small number of renal cysts were identified by MRI (Figure 3f). In subject II.3 from pedigree L, who had an estimated glomerular filtration rate of 30 ml/min/1.73 m^2 at age 62, a non–contrast-enhanced computed tomography scan examination did not show any renal or liver cysts. Only 1 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 of 1445 ml (Figure 3h). No other likely pathogenic variants were identified in *PKD1*, *PKD2*, or any other cystogenes.

Extrarenal phenotypes.—Information regarding the presence of liver cysts was available in 39 subjects, and at least 1 liver cyst was reported in 19 patients (48.7%) (e.g., Figure 3n and o), 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 10-cm liver cyst compressing the common bile duct (Supplementary Figure S3A). Female subject II.2 from family K had multiple large liver cysts at age 74 (Supplementary Figure S3F). Gout was reported only in individual II.3 from pedigree I, a 79-year-old man 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 4 pedigrees. Subject I.1 from family F underwent a cerebral MRI at the age of 57 years because of chronic headaches. This led to the detection of a saccular aneurysm of the anterior circulation, measuring 6 mm in diameter. Because most of her family members lived in different countries, to date, no affected relative has been identified and screened for intracranial aneurysms. In subject II.4 from family L, systematic screening at age 66 led to the incidental diagnosis of a 3-mm intracranial aneurysm 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 ages 45 and 50 in 2 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 were analyzed for rare and likely pathogenic variants in *DNAJB11*. As of September 2019, whole-genome sequencing was performed in 35,042 probands affected by rare diseases, including 3934 probands with various renal and urinary tracts disorders (see details in Supplementary Table S1). Pathogenic variants (truncating or otherwise described) of *DNAJB11* were searched for in the participants with renal disorders and identified in 8 probands (9 individuals) in the cystic kidney disease subgroup, and 1 proband in the wider renal and urinary tract disease cohort. Details on the variants identified and the clinical information available for these 9 probands are listed in Table 3. No other pathogenic variants likely to explain the renal disorder were identified in any of the 10 individuals, and variants of unknown significance in other cystogenes are reported in the footnotes of Table 3. Although incomplete phenotypic data were available for these patients, multiple bilateral renal cysts were reported in 8 of 9 individuals, and liver cysts were reported in 2 individuals. Two unrelated individuals had abdominal wall hernias.

DNAJB11 nephropathy genetic prevalence

Eleven *DNAJB11* likely pathogenic variants were identified in 12 subjects from the GnomAD database (Supplementary Table S2). Thus, *DNAJB11* genetic prevalence is estimated at 0.85 (95% confidence interval, 0.44–1.48) per 10,000 in the whole GnomAD population (n = 141,456). Because the GnomAD database comprises patients with different ethnicities, we also considered separately the European population (n = 64,603), in which 6 individuals were found to have a *DNAJB11* pathogenic variant, corresponding to a prevalence of 0.93 (95% confidence interval, 0.34–2.02) per 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 generally are 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 6 expert inherited kidney disease centers across 3 continents has provided a description of the phenotype in a much larger *DNAJB11* nephropathy population, only 2 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 whole-exome sequencing, whole-genome sequencing, 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 1 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 10,000 individuals, appears as a good lower estimate of the lifetime risk of developing *DNAJB11* nephropathy. Some rare missense variants of *DNAJB11* identified in GnomAD actually may be pathogenic, resulting in a possible underestimation of this genetic prevalence. However, predicting the pathogenicity of such changes is difficult and unreliable, and a large majority (~88%) of the mutations identified in affected individuals to date are loss-of-function variants, and thus we have not considered these missense changes. A similar approach was used previously that resulted in an estimated ADPKD genetic prevalence (*PKD1* and *PKD2*) of 9.3 in 10,000 individuals.[12] Although these figures suggest that *DNAJB11* disease is only approximately 11 times less common than *PKD1/PKD2*-associated ADPKD, the contribution of *DNAJB11* in the ADPKD patient 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 1 previously reported family), and 1.3% of the 457 *PKD1/PKD2*-

negative pedigrees analyzed at Mayo Clinic (6 pedigrees including 3 previously reported families).[4] However, the median age at diagnosis of 63.5 years in the probands suggests that a majority of *DNAJB11* patients currently remain under the radar, owing to the 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 initially were considered unaffected when imaging-based diagnosis was used. One of these individuals was even considered as a living-related kidney donor. One of the key messages of this study is that imaging-based diagnosis criteria developed in *PKD1* and *PKD2* patient cohorts should not be used in cases of atypical polycystic kidney disease, in which only genetic diagnosis can be used to rule out the diagnosis in at-risk individuals.[13,14] Similarly, prognostic tools based on total kidney volume, such as the Mayo Imaging Classification, or the height-adjusted total kidney volume, should not be used in *DNAJB11* patients, because, unlike in *PKD1*- or *PKD2*-associated ADPKD, kidney function decline is not driven mainly by cystogenesis, and, hence, kidney enlargement does not precede estimated glomerular filtration rate 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 younger than 20 years to older than 80 years, and median ages at ESRD of 56 and 51 years, respectively.[18–20] In contrast, the DNAJB11 disease course appears more consistent among 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% to 70% and 7% to 24% in ADTKD-*UMOD* and ADTKD-*MUC1* affected individuals, respectively.[18–21] The pathogenesis of *DNAJB11* nephropathy remains incompletely understood. Although mature PC1 deficiency likely accounts for the cystic component of the phenotype, kidney function decline seems to be driven mainly 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 burdened increasingly 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 a 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] also could play an aggravating role in *DNAJB11* nephropathy's course. Larger patient cohorts and functional/tissue analyses will be needed to better understand DNAJB11 pathogenesis. Although no specific treatment currently is available to slow the kidney function decline in *DNAJB11* disease, emerging therapies in ADTKD, improving

cellular proteostasis, might be of interest in the future. Indeed, a recent study showed 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 intracranial aneurysm in 2 pedigrees, carotid dissection in 1 individual, and dilatation of the thoracic aorta in 2 siblings. Interestingly, data generated by the International Mouse Phenotyping Consortium indicate that mice with heterozygous inactivation of *Dnajb11* show aortic dilatation.[27] Abdominal wall hernias segregated with the disease in 2 siblings and were reported in 2 of 9 pedigrees identified in the Genomes England 100,000 data set. Abdominal wall hernias have been noted more frequently in patients with ADPKD compared with ESRD patients without ADPKD.[28] It has been hypothesized that abdominal wall hernias result from the combination of altered matrix integrity and increased abdominal pressure from cyst burden.[29,30] Although the latter seems unlikely in *DNAJB11* patients, who generally present with nonenlarged polycystic kidneys and mild liver involvement, reduced mature PC1 might cause altered extracellular matrix organization. Interestingly, abdominal wall hernias and arterial phenotypes also are described in hereditary connective tissue disorders such as vascular Ehlers-Danlos syndrome, an autosomal-dominant disorder resulting from mutations of the *COL3A1* gene.[31] A recent transcriptome analysis of skin fibroblasts of vascular Ehlers-Danlos syndrome patients has highlighted, among different pathways, significant changes in the expression levels of genes involved in ER-related homeostasis, including *DNAJB11*.[32]

Liver involvement in *DNAJB11* disease is highly variable, ranging from symptomatic polycystic liver disease in a minority of patients, to the absence of liver cysts detected by MRI. In our cohort, approximately 49% of the patients had at least 1 liver cyst, compared with approximately 18% in the general population.[33]

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 physicians to consider this diagnosis, with important implications in terms of follow-up evaluation, prognostic evaluation, therapeutic management, and for the selection of living kidney donors. *DNAJB11* nephropathy and classic ADPKD (i.e., caused by mutations of *PKD1* or *PKD2*) have distinct disease courses, at least in part different pathogeneses, and likely will necessitate different therapeutic strategies. Although *DNAJB11* nephropathy can present in some patients as a phenocopy of ADPKD, it should not be considered, per our opinion, as a subtype of ADPKD, but as a distinct disorder. In the future, increased awareness among nephrologists, combined with better access to genetic testing, likely will translate to 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 6 genetic laboratories of expertise in inherited kidney diseases. The identified pedigrees originate from France (families A–J), the United States (families K–M), United Kingdom (families N–P), the Netherlands (family Q), and Australia (families R–T). Families came from various study cohorts: GeneQuest (NCT02112136) (families A, B, G, I, and J), Brest University Hospital in France (C–F and H), the Mayo PKD Center (families K–M), The National Registry of Rare Kidney Diseases cohort (family P), the Sheffield Kidney Institute (families N and O), and the KidGen collaborative cohort (families R–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 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 used at the different centers: targeted NGS panels of 9, 15, and 137 cystogenes in Brest, Sheffield, and the Mayo Clinic, respectively; a cystogene panel filtered from whole-exome sequencing in Utrecht, the Netherlands; and whole-genome sequencing for the pedigree from Newcastle, UK (as part of the 100,000 Genome Project), and for the pedigrees from Australia. The targeted NGS panel used in Brest (Nimblegen) includes the following genes: *PKD1*, *PKD2*, *GANAB*, *DNAJB11*, *HNF1*0, *PKHD1*, *UMOD*, *SEC63*, and *PRKCSH*; the targeted NGS panel used in Sheffield (SureSelect) includes, in addition to the aforementioned genes, the following genes: *REN*, *SEC61A1*, *TSC1*, *TSC2*, *LRP5*, and *AGT*. Details about the targeted NGS panel used in Mayo have been published recently.[34] 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 computed tomography, MRI and ultrasound images, and/or 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 stratified further into 5 subclasses based on height-adjusted total kidney volume and age, whenever available, as previously described.[17] Individuals with asymmetric, 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 less than 14.5 cm, were classified as 2B.[17]

Statistical analysis

All statistical analyses were performed using SPSS software, version 20 (IBM Corp, Armonk, NY), and GraphPad Prism 5.00 for Windows (GraphPad Software, La Jolla, CA). 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

GnomAD is a collection of 125,748 exome and 15,708 genome data of unrelated individuals from different origins.[35] 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 for prevalence rates were computed assuming that the observed number of cases followed a binomial distribution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank the families and coordinators for involvement in the study. We would like to thank the nephrologists and other physicians who helped with the study: Julie Albaret, MD (Vichy, France); Franck Bridoux, MD, PhD (Poitiers, France); Fouad Chebib, MD (Rochester, MN); Lionel Couzi, MD, PhD (Bordeaux, France); Camille Domenger, MD (Poitiers, France); Laurent Doucet, MD (Brest, France); Jean-Michel Halimi, MD, PhD (Tours, France); Thierry Frouget, MD (Rennes, France); Marie Hogan, MD, PhD (Rochester, MN); Andrea Kattah, MD (Rochester, MN); Agnes La Batide-Alanore, MD (Paris, France); Hélène Longuet, MD (Tours, France); Pierre Paille (Roeschwoog, France); Aurélie Pajot, MD (Angers, France); Mathilde Prezelin-Reydit, MD (Bordeaux, France); Kimon Runge, MD (Freiburg, Germany); Guillaume Seret, MD (Le Mans, France); and Vicente Torres, MD, PhD (Rochester, MN).

We would like to acknowledge the study coordinators Christelle Guillerm-Regost, Christelle Ratajczak, and Noée Gales (Brest, France), Fabien Duthe (Poitiers, France), and Charles Madsen (Rochester, MN).

This study was supported by a National Plan for Clinical Research (Plan Hospitalier de Recherche Clinique inter-regional GeneQuest, NCT02112136 to ECLG), National Institute of Diabetes and Digestive and Kidney Diseases grant DK058816 (PCH), the Mayo Translational PKD Center (DK090728), and Dutch Kidney Foundation grant 18OKG19 (AMVE).

This research was made possible through access to the data and findings generated by the 100,000 Genomes Project. The 100,000 Genomes Project is managed by Genomics England Limited (a wholly owned company of the Department of Health). The 100,000 Genomes Project is funded by the National Institute for Health Research and NHS England. The Wellcome Trust, Cancer Research UK, and the Medical Research Council also have funded research infrastructure. The 100,000 Genomes Project uses data provided by patients and collected by the National Health Service as part of their care and support.

REFERENCES

1. Cornec-Le Gall E, Torres VE, Harris PC. Genetic complexity of autosomal dominant polycystic kidney and liver diseases. J Am Soc Nephrol. 2018;29:13–23. [PubMed: 29038287]
2. Besse W, Chang AR, Luo JZ, et al. *ALG9* mutation carriers develop kidney and liver cysts. J Am Soc Nephrol. 2019;30:2091–2102. [PubMed: 31395617]

3. Besse W, Dong K, Choi J, et al. Isolated polycystic liver disease genes define effectors of polycystin-1 function. J Clin Invest. 2017;127:1772–1785. [PubMed: 28375157]
4. Cornec-Le Gall E, Olson RI, Besse W, et al. Monoallelic mutations to *DNAJB11* cause atypical autosomal-dominant polycystic kidney disease. Am J Hum Genet. 2018;102:832–844. [PubMed: 29706351]
5. Porath B, Gainullin VG, Cornec-Le Gall E, et al. Mutations in *GANAB*, encoding the glucosidase IIalpha subunit, cause autosomal-dominant polycystic kidney and liver disease. Am J Hum Genet. 2016;98:1193–1207. [PubMed: 27259053]
6. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. Lancet. 2019;393:919–935. [PubMed: 30819518]
7. Verhave JC, Bech AP, Wetzels JF, Nijenhuis T. Hepatocyte nuclear factor 1beta-associated kidney disease: more than renal cysts and diabetes. J Am Soc Nephrol. 2016;27:345–353. [PubMed: 26319241]
8. Cnossen WR, Drenth JPH. Polycystic liver disease: an overview of pathogenesis, clinical manifestations and management. Orphanet J Rare Dis 2014;9:69. [PubMed: 24886261]
9. Shen Y, Hendershot LM. ERdj3, a stress-inducible endoplasmic reticulum DnaJ homologue, serves as a cofactor for BiP's interactions with unfolded substrates. Mol Biol Cell. 2005;16:40–50. [PubMed: 15525676]
10. Cybulsky AV. Endoplasmic reticulum stress, the unfolded protein response and autophagy in kidney diseases. Nat Rev Nephrol. 2017;13:681–696. [PubMed: 28970584]
11. Devuyst O, Olinger E, Weber S, et al. Autosomal dominant tubulointerstitial kidney disease. Nat Rev Dis Primers. 2019;5:60. [PubMed: 31488840]
12. Lanktree MB, Haghighi A, Guiard E, et al. Prevalence estimates of polycystic kidney and liver disease by population sequencing. J Am Soc Nephrol. 2018;29:2593–2600. [PubMed: 30135240]
13. Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2015;26:746–753. [PubMed: 25074509]
14. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009;20:205–212. [PubMed: 18945943]
15. Chapman AB, Bost JE, Torres VE, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2012;7:479–486. [PubMed: 22344503]
16. Grantham JJ, Chapman AB, Torres VE, et al. Volume progression in polycystic kidney disease. N Engl J Med. 2006;354:2122–2130. [PubMed: 16707749]
17. Irazabal MV, Rangel LJ, Bergstrahl EJ, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. J Am Soc Nephrol. 2015;26:160–172. [PubMed: 24904092]
18. Ayasreh N, Bullich G, Miquel R, et al. Autosomal dominant tubulointerstitial kidney disease: clinical presentation of patients with ADTKD-*UMOD* and ADTKD-*MUC1*. Am J Kidney Dis. 2018;72:411–418. [PubMed: 29784615]
19. Bollee G, Dahan K, Flamant M, et al. Phenotype and outcome in hereditary tubulointerstitial nephritis secondary to UMOD mutations. Clin J Am Soc Nephrol. 2011;6:2429–2438. [PubMed: 21868615]
20. Moskowitz JL, Piret SE, Lhotta K, et al. Association between genotype and phenotype in uromodulin-associated kidney disease. Clin J Am Soc Nephrol. 2013;8:1349–1357. [PubMed: 23723338]
21. Bleyer AJ, Kmoch S, Antignac C, et al. Variable clinical presentation of an *MUC1* mutation causing medullary cystic kidney disease type 1. Clin J Am Soc Nephrol. 2014;9:527–535. [PubMed: 24509297]
22. Klaips CL, Jayaraj GG, Hartl FU. Pathways of cellular proteostasis in aging and disease. J Cell Biol. 2018;217:51–63. [PubMed: 29127110]
23. Hartl FU. Cellular homeostasis and aging. Ann Rev Biochem. 2016;85:1–4. [PubMed: 27050288]
24. Hipp MS, Kasturi P, Hartl FU. The proteostasis network and its decline in ageing. Nat Rev Mol Cell Biol. 2019;20:421–435. [PubMed: 30733602]

25. Wang M, Kaufman RJ. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. Nature. 2016;529:326–335. [PubMed: 26791723]
26. Dvela-Levitt M, Kost-Alimova M, Emani M, et al. Small molecule targets TMED9 and promotes lysosomal degradation to reverse proteinopathy. Cell. 2019;178:521–535.e523. [PubMed: 31348885]
27. Dickinson ME, Flenniken M, Ji X, et al. High-throughput discovery of novel developmental phenotypes. Nature. 2016;537:508–514. [PubMed: 27626380]
28. Morris-Stiff G, Coles G, Moore R, et al. Abdominal wall hernia in autosomal dominant polycystic kidney disease. Br J Surg. 1997;84:615–617. [PubMed: 9171744]
29. Drummond IA. Polycystins, focal adhesions and extracellular matrix interactions. Biochim Biophys Acta. 2011;1812:1322–1326. [PubMed: 21396443]
30. Mikolajczyk AE, Te HS, Chapman AB. Gastrointestinal manifestations of autosomal-dominant polycystic kidney disease. Clin Gastroenterol Hepatol. 2017;15:17–24. [PubMed: 27374006]
31. Byers PH. Vascular Ehlers-Danlos syndrome. Published September 2, 1999. Updated February 21, 2019. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1494/. Accessed May 4, 2020.
32. Chiarelli N, Carini G, Zoppi N, et al. Transcriptome analysis of skin fibroblasts with dominant negative *COL3A1* mutations provides molecular insights into the etiopathology of vascular Ehlers-Danlos syndrome. PLoS One. 2018;13:e0191220. [PubMed: 29346445]
33. Carrim ZI, Murchison JT. The prevalence of simple renal and hepatic cysts detected by spiral computed tomography. Clin Radiol. 2003;58:626–629. [PubMed: 12887956]
34. Hopp K, Cornec-Le Gall E, Senum SR, et al. Detection and characterization of mosaicism in autosomal dominant polycystic kidney disease. Kidney Int. 2020;97:370–382. [PubMed: 31874800]
35. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. bioRxiv. Available at: 10.1101/531210. Accessed May 4, 2020

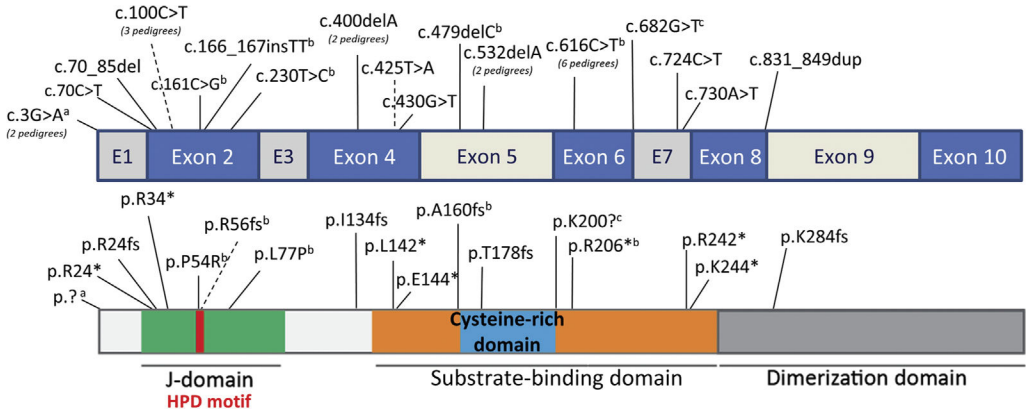

Figure 1 |. Distribution of the 17 previously reported and newly described pathogenic variants identified in *DNAJB11* (27 pedigrees), and domain organization of DNAJB11.

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 binding immunological protein (BiP), a substrate-binding domain, and a dimerization domain. Although most of the variants identified are loss-of-function variants, the only 2 pathogenic missense variants described occurred in the J domain. [a]Nucleotide substitution causing a disruption of the initiation codon. [b]Pathogenic variants previously reported by Cornec-Le Gall *et al.*[4] [c]Last nucleotide of exon 6, the substitution is predicted to weaken the donor site (Berkeley Drosophila Genome Project [BDGP], 0.06 to <0.01; Human Splicing Finder [HSF], 83.39–72.52; and the motif entropy score for the donor site goes from +4.51 to −4.94).

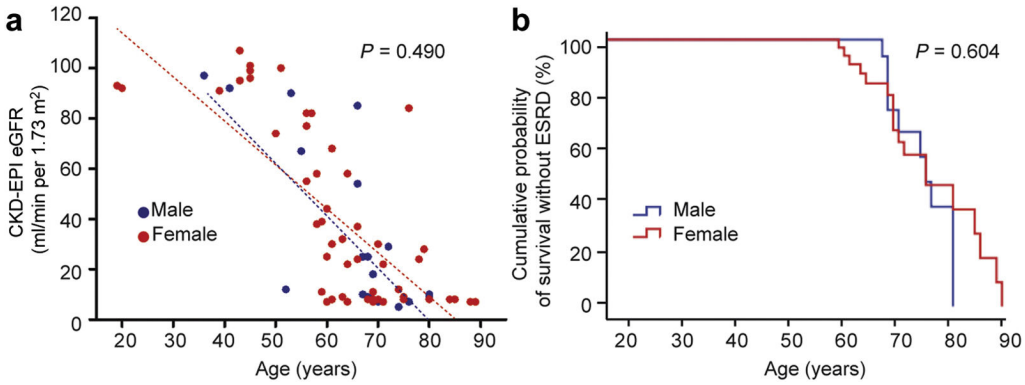

Figure 2 |. Kidney functions and renal survival in *DNAJB11*-affected individuals.

(**a**) Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) values are plotted against age in 77 patients from 27 families (comprising the 7 previously reported and the 20 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 end-stage renal disease (ESRD) of 75 years (0.95 confidence interval, 72.5–77.5 years).

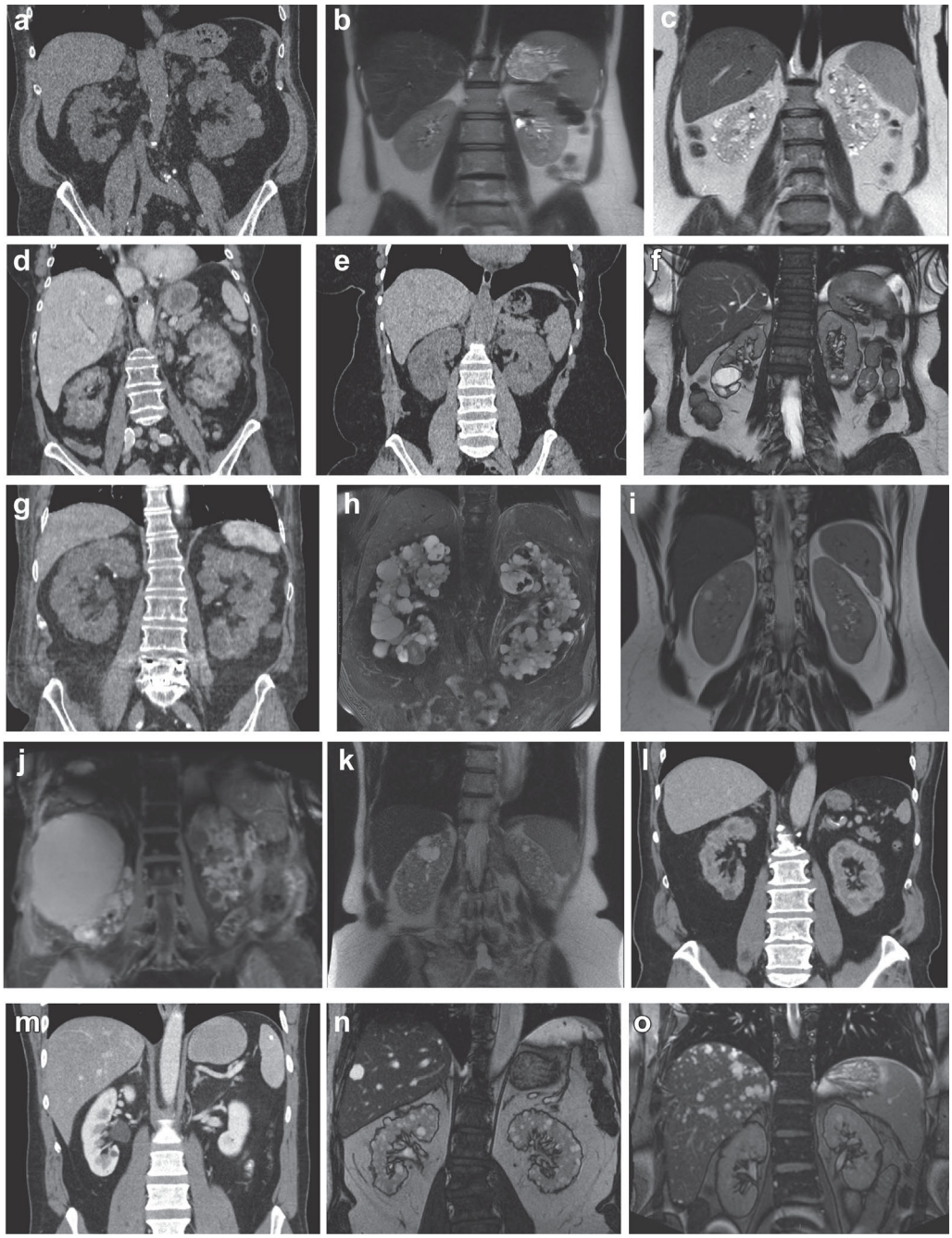

Figure 3 |. Representative abdominal imaging of 15 individuals from 12 families.
(**a,e,g,l**) Non–contrast-enhanced and (**d,m**) contrast-enhanced computed tomographies are shown for 6 individuals. (**b,c,f,h,i,k,n,o**) T2-weighted and (**j**) T1-weighted magnetic resonance imaging is shown for 10 individuals. Detailed clinical information is available in Table 2.

Table 1 |

Pathogenic variants, clinical features, and radiologic features in the 54 affected individuals from 20 *DNAJB11* pedigrees

					Morphology of the kidneys								
Family	**Mutation**	**Subject**	**Sex**	**eGFR or ESRD (age, yr)**	**Type**	**Age, yr**	**Description of the cysts**	**Kidney length, cm (TKV ml)**	**Figure**	**High blood pressure**	**Liver cysts (n)**	**ADPKD classification**	**Other significant conditions (age, yr), and if deceased cause of death**
A PK12819	c.532delA p.T178fs	I.1[a]	M	ESRD (80)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	COD uremia (80)
		II.1[a]	F	ESRD (63)	CT	74	MBSC	N/A	Supplementary Figure S3A	Yes	Yes (~20, largest, 100 mm)	2B	Gastric adenocarcinoma (80)
		III.2	M	ESRD (67)	CT	66	MBSC	R, 12.7; L, 12.9 (1169)	Figure 3a	Yes	Yes	2B	Pancreatic cysts
		III.4[b]	F	58 (64)	CT	66	MBSC	R, 9.5; L, 9.3 (443)	Supplementary Figure 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	N/A	No	No	N/A	None
		IV.4	F	91 (39)	MRI	36	2 small cysts LK, 5 small cysts RK	R, 12; L, 12 (380)	Figure 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)	Supplementary Figure 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)	Supplementary Figure 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)	Figure 3c	Yes	No	2B	Grave's disease T2DM (65)
		III.2	F	107 (43)	MRI	43	MBSC	R, 12; L, 13	N/A	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)	Figure 3d	Yes	Yes	2B	None
		III.6[b]	F	30 (61)	US	61	MBSC	R, 9.4; L, 7.6	N/A	Yes (58)	No	2B	None
		III.7	F	32 (63)	US	63	MBSC, microcalcifications	R, 8.5; L, 8.8	N/A	Yes	No	2B	None
E PK13223	c.100C>T p.R34*	III.2	F	ESRD (64)	CT	66	MBSC	R, 12; L, 10 (381)	Supplementary Figure S3E	Yes	Yes	2B	Obesity
		III.6[b]	F	24 (78)	MRI	74	MBSC, microcalcifications	R, 9; L, 10	N/A	Yes	Yes	2B	Acute rheumatic fever in

Family	Mutation	Subject	Sex	eGFR or ESRD (age, yr)	Morphology of the kidneys					High blood pressure	Liver cysts (n)	ADPKD classification	Other significant conditions (age, yr), and if deceased cause of death
					Type	Age, yr	Description of the cysts	Kidney length, cm (TKV ml)	Figure				
													childhood, Meniere 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)	Figure 3e	Yes (58)	No	2B	ICA (anterior, 6 mm, 57 yr), SLE
G PKD13331	c.724C>T p.R242*	II.2[b]	F	12 (74)	MRI	74	Few kidney cysts, 1 kidney stone, and microcalcifications	R, 9.5; L, 10.2 (223)	Figure 3f	Yes (74)	No	2B	None
		II.4	F	22 (64)	CT	60	MBSC and microcalcifications	Normal-sized	N/A	Yes	N/A	2B	None
H PK13332	c.3G >A	I.1[a]	M	ESRD (70)	N/A	N/A	Polycystic kidneys	Normal-sized	N/A	N/A	N/A	N/A	COD prostate cancer
		II.3[b]	F	44 (60)	US	61	MBSC (largest, 34 mm)	Normal-sized	N/A	Yes	No	2B	Multiple sclerosis
I PK13429	c.3G >A	I.1[a]	F	ESRD (80)	N/A	N/A	Polycystic kidneys	N/A	N/A	N/A	N/A	N/A	COD uremia (80)
		I.2[a]	M	ESRD (80)	N/A	N/A	Polycystic kidneys	N/A	N/A	N/A	N/A	N/A	COD PD-related peritonitis
		II.2[b]	M	ESRD (80)	CT	79	MBSC (largest, 20 mm)	R, 14; L, 14.5 (954)	Figure 3g	Yes	No	1B	None
		II.3	M	ESRD (80)	MRI	80	MBSC	R, 19; L, 19.5 (1449)	Figure 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	N/A	Yes	No	2B	Pre-emptive transplantation (52), BMI 31
		III.2[b]	F	99 (45)	MRI	45	8 small cysts LK, 12 RK (largest, 1.4 cm)	R, 13; L, 12 (458)	Figure 3i	Yes (39)	No	1A	None
K M1092	c.425T>A p.L142*	I.2[a]	F	ESRD (69)	Autopsy	69	MBSC	Autopsy: atrophy total weight, 95 g	N/A	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)	Figure 3j, Supplementary Figure S3F	Yes	Yes (multiple)	2A	None
		II.3[a]	M	ESRD (68)	US	71	MBSC	R, 11.3; L, 12.0	N/A	Yes	Yes (multiple)	2B	Meningioma, COD CVA (72)
		III.2	F	68 (61)	US	61	MBSC (largest, 27 mm)	R, 13.1; L, 14.1	Supplementary Figure S3G	Yes	Yes (multiple)	N/A	None

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Family	Mutation	Subject	Sex	eGFR or ESRD (age, yr)	Morphology of the kidneys					High blood pressure	Liver cysts (n)	ADPKD classification	Other significant conditions (age, yr), and if deceased cause of death
					Type	Age, yr	Description of the cysts	Kidney length, cm (TKV ml)	Figure				
		III.4	F	25 (60)	CT	57	MBSC	Normal-sized	N/A	Yes	Yes (multiple)	2B	None
L M1260	c.616C>T p.R206*	I.2[a]	F	ESRD (69)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	COD ESRD and CVA
		II.1[a]	F	ESRD (68)	N/A	N/A	MBSC	N/A	N/A	N/A	N/A	N/A	COD CVA (68)
		II.2	F	22 (71)	MRI	71	MBSC	R, 10.5; L, 11.2 (314)	Figure 3k	Yes	Yes (multiple)	2B	Meningioma
		II.3	F	30 (70)	CT	62	None observed	Small-sized (283)	N/A	N/A	No	N/A[c]	None
		II.4[b]	M	25 (67)	CT	65	MBSC	R, 10.9; L, 9.9 (542)	Figure 3l	Yes (64)	No	2B	ICA (posterior, 3 mm), kidney stones, colon cancer
M M555	c.682G>T[d] p.G228C	I.1	F	24 (66)	N/A	N/A	MBSC	N/A	N/A	Yes	N/A	N/A	None
		II.1[b]	M	90 (53)	ceCT	43	9 small cysts	R, 12.8; L, 11.9 (489)	Figure 3m	No	No	1A	None
N S256	c.400delA p.I134fs	II.1[a]	M	ESRD (76)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	None
		II.3[b]	M	29 (72)	CT	67	MBSC, a few larger cysts	R, 11.3; L, 11.7	Supplementary Figure 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	Figure 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	Supplementary Figure S3I	No	No	1A	Left inguinal hernia repair (25)
		II.2	F	102 (40)	ceCT	40	2 cysts RK, 8 cysts LK	R, 12.5; L, 12.3	Supplementary Figure S3J	No	No	1A	Umbilical hernia in childhood
P Newcastle	c.730A>T p.K244*	II.1[a]	M	ESRD (68)	US	68	MBSC	Nonenlarged	N/A	N/A	N/A	2B	None
		III.1[b]	F	74 (50)	MRI	50	MBSC	R, 10.4; L, 10.8 (360)	Figure 3o	No	Yes (multiple)	1A	Thoracic aortic aneurysm (45)
		III.2[a]	F	ESRD (60)	CT	60	MBSC	Nonenlarged	N/A	N/A	N/A	2B	Thoracic aortic aneurysm (50)

Family	Mutation	Subject	Sex	eGFR or ESRD (age, yr)	Morphology of the kidneys					High blood pressure	Liver cysts (n)	ADPKD classification	Other significant conditions (age, yr), and if deceased cause of death
					Type	Age, yr	Description of the cysts	Kidney length, cm (TKV ml)	Figure				
Q Utrecht	c.532delA p.T178fs	II.5	F	55 (56)[e]	US	56	MBSC (largest, 11 mm)	R, 11.3; L, 10.3	N/A	No	No	N/A	Poliomyelitis
R AUS1	c.430G>T p.E144*	I.1[a]	F	ESRD (75)	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	COD uremia (75)
		II.1[b]	F	ESRD (69)	US	69	MBSC	R, 13.0; L, 10.6	N/A	Yes	No	2B	Melanoma
		III.1	F	95 (43)	ceCT	39	Small number of millimeter-sized cysts	R, 11.1; L, 10.3	N/A	Yes	Yes (1)	2B	Recurrent UTI
S AUS2	c.616C>T p.R206*	I.1[a]	M	ESRD (75)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	COD uremia (75)
		II.1[b]	F	58 (58)	US	56	MBSC	R, 10.9; L, 11.8	N/A	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	N/A	N/A	Yes (1)	2B	COD: metastatic prostate cancer
		II.1[b]	M	67 (55)	US	54	At least 7 small cortical cysts in LK and RK	R, 12.5; L, 11.6	N/A	Yes (39)	No	N/A	None

BDGP, Berkeley Drosophila Genome Project; BMI, body mass index; CVA, cerebral vascular accident; COD, cause of death; CT, computed tomography; ceCT, contrast-enhanced computed tomography; ESRD, end-stage renal disease; HSF, Human Splicing Finder; ICA, intracranial aneurysm; LK, left kidney; MBSC; multiple bilateral small cysts; MRI, magnetic resonance imaging; N/A, not available; PD, peritoneal dialysis; RK, right kidney; SLE, systemic lupus erythematosus; TKV, total kidney volume; T2DM, type 2 diabetes mellitus; US, ultrasound; UTI, urinary tract infections.

[a]No blood sample was available; the presence of the familial variant was not confirmed.

[b]Proband.

[c]Despite being affected, a nonenhanced CT scan did not show any renal cyst and 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]Twenty-four-hour creatinine clearance was reported instead of Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate because the patient has been wheelchair-bound since childhood and has severe sarcopenia.

Table 2 |

Distribution of the 77 *DNAJB11*-affected individuals according to CKD stage

CKD stage	Subjects, n (%)
1	14 (18.2)
2	9 (11.7)
3a	5 (6.5)
3b	4 (5.2)
4	12 (15.6)
5	33 (42.9)

CKD, chronic kidney disease.

Table 3 |

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

Individual	Pathogenic variant	Sex	Age, yr	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[b] p.Arg34*	F	63	Cystic kidney disease	Multiple renal cysts, HBP, CKD stage 4
5[c]	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 was not reported in the database.

[b]Identification of a variant of unknown significance in *PKD2* c.2140A>G (p.Lys714Glu): conservative change affecting a moderately conserved residue; variant was reported twice in GnomAD.

[c]This patient also was included in Table 1 (individual III.1 of pedigree P).

[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 was reported once in GnomAD.