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Atypical ADPKD Due to a *DNAJB11* Pathogenic Variant: An Educational Case Report

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Abstract

Rationale: Due to next-generation sequencing, variants in new genes such as *DNAJB11* are recently being identified as causing atypical autosomal dominant polycystic kidney disease (ADPKD). It is important to describe phenotypes associated with these variants in order to increase awareness among clinicians, especially since genetic variability affects ADPKD severity.

Presenting Concerns of the Patient: We describe a 55-year-old female patient of Haitian origin who presented with slowly deteriorating kidney function, microscopic hematuria, proteinuria, enlarged kidneys with innumerable small cysts, and a family history of chronic kidney disease and cysts. The phenotype was atypical for ADPKD caused by *PKD1* or *PKD2* variants, since cysts were of small size, kidneys were only moderately enlarged, and the patient had no extra-renal involvement suggestive of typical ADPKD such as liver cysts, pancreatic cysts, cranial aneurysms, or cardiac abnormalities.

Diagnoses: A panel of genes was analyzed by next-generation massive sequencing techniques, including *DNAJB11, DZIP1L, GANAB, HNF1B, PKD1, PKD2*, and *PKHD1*. Genetic testing revealed a heterozygous variant in the *DNAJB11* gene (c.123 dup), which is predicted to result in premature protein termination (p. Lys42*) and was classified by the laboratory as likely pathogenic.

Interventions: She was treated with candesartan 16 mg once daily to address her proteinuria.

Outcomes: At the time of the most recent follow-up, her proteinuria has increased, and her kidney function continues to slowly deteriorate.

Teaching Points: *DNAJB11* variants are a rare cause of atypical ADPKD. It is important to recognize the clinical features that help distinguish *DNAJB11* from *PKD1* and *PKD2* variants. Atypical ADPKD due to *DNAJB11* variants is usually characterized by small cysts, normal kidney size, proteinuria, progressive chronic kidney disease, and phenotypic overlap with autosomal dominant tubulointerstitial kidney disease (ADTKD). It may, however, present itself with enlarged kidneys as was seen in our patient. Genetic testing should be offered whenever a patient presents atypical features of ADPKD, which also requires increased awareness among clinicians regarding the various phenotypes of atypical ADPKD.

Abrégé

Justification: Grâce au séquençage de nouvelle génération, on a récemment identifié des variants de nouveaux gènes tels que *DNAJB11* qui causeraient une forme atypique de polykystose rénale autosomique dominante (PKRAD). Afin de sensibiliser davantage les cliniciens, il est important de décrire les phénotypes associés à ces variants, d'autant plus qu'on sait que la variabilité génétique affecte la gravité de la PKRAD.

Présentation du cas: Nous décrivons le cas d'une patiente de 55 ans d'origine haïtienne qui présentait une lente détérioration de la fonction rénale, une hématurie microscopique, une protéinurie et des reins avec d'innombrables petits kystes. La patiente avait également des antécédents familiaux de néphropathie et de kystes. Le phénotype était atypique pour une PKRAD causée par les variants *PKD1* ou *PKD2*, car les kystes étaient petits, que la taille des reins n'était que modérément augmentée et qu'elle ne présentait aucune atteinte extra-rénale suggérant une PKRAD typique tels que des kystes hépatiques, des kystes pancréatiques, des anévrismes crâniens ou des anomalies cardiaques.

Diagnostic: Un groupe de gènes a été analysé par des techniques de séquençage massif de nouvelle génération, notamment les gènes *DNAJB11, DZIP1L, GANAB, HNF1B, PKD1, PKD2* et *PKHD1*. Le dépistage génétique a révélé un variant hétérozygote dans le gène *DNAJB11* (c.123 dup), qui est prédite comme entraînant une terminaison protéique prématurée (p.Lys42*) et qui a été classé par le laboratoire comme étant probablement pathogène.

Interventions: La patiente a reçu 16 mg de candesartan une fois par jour pour traiter sa protéinurie.

Résultats: Lors du plus récent suivi, la protéinurie avait augmenté et la fonction rénale avait continué de se détériorer lentement.

Enseignements tirés: Les variants de *DNAJB11* sont une cause rare de PKRAD atypique. Il est important de reconnaître les caractéristiques cliniques qui aident à distinguer les variants de *DNAJB11* des variants *PKD1* et *PKD2*. La PKRAD atypique due à des variants du gène *DNAJB11* est généralement caractérisée par de petits kystes, des reins de taille normale, une protéinurie, une insuffisance rénale chronique progressive et un chevauchement phénotypique avec la néphropathie tubulo-interstitielle autosomique dominante. Elle peut cependant se présenter avec des reins de taille augmentée, comme on l'a vu chez cette patiente. Le dépistage génétique devrait être offert dès qu'un patient présente des caractéristiques de PKRAD atypique, ce qui nécessite également une sensibilisation accrue des cliniciens aux divers phénotypes de la PKRAD atypique.

Keywords
ADPKD, chronic kidney disease, cystic kidney disease, *DNAJB11*, genetic kidney disease

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a monogenic disease characterized by the development and growth of kidney cysts along with the expansion of kidney volume.[1] With time, this leads to kidney failure (KF), making ADPKD the fourth leading cause of KF worldwide.[2] Most cases of ADPKD are due to variants in 2 genes, *PKD1* and *PKD2*, which encode membrane proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively.[1] Pathogenic variants to *PKD1* and *PKD2* are identified in about 72% to 75% and 15% to 18% of genetically positive ADPKD cases, respectively,[2] and cause typical ADPKD, characterized by enlarged kidneys with innumerable cysts, progression to KF, as well as extra-renal features.[3-5] In around 10% of cases, no variants in *PKD1* or *PKD2* are detected.[1] With next-generation sequencing (NGS), new genes are being identified as causing ADPKD, such as *GANAB, ALG5, ALG8, ALG9, IFT140*, and *DNAJB11*.[2,6-10] Variants in these genes often cause atypical ADPKD, a heterogenous group with usually less severe presentation, as can be seen outlined in Table 1.

The gene product of *DNAJB11* is a glycoprotein cofactor of binding immunoglobulin protein (BiP), which functions as a chaperone in the endoplasmic reticulum for control of folding, trafficking, and degradation of membrane proteins, including PC1 and PC2.[13] Variants in *DNAJB11* reduce the functional PC1 dosage within individual tubular epithelial cells and cause cyst formation.[1]

Heterozygous pathogenic variants in *DNAJB11* have recently been described as causing atypical ADPKD (Table 1).[2,11,12] In fact, *DNAJB11* variants have been identified in up to 2.6% of the *PKD1/PKD2*-negative pedigrees of 1 cohort.[12] ADPKD due to *DNAJB11* variants is characterized by small renal cysts, resulting in nonenlarged kidneys.[2,11,12] Evolution to KF is usually seen after the sixth decade.[2] Also, there seems to be phenotypic overlap between ADPKD and autosomal dominant tubulointerstitial kidney disease (ADTKD) in patients with *DNAJB11* variants.[2,12] In fact, interstitial fibrosis occurs in noncystic parenchyma, and recurring episodes of gout have been reported.

Liver cysts may develop in *DNAJB11*-related disease, but no severe liver phenotype has been reported.[13] Vascular phenotypes, including intracranial aneurysms, dilatation of thoracic aorta, and dissection of carotid artery, were noted in 5 patients among 77 cases described by Huynh et al.[12] Abdominal wall hernias were also present in 4 cases.[12] In a retrospective cohort study of 27 patients recently published by Pisani et al,[11] diabetes mellitus was more prevalent compared to typical ADPKD (19% vs 0%; $P = .007$), whereas cardiac valvular defects were rarer (4% vs 51%; $P < .001$). Pancreatic cysts were reported in 1 patient, nephrolithiasis was present in 61.5% of patients, and proteinuria, predominantly albuminuria, was found in various degrees, from mild to nephrotic range.[11]

Here, we describe a patient who presented with atypical ADPKD due to a pathogenic variant in *DNAJB11*, with a few different characteristics compared to what has been described regarding ADPKD due to *DNAJB11* variants.

Presenting Concerns

A 55-year-old female patient of Haitian origin was seen in our nephrology clinic in 2019 for kidney cysts and microscopic hematuria.

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Table 1. Clinical Features of ADPKD Depending on the Affected Gene.

Variant	Evolution to KF	Kidney cysts/size	Liver cysts	Other features
PKD1	Median age 58 years with truncating variants versus 67 years with nontruncating variants.[2]	Large kidneys with innumerable cysts.[4]	Liver cysts in up to 83% of patients.[3] More frequent in women, frequency increases with age.[3]	Hypertension.[4] Intracranial and other arterial aneurysms (10% of individuals, higher risk with a positive family history).[4,5]
PKD2	Median age 79 years.[2]	Large kidneys, less cysts than PKD1.[4]		Heart anomalies (mitral valve prolapse in up to 25%, dilatation of the aortic root, dissection of the thoracic aorta, increased left ventricular mass with diastolic dysfunction and predisposition to idiopathic dilated and hypertrophic obstructed cardiomyopathy).[4] Abdominal wall hernia.[4] Pancreatic cysts (8% of individuals).[4] Seminal vesicle cysts (40% of males, rarely result in infertility).[4] Arachnoid membrane cysts (8% of individuals, may increase the risk for subdural hematomas).[4] Congenital hepatic fibrosis (rare).[4] Colonic diverticulosis and diverticulitis.[4]
GANAB	No evolution to KF.[6]	Few to multiple cysts.[6]	Many liver cysts, may cause severe polycystic liver disease.[6]	
DNAJB11	Median age 75 years.[11,12] Reported in individuals between ages 55 and 89 years.[2,11,12]	Small cysts, normal kidney size.[2,12]	Liver cysts may be seen, described in up to 49% of cases.[11-13] No liver fibrosis.[13]	Overlap with ADTKD.[2] Gout.[2,12,13] Pancreatic cysts described in 1 patient.[11] Nephrolithiasis in up to 61.5% of patients.[11] Diabetes mellitus more prevalent than in typical ADPKD.[11] Cardiac valvular defects rare.[11] Arterial aneurysms described in 4 patients (intracranial and ascending thoracic aorta).[12] Carotid artery dissection described in 1 patient.[12] Abdominal wall hernias described in 4 patients.[12] Proteinuria ranging from mild levels to the nephrotic range.[11]
HNF1B	Median age 45 years.[14]	Glomerulocystic disease.[14]	No liver cysts.[14]	Renal dysplasia, renal-tract malformations.[14] Hyperuricemia, gout.[14] Maturity-onset diabetes of the young (MODY type 5).[14] Hypomagnesemia.[14] Abnormal liver function tests.[14] Genital tract malformations (vaginal aplasia, rudimentary uterus, bicornuate uterus, double vagina).[14]
IFT140	Out of the 66 cases described, only 1 patient developed KF at 64 years (of note, this patient had a single kidney).[7]	Bilateral large cysts, large kidneys with asymmetry.[7]	Rare small liver cysts.[7]	Hypertension.[7] Possible association with intracranial and aortic aneurysms.[7]
ALG9	Out of the 11 cases described, 1 patient reached KF at 66 years.[8]	Variable severity of cystic phenotype, generally milder than typical ADPKD.[8] Normal kidney size or mildly enlarged.[8]	Polycystic liver disease described in 1 case.[8]	Possible association with nephrolithiasis.[8]
ALG5	Evolution to KF after the sixth decade.[9] Out of the 23 cases described, 8 patients reached KF from 62 to 91 years of age.[9]	Bilateral small cysts, normal kidney size.[9]	Few liver cysts may be seen.[9]	Possible association with colonic diverticulosis.[9]
ALG8	No evolution to KF has been described.[10]	Bilateral cysts, normal kidney size.[10]	May cause polycystic liver disease.[10]	Possible association with nephrolithiasis [10].

Note. ADPKD = autosomal dominant polycystic kidney disease; ADTKD = autosomal dominant tubulointerstitial kidney disease; KF = kidney failure.

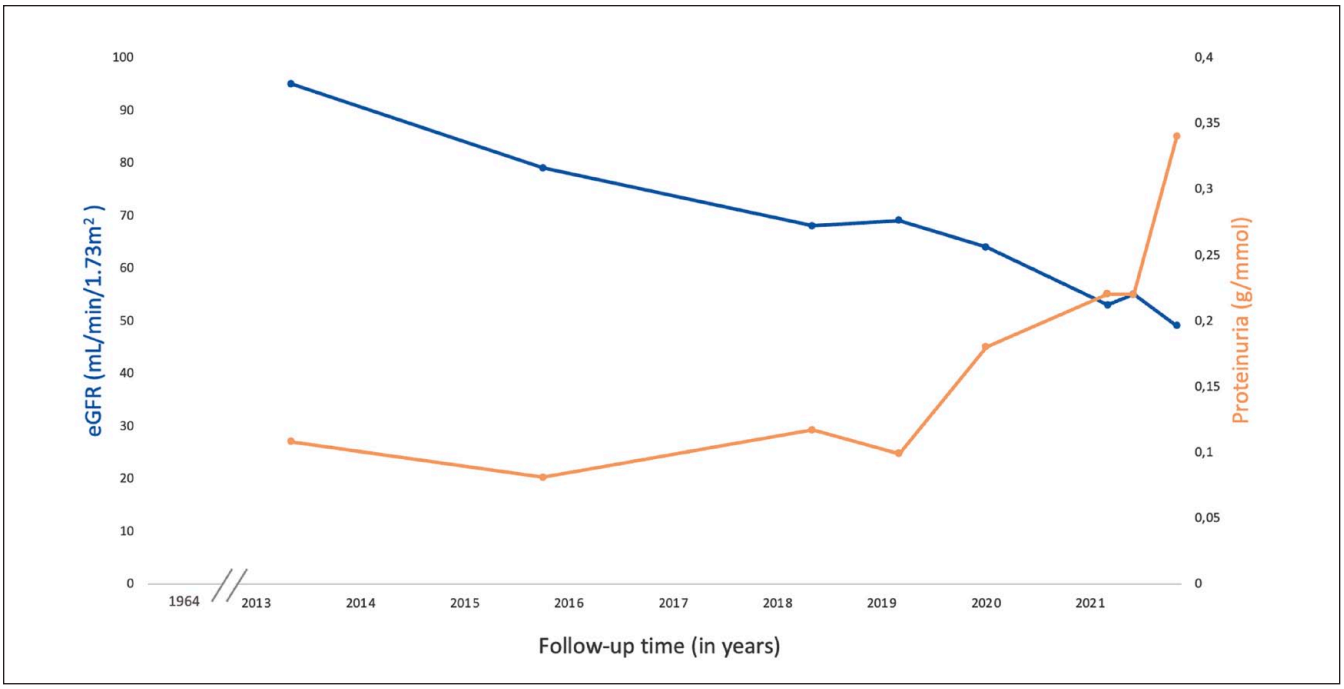

Figure 1. eGFR and proteinuria.
Note. Over time, eGFR decreased (blue line), with an average decline of 5 mL/min/1.73 m^2 per year. On the other hand, proteinuria increased (orange line), up to 0.34 g/mmol at the last follow-up. eGFR = estimated glomerular filtration rate.

Clinical Findings

The patient had a past medical history of obesity and type 2 diabetes mellitus, which was diagnosed 9 years prior, treated with oral antidiabetic medication and caused mild retinopathy. She had high blood pressure and dyslipidemia, diagnosed 11 years prior. Other medical conditions included uterine fibromas, an umbilical hernia, and a previous cholecystectomy. She had a total of 4 pregnancies, including 1 abortion. Sleep apnea was diagnosed on follow-up, as well as colonic polyps.

As for family history, her mother had high blood pressure and kidney cysts. The patient had a sister who had KF at the age of 55 years, attributed to diabetic nephropathy, in whom kidney cysts were also described. The rest of her family history was unremarkable; her 3 kids were healthy, and there was no notion of liver or pancreatic cysts nor cranial aneurysms. Of note, she was born of a nonconsanguineous union.

Diagnostic Focus and Assessment

At the time of initial evaluation in 2019, her serum creatinine level was 82 mmol/L, with an estimated glomerular filtration rate (eGFR) of 69 mL/min/1.73 m^2. Urinalysis showed microscopic hematuria. She also had albuminuria, with an albumin to creatinine ratio of 0.099 g/mmol. A urinary collection was performed, detecting a proteinuria of 0.89 g per day. eGFR tended to decrease moderately over time, with an average decline of 5 mL/min/1.73m^2 per year (Figure 1). Proteinuria remained stable at around 0.1 g/mmol until October 2019 and then started to increase, reaching 0.34 g/mmol in June 2022, despite treatment with candesartan. Complementary laboratory tests showed previous hepatitis B infection and a monoclonal gammopathy of unknown significance (IgG kappa at 0.45 g/L, normal serum light chains). Electrolytes, including potassium and magnesium, were normal. Investigations for autoantibodies, including ANA and ANCA, were negative. She had urinary cytology, which came back normal, as well as a cystoscopy, which only revealed cystitis cystica.

Abdominal ultrasound showed enlarged kidneys (13 cm bilaterally) with multiple cortical infracentimetric cysts, including a few calcified cysts. No liver cysts were detected. Notably, left hydronephrosis was also discovered, for which a mercapto-acetyl-triglycine (MAG3) furosemide renal scan was performed, consisting of simultaneous injection of MAG3, a radiopharmaceutical agent, and furosemide to evaluate the effect of the diuretic on drainage and assess urinary obstruction.[15] The scan showed no significant obstruction.

A computed tomography scan was performed as well, and it showed kidneys of similar size as previous imaging studies with many bilateral cysts, the biggest ones measuring 1.5 cm (Figure 2). The rest of the organ findings were unremarkable, with notably the absence of gynecological or genital tract anomalies aside from uterine fibromas.

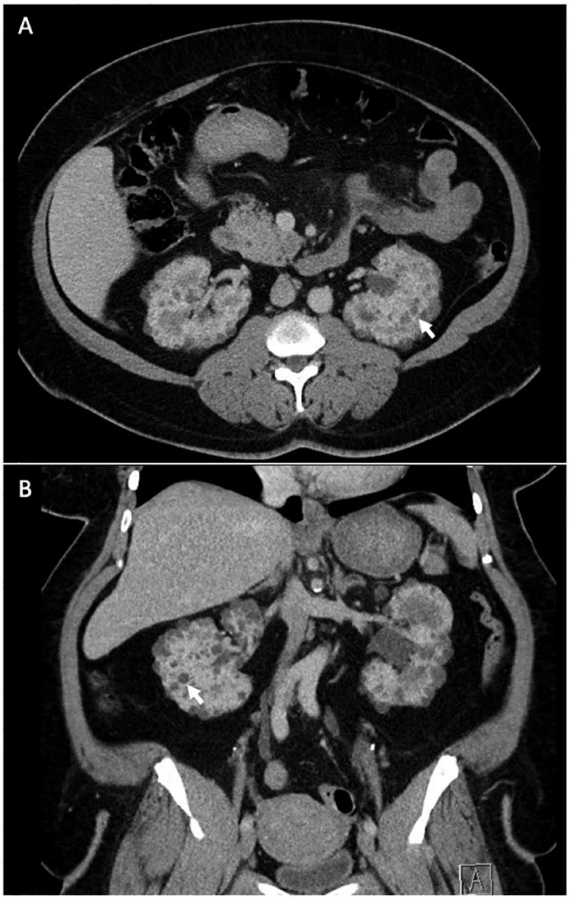

Figure 2. Computed tomographic imaging of the kidneys in axial (A) and coronal (B) planes, revealing bilateral small kidney cysts (arrows).

We thus had a 55-year-old patient presenting with slowly deteriorating kidney function, hematuria, proteinuria, innumerable small cysts with modest kidney enlargement, and a family history of chronic kidney disease and cysts. The phenotype was atypical for *PKD1* or *PKD2*, since cysts were of small size, kidneys were only moderately enlarged, and the patient had no extra-renal involvement alluding to ADPKD such as liver cysts, pancreatic cysts, cranial aneurysms, or cardiac abnormalities.[3-5]

Diabetic nephropathy could explain proteinuria and enlarged kidneys to a certain extent, but hematuria and cysts suggested an alternative diagnosis. In fact, hematuria in diabetic patients usually suggests nondiabetic renal disease.[16] Acquired cysts may be seen in up to 18% of diabetic patients between the ages of 50 and 59 years, but only 28% of these patients have multiple bilateral cysts.[17] A monoclonal gammopathy of renal significance could cause proteinuria and decreased eGFR, although it would not account for the whole phenotype and family history. Given the presence of numerous cysts and slow progression of the nephropathy, renal biopsy was not performed.

Further investigations were carried out to identify a variant explaining the phenotype. Genetic testing was performed at Prevention Genetics, a Clinical Laboratory Improvement Amendments-certified laboratory. DNA was extracted from whole blood specimen. A panel of genes was analyzed by NGS and Sanger sequencing technologies, looking for point variants as well as deletions, duplications, and copy number variants. The following genes were analyzed with a commercial test, chosen according to ClinGen evidence: *DNAJB11, DZIP1L, GANAB, HNF1B, PKD1, PKD2*, and *PKHD1*.

Atypical polycystic kidney disease, hydronephrosis, diabetes, and family history made us initially consider a variant in the *HNF1B* gene. *HNF1B*-related disease is also inherited in an autosomal dominant manner. It is characterized by renal cysts, along with pancreatic hypoplasia, maturity-onset diabetes of the young (MODY type 5), hyperuricemia and gout, abnormal liver function, hypomagnesemia, and genital tract malformations (Table 1).[14]

GANAB variants can cause both ADPKD and autosomal dominant polycystic liver disease, although the predominant phenotype is liver disease, which was absent in our patient. *DZIP1L* gene impairment is associated with ciliary trafficking defects and renal cystogenesis, causing autosomal recessive polycystic kidney disease (ARPKD).[18] As for *PKHD1*, it is the primary causative gene for ARPKD.

ALG5, ALG8, ALG9, and recently, *IFT140* have also been identified as novel ADPKD genes (Table 1) but were not routinely included in the panel used in our patient at the time of investigation.

Genetic testing revealed our patient to be heterozygous in *DNAJB11* gene for a variant (c.123 dup), predicted to result in premature protein termination (p.Lys42*). This variant was classified as likely pathogenic per American College of Medical Genetics and Genomics (ACMG) guidelines.[19]

Therapeutic Focus and Assessment

The patient was treated with candesartan 16 mg once daily to address proteinuria and high blood pressure (148/86), as well as amlodipine 10 mg and hydrochlorothiazide 12.5 mg once daily. Since there was little increase in renal volume and the disease was related to a variant in *DNAJB11*, she was not a candidate for tolvaptan treatment.

Follow-Up and Outcomes

At the time of the most recent follow-up, proteinuria has increased (protein to creatinine ratio 0.34 g/mmol), and her kidney function continues to slowly deteriorate, with an eGFR of 49 mL/min/1.73 m^2 (Figure 1).

Discussion

We herein present a case of atypical ADPKD due to a non-previously reported pathogenic variant in the *DNAJB11*

gene, with a few different characteristics compared to what has been noted in the literature.

DNAJB11 variants have been described since 2018 as causing atypical ADPKD, characterized by small renal cysts and resulting in nonenlarged kidneys.[2,11,12] These cysts may not be detected by ultrasound but will be revealed by computed tomography or magnetic resonance scans.[11] Some individuals may only have few renal cysts at an advanced stage of nephropathy.[12] This has clinical implications, especially when evaluating a potential living-related kidney donor. Genetic diagnosis seems essential to rule out disease due to *DNAJB11* in at-risk patients, and imaging-based diagnostic criteria developed for typical ADPKD should not be used.[12] Interestingly, contrary to ADPKD due to *PKD1* and *PKD2* variants, normal total kidney volume is not necessarily associated with a good prognosis.[2,12] Our patient had in fact small kidney cysts, as seen with this atypical form of ADPKD. However, her kidneys were slightly enlarged. Out of the cases described, 12 other patients had enlarged kidneys as well, with kidney length $\geq$ 13 cm (up to 19.6 cm in 1 patient).[2,12] Although a rare feature of *DNAJB11*-related disease, enlarged kidneys may be present and do not rule out the disease.

Duplications in *DNAJB11*, as seen in our patient, have been only exceptionally reported.[2,11-13] The duplication carried by our patient had not been previously documented on gnomAD or ClinVar.

There seems to be a phenotypic overlap between ADPKD and ADTKD in patients with *DNAJB11* variants.[2,12] Analysis of kidney tissue samples from *DNAJB11*-affected patients showed intracellular retention of UMOD and MUC1 in thick ascending loop epithelial cells.[2] Also, maturation and localization of PC1 were found to be impaired in *DNAJB11*-null cells. In all, these results suggest that *DNAJB11* variants may cause kidney disease through maturation and trafficking defects involving both PC1 and ADTKD proteins, such as UMOD and MUC1.[2] Our patient did not have any gout episodes, which could have helped us suspect a variant in *DNAJB11*. Since she did not have a kidney biopsy, we do not know whether she had interstitial fibrosis in noncystic parenchyma.

In addition to kidney disease, liver cysts may develop in ADPKD due to *DNAJB11* variants,[13] but were not observed in our patient. Abdominal wall hernias were also described, possibly due to altered matrix integrity caused by reduced mature PC1.[12] Of note, our patient had an umbilical hernia. In 1 cohort, diabetes mellitus seemed to be more prevalent in patients with *DNAJB11*-related disease compared to typical ADPKD.[11] Whether this is merely an incidental finding remains unknown, but it could potentially explain the family history of diabetes mellitus in our patient. However, the diabetes also occurred in the context of her obesity.

Kidney disease severity usually correlates with the variant class and gene involved.[1,2] Protein-truncating *PKD1* variants are associated with the most severe disease, followed by nontruncating *PKD1* variants and *PKD2* variants (Table 1).[1,2] Progression to KF has not been observed with *GANAB* variants and seems rare with newly identified *IFT140, ALG8*, and *ALG9* variants, whereas it is seen after the sixth decade with *ALG5* variants (Table 1).[2,6-10,20] Evolution to KF is usually also seen after the sixth decade with *DNAJB11* variants.[2] Our patient is now 58 years old and has mild chronic kidney disease.

Detecting the causative variant in a patient with ADPKD can thus be interesting in several ways. It provides prognostic information, informs the patient about their disease, and is useful for genetic counseling. An accurate diagnosis is also relevant to avoid further investigations, to evaluate a potential family donor for renal transplantation, and, in some cases, to refer to a targeted treatment such as in patients with *PKD1* or even *PKD2* variants.

Lastly, it is to be noted that ADPKD is currently described as typical or atypical based on our knowledge of different phenotypes. With recent advances in molecular biology, we now know that atypical forms of ADPKD are often due to variants in genes that were not tested in the past and, despite clinical similarities, can vastly differ from typical ADPKD regarding pathophysiology and prognosis. Modifying the classification and designation of these conditions should thus be considered. In that sense, some authors have recently proposed to call this group of disorders the ADPKD-spectrum and to use dyadic terminologies comprising both the clinical condition and gene name when describing the disease (for instance, employing the term ADPKD-*DNAJB11* for ADPKD due to *DNAJB11* variants).[7,9] Other authors have also suggested the use of the term *DNAJB11* nephropathy rather than ADPKD, considering the variability in clinical presentation, with some patients having few renal cysts despite advanced kidney disease.[12]

In conclusion, our case highlights that *DNAJB11* variants should always be included in the differential diagnosis of atypical ADPKD, especially in the context of normal-sized or slightly enlarged kidneys, smart cortical cysts, and slowly deteriorating kidney function. *DNAJB11* variants are a rare cause of atypical ADPKD, but prevalence may be underestimated, notably because NGS is relatively new. It is important to recognize the clinical features that help distinguish *DNAJB11* from *PKD1* and *PKD2* variants and acknowledge that patients with variants in the same gene, such as *DNAJB11*, can present phenotypic heterogeneity.

With the help of NGS, we are now able to identify new variants that explain different phenotypes associated with ADPKD and guide us when counseling our patients. The use of NGS will also allow us to better determine the prevalence of certain variants in the future and possibly help recognize patients with more than 1 variant.

Better characterization of *DNAJB11*-associated disease may as well be useful to improve our understanding of mechanisms underlying other forms of kidney disease, considering the suspected interplay between *DNAJB11* on the one

hand and ADPKD and ADTKD proteins on the other hand. Identification of these mechanisms and enhanced comprehension of the pathophysiology of those diseases may hopefully lead to the future development of specific therapeutic strategies.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient for the publication of this case report, in accordance with the requirements of our institution's ethics committee.

Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report, in accordance with the requirements of our institution's ethics committee.

Availability of Data and Materials

The data used for this case report are available from the corresponding author upon reasonable request.

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Author Contributions

GB and ZE-H were involved in the care of the patient. JK and GB wrote the main manuscript text. All authors contributed to the revision of the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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