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Is It Time to Utilize Genetic Testing for Living Kidney Donor Evaluation?

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Abstract

Living donor kidney transplantation is an effective strategy to mitigate the challenges of solid organ shortage. However, being a living kidney donor is not without risk, as donors may encounter short- and long-term complications including the risk of developing chronic kidney disease, end-stage kidney disease, hypertension, and possible pregnancy-related complications. Although the evaluation of potential living donors is a thorough and meticulous process with the intention of decreasing the chance of complications, particularly in donors who have lifetime risk projection, risk factors for kidney disease including genetic predispositions may be missed because they are not routinely investigated. This type of testing may not be offered to patients due to variability and decreased penetrance of symptoms and lack of availability of appropriate genetic testing and genetic specialists. We re-port a case of a middle-aged woman with a history of gestational diabetes and preeclampsia who underwent an uneventful living kidney donation. She developed postdonation nonnephrotic range proteinuria and microscopic hematuria. Given the risk of biopsy with a solitary kidney, genetic testing was performed and revealed autosomal dominant Alport syndrome. Our case underscores the utility of genetic testing. Hopefully, future research will examine the incorporation of predonation genetic testing into living kidney donor evaluation.

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Introduction

Living donor kidney transplantation provides superior allograft outcomes compared to deceased donor kidney transplantation [1]; however, it can increase the donors' short- and long-term complications including chronic kidney disease (CKD) [2], end-stage kidney disease (ESKD) [3–5], hypertension [6], and pregnancy-related complications [7].

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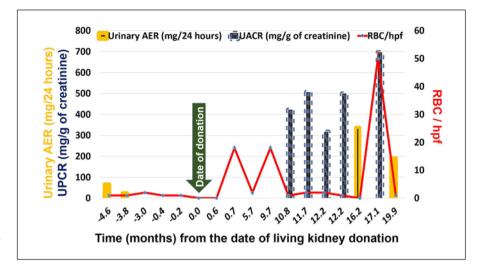Ekamol Tantisattamo, etantisa@hs.uci.edu

Fig. 1. Clinical course from pre- through post-living kidney donation periods. AER, albumin excretion rate; hpf, high power field; RBC, red blood cell; UACR, urinary albumin/creatinine ratio.

There is an increasing awareness of the risk for genetic kidney diseases. Thorough family history taking and some genetic testing such as genetic variants in the *Apolipoprotein L1 (APOL1)* gene are suggested as part of the living donor evaluation in at-risk individuals [8]. Obtaining a detailed family history may not fully ascertain such risk in a potential living donor as family history information may be limited due to adoption or failure to recognize affected family members with mild or unrecognized symptoms.

We report a case of a middle-aged woman who developed new-onset nonnephrotic range proteinuria after a kidney donation. Given relative contraindication for a native kidney biopsy in a remaining native kidney, a genetic test was performed and revealed a likely pathogenic heterozygous variant in the *COL4A3* gene associated with Alport syndrome. We discuss the information provided by genetic testing and propose revisiting guidelines of living donor evaluation.

Case Report

A 38-year-old non-Hispanic Caucasian woman presented for kidney donor evaluation. She intends to donate her kidney to her 50-year-old female friend who had ESKD secondary to lupus nephritis.

Her past medical history was significant for borderline gestational diabetes mellitus (GDM) and preeclampsia. She had 5 pregnancies and 6 children, including a twin pregnancy. The first and second pregnancies were uneventful at age 20 and 21 years, respectively, except for a cesarean section with her second pregnancy. At age 32, she developed borderline GDM during her third pregnancy which was controlled by diet. One year later, she had her fourth pregnancy without any complications. At age 34, she had her last pregnancy, which was a twin pregnancy that resulted from in vitro fertilization from another couple. She developed preeclampsia which resolved after delivery. She underwent a hysterectomy 3 months after the last pregnancy due to menorrhagia from uterine fibroids. Notably, she is an adopted child and does not know her biological family history.

Physical examination was unremarkable. The average blood pressure was 127/81 mm Hg and pulse was 71/min. Weight was 49.4 kg, height was 147.3 cm, and BMI was 22.76 kg/m^2.

Creatinine clearance (CrCl) at 4 months before the donation was 156.44 mL/min/1.73 m^2, and urinary microalbumin and total protein excretion rates (AER and PER) were 65 and 121 mg/24 h, respectively. A dietary protein intake (DPI) was 1.43 g/kg/day, and dietary sodium intake (DSI) was 2.23 g/day. Concerning were slightly elevated urinary AER and PER, which may reflect glomerular hyperfiltration from high DPI, and she was advised to have a low protein diet of 0.6 g/kg/day. The second 24-h urine collection at 3.5 months before the donation revealed a lower CrCl of 109.69 mL/min/1.73 m^2. Although DPI slightly increased to 1.47 g/kg/day, urinary AER significantly decreased to 24 mg/24 h and urinary PER became undetectable. Urinalysis showed small hemoglobin with 0–1 RBC/hpf and negative protein. She had unremarkable cystoscopy performed at the time of hysterectomy 3 years before the donation. She denies a history of gross hematuria. Predonation abdominal ultrasound and CT scan did not reveal evidence of kidney stone or kidney mass. Hemoglobin A1c was 5.4%, and oral glucose tolerance tests were 87 and 122 mg/dL at 0 and 2 h, respectively. She was approved as a living kidney donor and underwent a hand-assisted laparoscopic right nephrectomy without complication.

A routine urinalysis at 3 weeks after donation revealed 100 mg of protein and small hemoglobin with 11–25 RBC/hpf. Serum creatinine was 1 mg/dL from the baseline predonation creatinine of 0.7–0.8 mg/dL. At 5.5 months after donation, a repeated urinalysis still showed 100 mg/dL of protein, moderate hemoglobin, and 2 RBC/hpf.

Follow-up proteinuria and microscopic hematuria every month during the first year after donation revealed fluctuation of proteinuria of 0–100 mg/dL and moderate hemoglobin with 0–3 RBC/hpf. Spot urinary microalbumin/urinary creatinine ratio

(UACR) ranged 318–507 mg/g of creatinine, and a spot urinary total protein/urinary creatinine ratio (UPCR) ranged 537–787 mg/g of creatinine (Fig. 1). A urine dipstick showed 2+(moderate) blood, 2+(100) protein, and negative glucose. Urine microscopy revealed 0–1 normal-appearing RBC/hpf (Fig. 2). A 24-h urine collection at 16 months after donation showed a CrCl of 75.66 mL/min/1.73 m^2 and a urinary PER of 0.533 g/day. The estimated DPI and DSI were 0.95 g/kg/24 h and 3.266 g/24 h, respectively. Serum creatinine remained stable at 0.8–0.9 mg/dL, and serum cystatin C was 0.98 mg/L. The allograft function of the recipient has been stable with a serum creatinine of 1.1–1.3 mg/dL, and a spot UACR and UPCR ranged 50–113 and 21–483 mg/g of creatinine, respectively.

Given unclear etiology of new-onset nonnephrotic range proteinuria and microscopic hematuria after donation and a relative contraindication for a native kidney biopsy in this living donor, a next-generation sequencing genetic test (Renasight 382-gene panel test from Natera) was performed, and reportable variants (i.e., pathogenic variants, likely pathogenic variants, and variants of uncertain significance) in all the coding and adjacent intronic regions were analyzed. A heterozygous likely pathogenic variant in the *COL4A3* gene NM_000091.4: c.2083G>A (p.Gly695Arg) was revealed; however, no additional reportable variants in collagen IV genes (i.e., *COL4A3*, *COL4A4*, and *COL4A5*) were identified. She denies a history of vision or hearing problems. She had routine eye checkup and hearing test when she had chronic sinusitis several years before the kidney donation, and both were unremarkable. All of her children have neither vision nor hearing problems. They never had gross hematuria or kidney disease. The patient and her children were referred for genetic counseling.

Discussion

Living kidney donation is a process that requires a comprehensive predonation evaluation to assess the potential lifetime risk for medical complications and life-long postdonation follow-up to detect any complications early on. Results from epidemiologic studies related to the long-term risks for living donors especially the risk of developing CKD, ESKD, and death have varied from lower [9–12] to higher [3–5] when compared to the controlled general population.

Regarding the risk of developing ESKD in living donors, the 3 most common causes are diabetes, hypertension, and glomerulonephritis. While diabetes and hypertension remain the leading causes of the long-term risk of ESKD beyond 10 years after donation, glomerulonephritis is the most common during the first 10 years after donation [13]. This is likely due to previously undetected risks for glomerular diseases in living donor candidates during predonation evaluation.

Our patient is a young woman with a significant history of borderline GDM and preeclampsia at 6 and 4 years
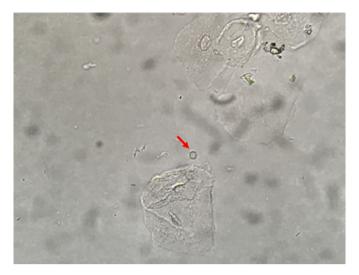

Fig. 2. Urine microscopy reveals 0–1 normal-appearing RBC/hpf (red arrow) and 5–10 squamous epithelial cells/hpf.

before the kidney donation, respectively. Although GDM increases the risk of type 2 diabetes especially within the first 5 years after pregnancy [14] and up to 50% over 20–30 years [15], her predonation laboratory showed no evidence of impaired fasting glucose.

Preeclampsia also increases the risk of long-term development of ESKD after kidney donation and may mask underlying kidney disease [7]. It accounts for gender-specific risk for CKD; on the other hand, female CKD patients are at risk for preeclampsia. A causal relationship between preeclampsia and CKD is bidirectional. Pathogenesis of CKD resulting from preeclampsia includes acute kidney injury, endothelial damage, and podocyte injury. However, kidney biopsy during pregnancy especially when blood pressure is elevated is very rare, and renal histological diagnosis of preeclamptic patients is lacking. On the contrary, the mechanism of preeclampsia in CKD patients involves underlying hypertension, impaired glycocalyx integrity, and alterations in the complement and renin-angiotensin-aldosterone systems [16].

The identification of a likely pathogenic heterozygous *COL4A3* variant through the genetic test in this patient is unexpected, although this variant is a known mutation causing Alport syndrome. Alport syndrome is a genetic disease that is characterized by progressive kidney failure, sensorineural hearing loss, and ocular abnormalities. It results from genetic variants of *COL4A3*, *COL4A4*, or *COL4A5* genes which express proteins for making components of type IV collagen. Up to 80% of Alport syndrome is caused by pathogenic variants in the *COL4A5*
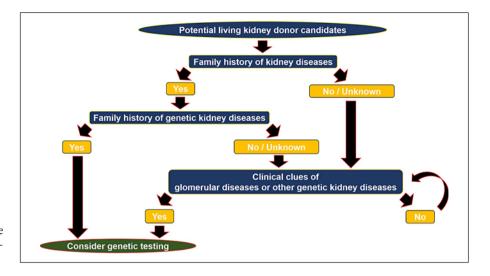
Fig. 3. A proposed algorithm to guide the decision to perform genetic testing in a living kidney donor candidate.

gene mutation and is inherited in an X-linked pattern. Around 15% of Alport syndrome results from 2 pathogenic/biallelic variants in the *COL4A3* and/or *COL4A4* genes and is therefore transmitted in an autosomal recessive pattern, and the remaining 5% are autosomal dominant (AD) Alport syndrome resulting from a single/heterozygous pathogenic variant in either *COL4A3* or *COL4A4* genes [17]. However, mutations of *COL4A3* are common in thin basement membrane disease (TBMD) and familial focal segmental glomerulosclerosis (FSGS) [18, 19], while *COL4A4* mutations are also common in familial FSGS [19]. The clinical phenotype of our patient with microscopic hematuria, proteinuria, absence of ocular and hearing abnormalities, and the genetic test findings is consistent with AD Alport syndrome which manifests with gradual progressive loss of kidney function without ocular abnormalities or sensorineural hearing loss [17, 20, 21].

Gross et al. [22] reported outcomes of 6 living kidney donors who were mothers of their children with ESKD from Alport syndrome. Five donors were X-linked chromosome carriers of Alport syndrome and one was an autosomal recessive carrier whose predonation kidney biopsy showed TBMD. All had microscopic hematuria, but none had proteinuria. During the average 6.7 years of follow-up, new-onset proteinuria and hypertension occurred in 33% and 50% of the donors, respectively. Compared to predonation, postdonation kidney function declined between 25 and 35% during the first 4 years in 3 donors and up to 60% after 14 years in 1 donor, but CrCl remained >40 mL/min in all donors. One recipient's allograft failed from chronic allograft dysfunction 10 years after transplantation. Another died from meningitis 6 years after transplant, and his donor had a postdonation biopsy which showed TBMD [22].

The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors recommends using urinary AER from a 24-h urine collection instead of urinary PER to assess proteinuria of living kidney donor candidates. Urinary AER <30 mg/24 h is an acceptable range for living kidney donation, whereas the candidacy of living kidney donor candidates whose urinary AER is between 30 and 100 mg/24 h should be individualized per patients' risk characteristics [8].

Retrospectively, although our patient initially had elevated urinary AER, her repeated measurements were below the recommended threshold [8]. She had intermittent microscopic hematuria with negative cystoscopy. Evaluation of her proteinuria and hematuria assessment was adequate, and there was no evidence to exclude her from kidney donation.

Worsening postdonation proteinuria with some degree of fluctuation in our patient is probably explained by increased intraglomerular pressure after unilateral nephrectomy which has resulted in glomerular hyperfiltration and hypertrophy. The long-term consequence of increased intraglomerular pressure can lead to podocyte injury and subsequently secondary FSGS [23].

Living kidney donation provides a survival advantage to the recipients and psychological benefit to donors. Oftentimes, it can even improve the donors' health in general such as when the living kidney donor candidates try to lose weight by predonation bariatric surgery and achieve blood pressure and/or glycemic control to meet acceptable criteria for donation.

Table 1. Proposed genetic tests for common genetic kidney diseases in living kidney donor candidates with clinical signs of glomerular diseases

Genes	Genetic kidney diseases	Inherited patterns	Clinical signs
PKD1	ADPKD	AD	Age-specific imaging criteria in a person with a family history of ADPKD
PKD2			
GANAB			
ALG9			
DNAJB11			
APOL1	*APOL1* risk alleles	AR	Sub-Saharan African ancestors with early-onset CKD and ESKD
COL4A5	X-linked Alport syndrome	XL	Progressive kidney failure Sensorineural hearing loss Ocular abnormalities
COL4A3 and/or *COL4A4*	Autosomal recessive Alport syndrome	AR	Microscopic hematuria Proteinuria Ocular involvement Sensorineural hearing loss
COL4A3 or *COL4A4*	Autosomal dominant Alport syndrome	AD	Microscopic hematuria, proteinuria without ocular or hearing abnormalities
COL4A3 or *COL4A4*	Thin basement membrane disease	AD	Microscopic hematuria Gross hematuria Flank pain AKI Proteinuria
CFH, MCP, CFI, or *C3*	Pregnancy-associated aHUS		History of microangiopathic hemolytic anemia, thrombocytopenia, AKI

AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; aHUS, atypical hemolytic uremic syndrome; AKI, acute kidney injury; *ALG9*, asparagine-linked glycosylation 9; *APOL1*, Apolipoprotein L1; AR, autosomal recessive; CFH, complement factor H; CFI, complement factor I; CKD, chronic kidney disease; *COL4A3*, collagen type IV alpha 3 chain; *COL4A4*; collagen type IV alpha 4 chain; *COL4A5*, collagen type IV alpha 5 chain; C3, complement component 3; *DNAJB11*, DnaJ homolog subfamily B member 11; ESKD, end-stage kidney disease; *GANAB*, glucosidase II alpha subunit; *MCP*, membrane cofactor protein; *PKD1*, polycystin 1, transient receptor potential channel interacting; *PKD2*, polycystin 2, transient receptor potential cation channel; XL, X-linked.

Similarly, kidney donation may open an opportunity, though rare, to earlier identify an underlying genetic kidney disease as in our patient. Although genetic testing is not currently standard practice for donor evaluations, the current focus of living donor evaluations is identifying potential donor candidates who are not at significant risk for genetic kidney or glomerular diseases. There is a wide spectrum of clinical manifestations in individuals with this mutation highlighting the potential role of modifier genes. This was first reported in family members with microscopic hematuria, mild proteinuria, variable degrees of kidney impairment, and heterozygous *COL4A3/CO-L4A4* mutations. Kidney biopsies revealed both thin basement membrane nephropathy and FSGS suggesting the presence of another genetic modifier responsible for FSGS and their resulting progressive kidney failure in some individuals. Given the potential for modifier genes, thin basement membrane nephropathy can no longer be assumed to be a benign condition with an excellent prognosis [24, 25]. Thinning of the glomerular basement membrane has been considered the mildest form of glomerular disease associated with type IV collagen defects resulting in isolated microscopic hematuria. However, Alport syndrome is the most severe form leading to ESKD

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and possibly concomitant hearing loss and ocular anomalies. The spectrum of this disease severity may be influenced by unknown modifier genes that predispose the mild disease to become a more severe form of the disease [24]. Therefore, appropriate genetic testing is suggested.

We propose that genetic testing, particularly when it can provide a definitive diagnosis of genetic kidney diseases, be utilized in 2 groups of living donor candidates. It should first be considered in patients whose family history of genetic kidney diseases is known or those without known family history but with symptoms or signs of genetic kidney disease or glomerular disease, for example, hematuria or proteinuria even if only to a small degree (Fig. 3).

According to the 2017 KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors, genetic diseases that are highlighted for evaluation in potential living kidney donors include the autosomal dominant polycystic kidney disease (ADPKD) and *APOL1* risk alleles [8]. Clinically, age-specific imaging criteria can be utilized to exclude the possibility of developing ADPKD in a person with a family history of ADPKD. Reliable genetic testing is another acceptable approach. For genetic testing for *APOL1* risk alleles, the test should be offered to donor candidates with sub-Saharan African ancestry [8]. In our case, signs of glomerular diseases such as hematuria, proteinuria, and pregnancy-related complications, for example, preeclampsia in a patient with normal kidney function, should lead to further investigation for genetic glomerular diseases which cause no or slow progressive decline in kidney function such as Alport syndrome and TBMD even when there is no family history of genetic kidney diseases. Genetic testing for collagen defects may be a noninvasive diagnostic tool which can help avoid biopsy in some cases. Pregnancy-associated atypical hemolytic uremic syndrome (aHUS) is a condition that occurs when thrombotic microangiopathy is triggered by pregnancy. Although it is a rare life-threatening disease, up to 60–70% are complicated by developing ESKD [26]. Moreover, 60% of patients with acute kidney injury from pregnancy-associated aHUS become ESKD within 1 year after the diagnosis of pregnancy-associated aHUS [27]. Unregulated alternative complement pathway causes diffuse endothelial damage, platelet activation, and subsequently thrombotic microangiopathy. Therefore, genetic tests for abnormal complement pathways should be offered to living donor candidates with a history of pregnancy-associated atypical hemolytic uremic syndrome. Genetic diseases that should be determined when clinically indicated are summarized in Table 1.

As in our patient, genetic testing can provide early identification of inherited previously unrecognized kidney diseases when native kidney biopsy is relatively contraindicated in an individual undergoing investigation for abnormal kidney function. Incorporating genetic professionals and counseling can inform patients, their families, and clinicians for future management. On the contrary, genetic testing, with positive results, may cause unintended consequences both psychological and socioeconomic. Therefore, utilizing any genetic testing particularly in living donor candidates requires patient education and plans for further post-test counseling.

In conclusion, our case demonstrates the potential utility of incorporating genetic testing as part of the living kidney donor evaluation in patients who may have risks for kidney diseases such as a prior history of hypertensive disorders of pregnancy, intermittent proteinuria, or microscopic hematuria, even with an unknown family history of kidney disease. Although additional and larger studies are warranted to elucidate the potential benefits and risks of genetic testing, a thorough preliving kidney donation evaluation may identify clues that guide additional workup and remains a critical responsibility of the transplant community.

Author Contributions

E.T. wrote the first draft, created figures, organized, and revised the manuscript. U.G.R., H.I., A.J.F., D.C.D., N.I., J.X., T.R.P., E.H., N.E., and K.K.Z. participated in writing and revising the manuscript. N.I., J.X., T.R.P., and E.H. interpreted the genetic tests.

Data Availability Statement

The genetic tests were reported for this case report, and there was no dataset generated from this case report.

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