

DNAJB11-Related Atypical ADPKD in a Kidney Transplant Donor



Gregory J. Wilson^{1,2}, Simon Wood³, Chirag Patel⁴, Kimberley Oliver⁵, George John⁶, Dwarakanathan Ranganathan^{6,7}, Andrew Mallett^{2,6,8,9} and Nicole Isbel^{1,2,9}

¹Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; ²Faculty of Medicine, The University of Queensland, Brisbane, Australia; ³Department of Urology, Princess Alexandra Hospital, Brisbane, Australia; ⁴Genetic Health Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia; ⁵Pathology Queensland, Princess Alexandra Hospital, Brisbane, Australia; ⁶Department of Renal Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia; ⁷School of Medicine, Griffith University, Brisbane, Australia; and ⁸Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia

Correspondence: Gregory J. Wilson, Princess Alexandra Hospital, 199 Ipswich Road, Woolloongabba, QLD, 4102, Australia. E-mail: gregory.wilson@uqconnect.edu.au

⁹These authors contributed equally to this work.

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INTRODUCTION

Genetic kidney disease is increasingly identified as a cause of chronic kidney disease (CKD) in patients who have previously had no known etiology.¹ Following advances in genetic sequencing and understanding, more than 500 monogenic etiologies have been identified as causes of CKD, and there are likely many additional genes yet to be identified.¹ Kidney transplantation is currently the most effective form of kidney replacement therapy, and living kidney transplants continue to have the greatest short- and long-term patient and allograft survival.² However, living-related kidney transplantation in patients with an unknown cause of end-stage kidney disease (ESKD) is clinically and ethically complex, as a donating family member may also have undiagnosed genetic kidney disease in a presymptomatic state. By removing a kidney, the time to ESKD for the donor is potentially shortened.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of CKD and ESKD.³ Although mutations in *PKD1* and *PKD2* are the 2 most common genetic causes,³ ADPKD is genetically heterogeneous, and approximately 7% of families remain genetically unresolved following genetic testing.⁴ The gene product of *DNAJB11* is a soluble glycoprotein cofactor of BiP/HSPA5, a key chaperone in the endoplasmic reticulum controlling folding, trafficking, and degradation of secreted and membrane proteins.⁵ Recently, this gene has been identified as a novel cause of late-onset, atypical ADPKD.⁴

We describe the case of a living related kidney transplant from a daughter to her mother with ESKD of unknown cause who was subsequently found to have a heterozygous likely pathogenic variant in *DNAJB11* and atypical ADPKD.

CASE PRESENTATION

A 42-year-old Caucasian woman was assessed as a potential living kidney donor for her mother. She had no past medical history other than occasionally elevated clinic blood pressures of up to 150/85 that had been diagnosed as white coat hypertension. She had 2 children, with no history of pre-eclampsia or pregnancy-induced hypertension and had completed her family. She had a normal body mass index (22 kg/m²) and was physically active. Her pre-donation investigations revealed no proteinuria, serum creatinine of 60 μmol/l, and a 51-Cr-EDTA glomerular filtration rate of 107 ml/min per 1.73 m². Ultrasound and computed tomographic imaging of the kidney and urinary tract were performed, and no abnormalities were reported (Figure 1a). An ultrasound of her liver reported a single simple cyst. A 24-hour ambulatory blood pressure monitor demonstrated a mean systolic blood pressure of 146 mm Hg and mean diastolic blood pressure of 88 mm Hg with a nocturnal dip. Her echocardiogram was normal, with no left ventricular hypertrophy. She was reviewed at the donor assessment clinic and informed that she had hypertension and that her blood pressure might rise postdonation, and was commenced on perindopril 5 mg with good

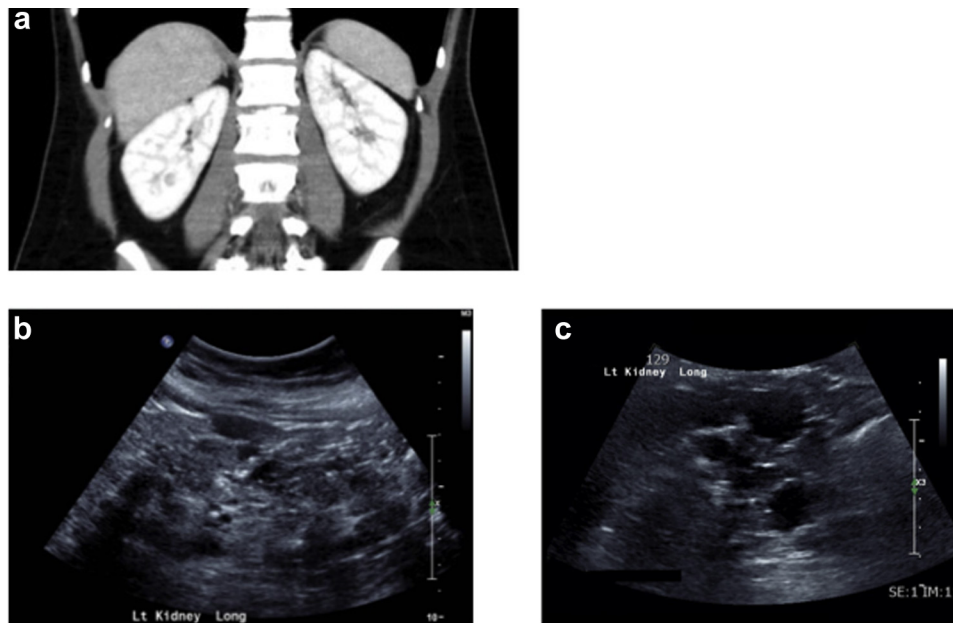


Figure 1. (a) Contrast-enhanced coronal plane computed tomographic image of the kidney transplant donor prior to surgery. (b) Ultrasound image of the left native kidney of the transplant recipient at the time of initial investigation of chronic kidney disease (CKD). (c) Ultrasound image of left native kidney of transplant recipient following kidney transplantation surgery, showing significant interval growth in renal cysts.

effect. Her projected pre-donation lifetime risk of ESKD (0.42%)⁶ was calculated and the result discussed with the donor and recipient. In addition, she was counseled that this risk would be increased following donor nephrectomy, but that this increased risk was unable to be quantified given her family history.

The planned recipient was a 73-year-old woman with slowly progressive CKD, which was presumed to be secondary to long-standing hypertension, and she had never undergone a renal biopsy. A kidney ultrasound performed 3 years before her transplantation had demonstrated several small cysts and nonenlarged kidneys that did not meet imaging criteria for a diagnosis of ADPKD. Her other past medical history included gout and treated skin cancers. The proposed transplantation was immunologically advantageous, as the recipient was highly sensitized (cPRA 93%), and there was 1 human leukocyte antigen (HLA) mismatch, negative flow cytometry result, and complement-dependent cytotoxicity cross-matches and no donor-specific antibodies. Both the donor and recipient were counseled extensively over 2 years about the possibility of an undiagnosed, inheritable cause of CKD in the recipient and donor and the potential risk to the donor of developing early ESKD following donation. Despite this risk, the donor, recipient, and their families remained committed to preemptive living kidney transplantation, and the donor consented to proceed to surgery.

The donor underwent a laparoscopic nephrectomy and, following removal of her kidney, was noted to have small but visible cysts (Figure 2). A biopsy was

urgently performed and demonstrated tubular cysts, moderate arteriosclerosis, and minimal tubulointerstitial scarring (Figure 3). As the donation surgery had already been completed, transplant surgery proceeded for the recipient. Postoperatively, the recipient underwent reimaging of her native kidneys again, which demonstrated a significant interval increase in the number of small cysts bilaterally (Figure 1b and c) but no liver cysts. Kidney cysts were still not appreciable on the donor's imaging following re-review.

Following recovery from surgery, the donor was referred to a renal genetics service for counseling and consideration of further investigation. She underwent clinical whole-genome sequencing with an analysis of a cystic kidney disease gene panel. Genetic testing demonstrated a heterozygous nonsense variant in *DNAJB11* (NM_016306.5, c.430G>T, p.Glu144Ter), which was classified by the laboratory as a likely pathogenic variant (American College of Medical Genetics and Genomics [ACMG] class 4). This variant was predicted to result in nonsense-mediated decay of the mRNA transcript with a likely loss of function and was supportive of a diagnosis of *DNAJB11*-related atypical ADPKD (Mendelian Inheritance in Man [MIM]: 618061). Genetic testing for the familial *DNAJB11* mutation was not performed in the recipient, as it was not believed to be clinically required, given her phenotypic presentation and the positive testing in her donor relative.

At 12 months postdonation, the donor had stable renal function (serum Cr 88 $\mu\text{mol/l}$; estimated

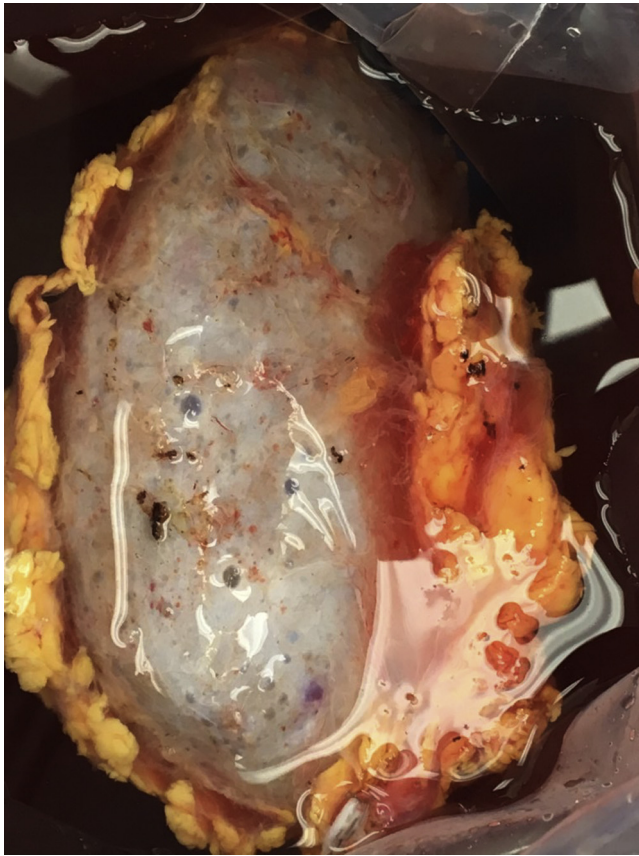


Figure 2. Macroscopic appearance of the donor kidney following nephrectomy.

glomerular filtration rate 67 ml/min per 1.73 m²). The recipient also had good allograft function (Cr 71 μmol/l) with no significant post-transplantation complications in this same period. Genetic testing has been offered to the siblings and children of the donor to allow them to assess their risk of CKD in later life. Despite the new diagnosis of genetic kidney disease and the increased risk of developing ESKD in her lifetime, the donor did not regret her decision to donate to her mother, and expressed satisfaction that it had allowed her family to become aware of their own risk of *DNAJB11*-related atypical ADPKD.

DISCUSSION

This is the first reported case of atypical ADPKD being diagnosed in a family through living donor kidney transplantation. Although genetic kidney disease is well recognized as an important cause of CKD in children and young adults, it is increasingly being recognized as a cause of adult-onset CKD (Table 1).⁷ The prevalence of CKD with unknown etiology is estimated to be 10% to 36% in adults.^{7,8} Genetic kidney disease is increasingly being identified as a cause of CKD in these patients, with 2 recent multicenter cohort whole-exome screening studies demonstrating that 20% to

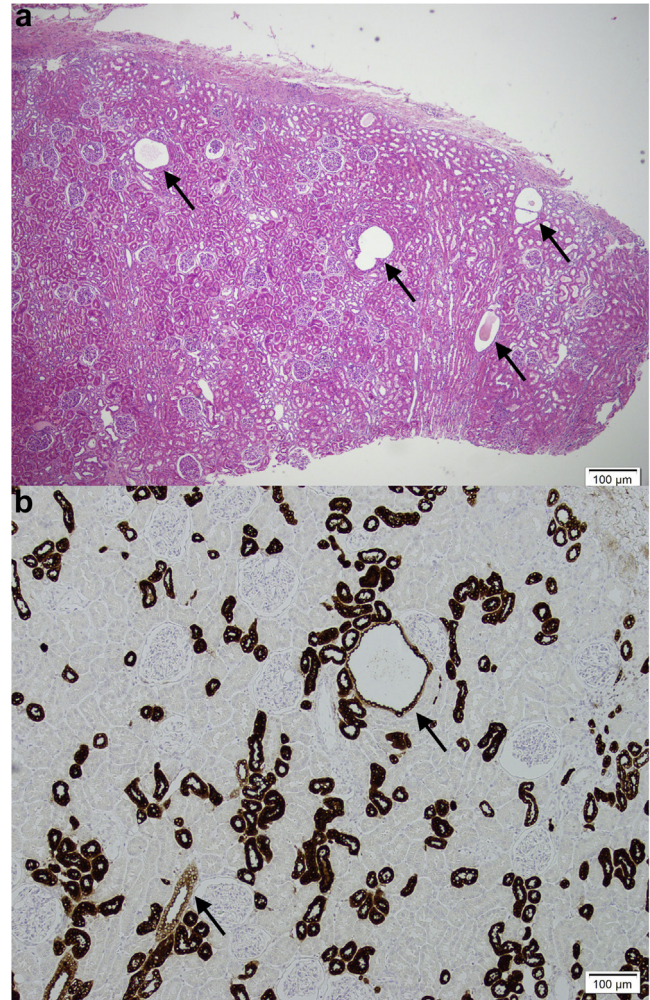


Figure 3. Donor kidney biopsy specimen showing tubular cysts. Antiepipithelial membrane antigen (EMA) immunoperoxidase stain demonstrates these microcysts arising from the distal tubule (arrows point to tubular cysts). (a) Hematoxylin and eosin stain, original magnification ×40. (b) EMA stain, original magnification ×100.

37% of patients with CKD of unknown etiology may have a monogenic cause.^{7,9}

DNAJB11-related atypical ADPKD is a recently discovered cause of atypical polycystic kidney disease.⁴ It is caused by variants in *DNAJB11*, a gene that encodes a soluble glycoprotein (GenBank: NP_057490.1) in the endoplasmic reticulum.⁴ This protein is one of the most abundant co-chaperones of binding immunoglobulin protein (BiP), a heat shock protein chaperone required for the proper folding and assembly of proteins in the endoplasmic reticulum.⁴ Errors in protein folding cause a loss of maturation and appropriate localization of polycystin 1,^{S1} the protein encoded by *PKD1*. This pathway of abnormal proteostasis results in renal or liver cystogenesis and is the disease paradigm postulated to cause many different forms of atypical renal and liver cystic diseases.^{S2}

Table 1. Teaching points

1. Genetic kidney disease is an important and underrecognized cause of adult-onset CKD and ESKD.
2. *DNAJB11*-related atypical autosomal dominant polycystic kidney disease is a newly identified cause of atypically presenting CKD and ESKD that is characterized by small renal cysts, normal size kidney, and progression to ESKD in the sixth decade of life. Early in the disease, the cysts may not be visible on US or computed tomography imaging.
3. Transplantation workup and assessment is a valuable opportunity to reassess the cause of CKD in potential transplant candidates. In patients with slowly progressive CKD from an unknown cause who are considering living-related kidney transplantation, reassessment of their diagnosis-targeted genomic diagnostics should be performed to exclude an inherited cause of ESKD.

CKD, chronic kidney disease; ESKD, end-stage kidney disease; US, ultrasound.

DNAJB11-related atypical ADPKD is a phenotypic hybrid of ADPKD and autosomal dominant tubulointerstitial kidney disease (ADTKD). Patients present with multiple small cysts and slowly progressive CKD, and most patients reach ESKD after the sixth decade of life.⁴ Cyst size remains small, and kidneys do not enlarge, with interstitial fibrosis developing instead. Liver cysts have been observed in some *DNAJB11*-affected individuals.⁴ However, unlike in typical ADPKD, there is no severe liver phenotype with *DNAJB11*-related atypical ADPKD.⁴ *DNAJB11* variants cause intracytoplasmic retention of uromodulin similar to ADTKD, resulting in a higher prevalence of gout in these patients.⁴ Ultrasound is the most commonly used imaging modality for diagnosing ADPKD. Although there are no validated imaging criteria for ADPKD using magnetic resonance imaging, it can also be used for the diagnosis of ADPKD and is also able to detect much smaller cysts (<1 cm) compared to ultrasound.⁵³ Because of these atypical features, ultrasound diagnostic criteria can be misleading,⁴ and magnetic resonance imaging should be considered to assess for smaller cysts that are commonly seen in *DNAJB11* atypical ADPKD (Table 1).

Living kidney donation is the preferred treatment for ESKD.² Although living donor kidney transplantation may represent the best outcome for recipients, there are significant risks to the donor. In addition to the operative and postoperative risks of donation surgery itself, kidney donation results in a significant decrease in the donor glomerular filtration rate and a higher risk of ESKD compared to pre-donation.⁵⁴ Also, there is a 2-fold increase in the risk of developing ESKD following donation in living related donors compared to unrelated donors,⁵⁵ and undiagnosed genetic kidney disease may contribute to this risk. In patients who have an unknown cause of ESKD and are considering a living related kidney transplant, early consideration of undiagnosed genetic kidney disease is essential to avoid poor outcomes for both the donor and recipient.

This case highlights the importance of considering genetic kidney disease in patients with ESKD of unknown etiology and has altered the clinical practice in our unit. Living donor kidney transplantation remains the preferred treatment for ESKD. However, for patients with an unknown etiology considering living related kidney transplantation, it is important to consider the possibility of a genetic kidney disease affecting both the donor and recipient, particularly in younger donors, donors with any features suggestive of early kidney disease, and donors of recipients who have slowly progressed to ESKD late in life. These patients and their potential donors should be considered for pre-donation genetic consultation and testing to help quantify the donor's risk of ESKD following donation.

DISCLOSURE

All the authors declared no financial conflicts of interest.

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SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary References.](#)

REFERENCES

1. Connaughton DM, Hildebrandt F. Personalized medicine in chronic kidney disease by detection of monogenic mutations. *Nephrol Dial Transplant.* 2020;35:390–397.
2. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant.* 2011;11:2093–2109.
3. Igarashi P, Somlo S. Polycystic kidney disease. *J Am Soc Nephrol.* 2007;18:1371–1373.
4. Corneec-Le Gall E, Olson RJ, Besse W, et al. Monoallelic mutations to *DNAJB11* cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet.* 2018;102:832–844.
5. Allison SJ. *DNAJB11*: another player in ADPKD. *Nat Rev Nephrol.* 2018;14:476.
6. Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med.* 2016;374:411–421.
7. Connaughton DM, Kennedy C, Shril S, et al. Monogenic causes of chronic kidney disease in adults. *Kidney Int.* 2019;95:914–928.
8. Neild GH. Primary renal disease in young adults with renal failure. *Nephrol Dial Transplant.* 2010;25:1025–1032.
9. Lata S, Marasa M, Li Y, et al. Whole-exome sequencing in adults with chronic kidney disease a pilot study. *Ann Intern Med.* 2018;168:100–109.