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CFHR5 Nephropathy in a Greek-Cypriot Australian Family: Ancestry-Informed Precision Medicine

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INTRODUCTION

C3 glomerulopathy is caused by alternative complement pathway dysfunction, leading to abnormal complement activation, deposition, and degradation in the glomerulus.[1] This disorder manifests as predominant glomerular C3 fragment deposition on immunofluorescence, with absent or scant Ig deposition, and electron-dense deposits on electron microscopy.[1] C3 glomerulopathy is subsequently classified into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), based on ultrastructure. Light microscopy of C3GN is more varied compared to DDD, with mesangial matrix expansion, mesangial proliferation, glomerular basement membrane thickening, endocapillary proliferation, leukocyte infiltration, and crescent formation. Electron microscopy demonstrates subendothelial, subepithelial, and mesangial deposits that are less electron dense and less confluent compared with those in DDD. Patients with C3 glomerulopathy can present with persistent microscopic hematuria, synpharyngitic macroscopic hematuria, heavy proteinuria, and progressive renal impairment.[2]

The alternative complement pathway is a component of the innate immune system, the activation of which leads to pathogen opsonization and killing (Figure 1).[3] This process is initiated by the spontaneous hydrolysis of C3 to form C3(H_2O), which binds factor B to form C3 convertase. C3 convertase cleaves additional complement factors, which leads to phagocytosis (iC3b), chemotaxis (C5a), and cellular lysis (C5b9). Complement factor H (CFH) and CFH-related proteins regulate C3 convertase activity to prevent uncontrolled complement activation. The 5 CFH-related proteins (CFHR1−CFHR5) are located in the regulator of complement activation gene cluster on chromosome 1. Complement factor H−related protein 5 (CFHR5) is a 65-kDA protein with 9 short consensus repeats.[1] CFHR5 downregulates the alternative complement pathway by (i) competitively binding C3b to prevent C3 convertase activity and (ii) acting as a cofactor for the proteolytic inactivation of C3b by complement factor I.[4] *CFHR5* mutations involving intragenic duplications (exon 2−3), amino acid substitutions (p.Cys269Arg), and the creation of fusion proteins (CFHR1–CFHR5, CFHR2–CFHR5, CFHR5–CFHR2) have been identified as rare causes of heritable C3GN and DDD (Table 1).[5−10]

This case presents the first reported Australian family with genetically confirmed CFHR5 nephropathy and discusses the importance of making such a diagnosis, the challenges in its confirmation, and the implications for affected and at-risk family members.

Case Presentation

A 41-year-old sugarcane farmer was referred for further assessment of decreased renal function found incidentally during an admission for an unrelated acute medical condition. He denied any known history of gross hematuria, renal stones, recurrent urinary tract infections, or pyelonephritis. Past medical history was significant for hypertension, dyslipidemia, thalassemia minor, gastroesophageal reflux disease with esophagitis, and diverticular disease. His medications included

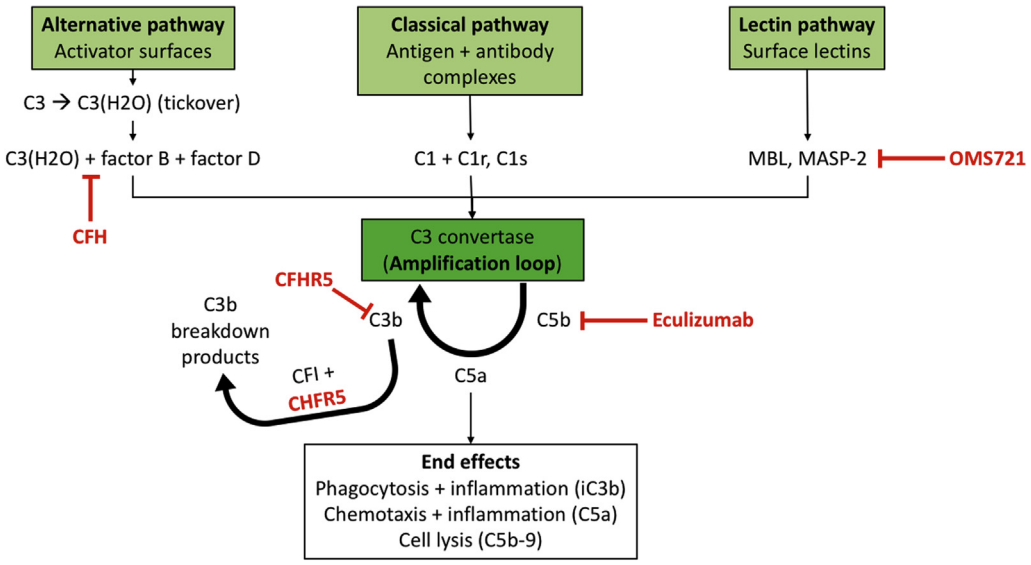

Figure 1. Complement pathway and targets of CFHR5 protein function. The classical and lectin pathways are typically activated during infections. In contrast, the alternative pathway exhibits baseline activation with spontaneous cleavage of C3 to C3(H_2O). Complement factor H (CFH)–related proteins downmodulate the alternative pathway by (i) binding C3b to prevent C3 convertase formation, and (ii) enhancing C3b inactivation by complement factor I (CFI). MASP-2, mannose-binding protein-associated serine protease 2; MBL, mannose-binding lectin.

escitalopram 20 mg once daily and esomeprazole 20 mg once daily.

A detailed family history confirmed that the patient's grandfather emigrated from Cyprus to Australia in the late 1920s; the family identified as Greek-Cypriot. The patient's father, his father's identical twin (the patient's paternal uncle), and his paternal aunt were affected by renal disease (Figure 2). Historic renal biopsy samples from affected family members were reported to show membranoproliferative glomerulonephritis with C3 (+++) deposition, but no Ig, C1q, or fibrin deposition. Electron microscopy demonstrated mesangial, subendothelial, and rare subepithelial electron-dense deposits. The patient's father and paternal uncle progressed to end-stage kidney disease and received kidney transplants in their 50s. The patient's father survived to 73 years of age, with the cause of death being colon cancer. In contrast, his paternal uncle was diagnosed with biopsy-proven disease recurrence at 76 years of age and is currently alive. The paternal aunt did not proceed to transplantation and died of breast cancer at 51 years of age. A summary of the clinical, histopathological, and genetic features of the family are provided in Table 2.

On examination, the patient's blood pressure was elevated at 150/100 mm Hg, and his heart rate was 70 bpm. His chest was clear to auscultation, and heart sounds were dual. His abdomen was soft and nontender, with no organomegaly. His jugular venous pressure was not elevated, and there was no pedal edema.

Full blood count demonstrated microcytic anemia (hemoglobin 12.2 g/dl, mean corpuscular volume 61 μm^3, red cell count 6.53 $\times$ 10^{12}/l, normal iron study results) consistent with thalassemia minor. White blood cell and platelet counts were normal at 10.9 $\times$ 10^9/l and 284 $\times$ 10^9/l, respectively. Serum biochemistry showed normal sodium (142 µmol/l), potassium (4.0 µmol/l), and albumin (45 g/l). Serum creatinine and urea were elevated to 180 µmol/l and 11.6 µmol/l, respectively. Estimated glomerular filtration rate (based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) was 39 ml/min per 1.73 m^2. Complement C3 and C4, antinuclear antibody, and anti–double-stranded DNA antibody were within normal limits. There was an active urinary sediment with >500 red blood cells per high-power field. Urine albumin:creatinine ratio was 24 mg/mmol creatinine, demonstrating subnephrotic proteinuria.

A renal biopsy was performed, and the sample included 13 glomeruli, of which 4 were globally sclerosed. There was diffuse mild mesangial hypercellularity (Figure 3a). No duplication of the basement membrane and no crescents were evident. There was moderate interstitial fibrosis and tubular atrophy, replacing 30% of the cortex. Immunofluorescence was 2 to 3+ positive for C3 deposition in the mesangium and peripheral capillary wall (Figure 3b). There was no Ig or C1q deposition. Electron microscopy showed electron-dense deposits that were subendothelial, mesangial, and subepithelial in location (Figure 3c).

The patient was subsequently referred to the statewide renal genetics clinic based on his prominent family history of C3 glomerulopathy. The clinical and histological phenotypes were evidential of an inherited

Table 1. Reported cases of CFHR5 nephropathy

Paper	*CFHR5* mutation	Age (yr)/gender	Ethnicity	Proteinuria	Hematuria	Serum C3/C4	Renal biopsy	ESKD[a]	Inheritance	Treatment
Gale *et al.* 2010,[6] Athanasiou *et al.* 2011[15]	Exon 2 + 3 duplication; heterozygous	30–80 Male and female	Greek-Cypriot	Mostly absent, <1.7 g/d if present	Recurrent synpharyngitic hematuria, microscopic hematuria	C3: normal C4: normal	C3GN	Yes	AD; 90% penetrance	Supportive care. Steroid pulse, oral daily prednisone, mycophenolate mofetil, reduced hematuria. No change in serum creatinine and proteinuria with steroid pulse + cyclophosphamide
Medjeral-Thomas *et al.* 2013[7]	Exon 2+3 duplication; heterozygous	46 Male	Caucasian	Absent	Recurrent synpharyngitic hematuria	C3: normal C4: normal	C3GN	Yes	AD	NR
Besbas *et al.* 2014[5]	p.Cys269Arg substitution; heterozygous	16 Female	Turkish	2.086 g/d	NR	C3: low C4: normal	C3GN	No	No family affected	No improvement with steroids (+/− pulse) + enalapril. Eculizumab improved serum creatinine but not proteinuria (3 g/d, 10 mo after diagnosis)
Xiao *et al.* 2016[10]	CFHR5–CFHR2 fusion protein; heterozygous	26 Female	European American	High-grade	Present	C3: normal C4: normal	C3GN	NR	AD	NR
Togarsimalemath *et al.* 2016[8]	CFHR1–CFHR5 fusion protein; heterozygous	8 Female	Indian	1.1 g/d	Microscopic hematuria	C3: low C4: normal	C3GN, DDD	Yes	AD	No improvement with steroid
Chen *et al.* 2014[9]	CFHR2–CFHR5 fusion protein; heterozygous	2 Female	German	Present	Present	C3: low C4: normal	DDD	Yes	AD	Plasma addition enhanced complement activation, plasmapheresis had no effect. Eculizumab reduced complement activation *in vitro*

AD, autosomal dominant; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; ESKD, end-stage kidney disease; NR, not reported.
[a]ESKD in any affected family members.

complement dysregulopathy. The ancestry indicated that a specific diagnosis of CFHR5 nephropathy was probable. Massively parallel sequencing, in a clinically accredited molecular genetics laboratory, did not identify any pathogenic variants in the genes in the complement dysregulopathy renal panel (*CFH, CFI, CD46, CFB, C3, MMACHC, THBD, CFHR5, ADAMTS13*). In light of the specific working diagnosis, Multiplex Ligation-dependent Probe Amplification was performed and identified a heterozygous duplication of exons 2 and 3 of *CFHR5*, previously associated with CFHR5 nephropathy.[6] The patient's paternal uncle was also seen in the renal genetics clinic, and further testing confirmed that he also had the *CFHR5* duplication of exons 2 and 3, confirming segregation of the mutation with the phenotype.

The patient was treated with perindopril 5 mg once daily to manage his hypertension and proteinuria. At his most recent follow-up, 30 months after his initial review in the renal clinic, his serum creatinine was 259 μmol/l, serum albumin was 42 g/l, and urine albumin:creatinine ratio was 34 mg/mmol creatinine. Because of the autosomal-dominant inheritance of CFHR5 nephropathy and the identified familial mutation, the patient was counseled about the implications for his relatives so that at-risk relatives could be referred to the genetics service to discuss presymptomatic genetic testing.

DISCUSSION

Here, we reported the first diagnosed case of CFHR5 nephropathy in a Greek-Cypriot Australian family. This diagnosis hinged on the awareness of several factors: (i) family medical history, (ii) ancestral ethnic information, and (iii) specific mutations associated with C3 dominant glomerulonephritis. The prevalence of this condition across both male and female relatives with 1 affected parent, as well as the inheritance of the condition by the male offspring of the affected men, strongly indicates an autosomal-dominant inheritance pattern (Figure 2). Knowledge of ancestral ethnicity led to the suspicion of CHFR5 nephropathy, which occurs in 1 per 4848 Greek-Cypriots,[11] with Australia having a resident diasporic population from Cyprus.[12] This demonstrated that familial ethnic information can provide invaluable evidence for the diagnosis of rare genetic conditions. It follows that family history should include both disease and ethnic information in modern multicultural societies. Importantly, diagnosis of CFHR5 nephropathy requires tests that can discern changes in copy number such as Multiplex Ligation-dependent Probe Amplification, TaqMan quantitative polymerase chain reaction, and genomic hybridization assays.[1] Methods used

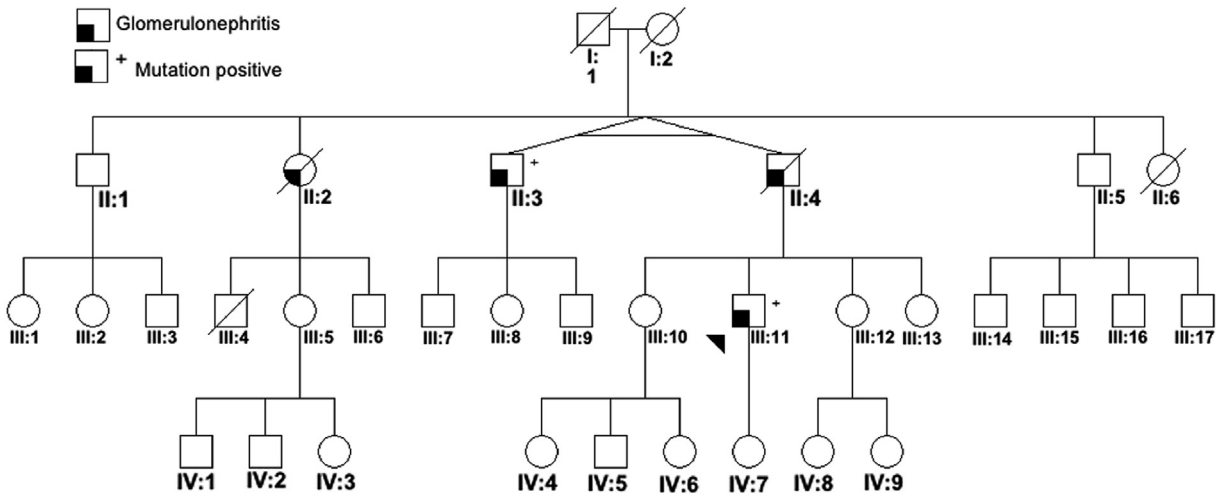

Figure 2. Pedigree of family.

primarily to detect point mutations, such as Sanger sequencing and massively parallel sequencing, are typically unable to detect copy number changes, as was observed in this case.[13] It follows that genetic testing should be tailored toward the suspected condition and its known specific genetic mechanisms. In addition, the use of a renal−histopathologic−genetic multidisciplinary approach was key for the diagnosis of this rare inherited kidney disease.

The CFHR5 nephropathy prevalent in Greek-Cypriot populations is caused by an intragenic duplication of exons 2 and 3 of the *CFHR5* gene.[6] The resultant mutant protein binds less effectively to surface-bound complement factors on glomerular membranes compared to wild-type CFHR5.[14] This leads to dysregulated complement activation, resulting in mesangioproliferative glomerulonephritis and glomerular C3 deposition. CFHR5 nephropathy is inherited in an autosomal-dominant manner with 90% penetrance.[6] In 91 patients across 16 families, CHFR5 nephropathy manifested with microscopic hematuria, synpharyngitic macroscopic hematuria, and proteinuria.[15] Microhematuria was observed in individuals of both genders under the age of 30 years. Of the men, 80% progressed to chronic kidney disease and end-stage kidney disease at age 51 to 85 years. In contrast, only

Table 2. Clinical, histopathological, and genetic features of affected members of family

Feature	II:2	II:3	II:4	III:11
Relationship	Aunt	Uncle (twin)	Father (twin)	Proband
Age at presentation (yr)	38	49	38	41
Clinical features	Unknown	Unknown	Hypertension	Hypertension
Proteinuria at diagnosis	4 g/d	Present	3 g/d	Subnephrotic
Hematuria at diagnosis	Microscopic	Microscopic	Macroscopic	Microscopic
CKD stage	Pre-ESKD	5	5	3B
Age at native kidney biopsy (yr)	First: 38 Second: 47	First: 49	First: 38 Second: 48	First: 41
Histopathology	MPGN type 1 FSGS	MPGN type 1 Lymphocytic interstitial infiltrate (patchy)	MPGN type 1 Lymphocytic interstitial infiltrate (patchy)	Mesangial expansion and hypercellularity Lymphocytic interstitial infiltrate (patchy)
Immunofluorescence	Unknown	Complement C3 positive (+) in capillary walls	Complement C3 positive	Complement C3 positive (++/+++) in mesangium + capillary loops
Ultrastructure	Dense deposits: subendothelial mesangial epimembranous (rare)	Dense deposits: subendothelial mesangial epimembranous (rare)	Dense deposits: subendothelial mesangial epimembranous (rare)	Dense deposits: subendothelial mesangial subepithelial
Genotype	Untested	*CFHR5* Exon 2 + 3 duplication; heterozygous	Untested	*CFHR5* Exon 2 + 3 duplication; heterozygous
Age at transplantation	—	55	51	—
Graft recurrence	N/A	Positive	Negative	N/A
Years posttransplantation at recurrence	N/A	21	N/A	N/A
Age at death	51	—	73	—
Cause of death	Breast cancer	N/A	Colon cancer	N/A

CKD, chronic kidney disease; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; MPGN, mesangioproliferative glomerulonephritis; N/A, not applicable.

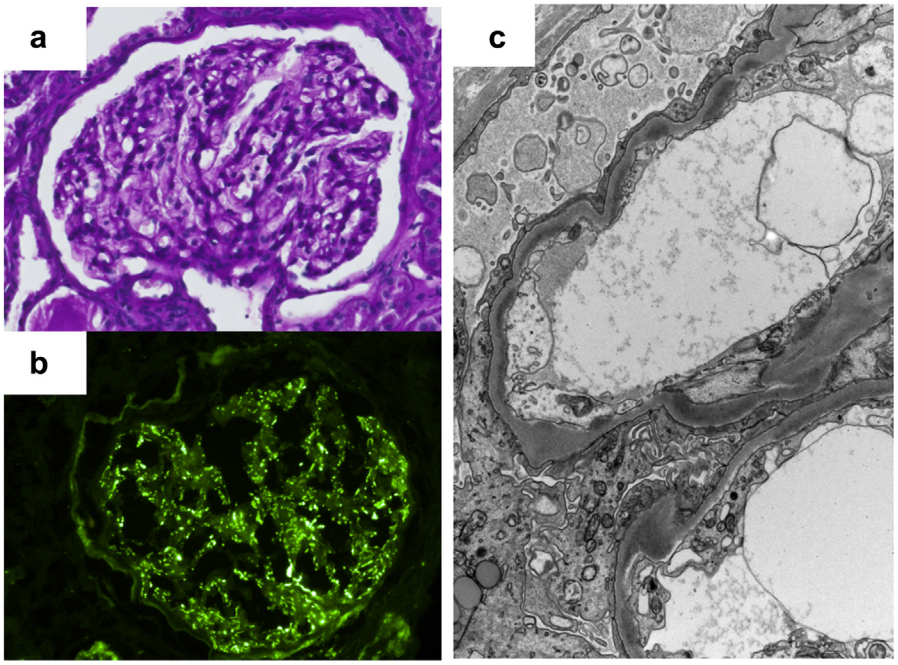

Figure 3. Renal biopsy findings. (a) Light microscopy showed diffuse mesangial hypercellularity. (b) C3-dominant immunofluorescence was observed. (c) Subepithelial and subendothelial deposits were observed on electron microscopy.

20% of women progressed to chronic kidney disease at 88 years of age, with the majority exhibiting only microhematuria throughout life. Vernon *et al*. reported the first case of CFHR5 nephropathy recurrence in a transplant kidney, demonstrating that donor renal-derived CFHR5 protein was insufficient to prevent disease pathogenesis.[16]

Diagnosis of the index case has facilitated potential clinical screening and predictive genetic testing for the patient's at-risk relatives. Such screening provides information regarding renal disease risk, potentially averts renal biopsy in newly presenting family members, and informs surveillance for chronic kidney disease and transplant recurrence. This is particularly relevant for this variant of CFHR5 nephropathy, for which the clinical course is well described across more than 16 other families.[15] Identification of unaffected family members may enable the recognition of potential living kidney donors. However, genetic testing for presenting unrelated probands may not always lead to a clear genetic diagnosis. Novel pathogenic *CFHR5* mutations have been identified as recently as 2016,[8,10] with the causation of renal disease by such novel *CFHR5* variants potentially requiring functional validation. Current American College of Medical Genetics and Genomics (ACMG) variant classification criteria may not sufficiently clarify the pathogenicity of such rare and unreported variants in some genes, although the potential for gene- or disease-specific adaptation may extend to genetic complement regulatory disorders in the future.[17,18]

Moreover, a genetic diagnosis of CFHR5 nephropathy provides limited information about the development and severity of subsequent renal disease. Among individuals with a causative *CFHR5* mutation, 10% do not express clinical features of CFHR5 nephropathy.[15] A single nucleotide polymorphism, miRSNP 1936T in the *heparin binding epidermal growth factor* (*HBEGF)* gene was associated with increased progression to chronic renal failure in 78 patients with CFHR5 nephropathy.[19] However, there is currently no clear method of predicting which individuals are at greater risk for progressing to end-stage renal disease.

Anticomplement therapies such as eculizumab have been proposed as a specific treatment for C3 glomerulopathy. In several case studies and small trials, eculizumab improved proteinuria, serum creatinine, and renal biopsy findings.[20–25] OMS721, a novel antibody against mannan binding lectin serine peptidase 2 (MASP-2), a lectin complement pathway effector, is currently undergoing phase II clinical trials for the treatment of IgA nephropathy, lupus nephritis, membranous nephropathy, and C3 glomerulopathy (NCT02682407).[26,27] Early results from phase 2 clinical trials showed that OMS721 improved serum creatinine in complement-mediated thrombotic microangiopathy.[26] In a retrospective cohort analysis of 60 patients with C3GN, steroid and mycophenolate mofetil combinations improved renal survival compared with other immunosuppressive regimens and untreated patients.[28] None of these treatments have been specifically applied to patients with CFHR5 nephropathy. However, the rapid development and

Table 3. Key teaching points of this case

1. Family medical history and ethnic history provide invaluable clues for the diagnosis of rare genetic renal conditions
2. Internal duplications require tests that can measure changes in copy number, such as Multiplex Ligation-dependent Probe Amplification (MLPA), TaqMan quantitative polymerase chain reaction, and genomic hybridization assays
3. Renal–histopathologic–genetic multidisciplinary team approach is critical for diagnosing rare familial renal conditions
4. Genetic testing for asymptomatic family members can provide information regarding their renal risk, identify potential living donors, and prevent unnecessary renal biopsies
5. Consider testing for CFHR5 nephropathy in familial cases of hematuria, chronic kidney disease, and C3 glomerulopathy.

characterization of treatment modalities for C3 glomerulopathy makes this a candidate therapeutic space for significant change in the next few years.

Notably, CFHR5 nephropathy has been identified in single families of Caucasian (exon 2 and 3 duplication), European American (CFHR5–CFHR2 fusion), Indian (CFHR1–CFHR5 fusion), German (CFHR2–CFHR5 fusion), and Turkish (p.Cys269Arg) descent.[5,7–10] Interestingly, CFHR5 nephropathy secondary to fusion proteins tended to present with high-grade proteinuria and facial edema in contrast to CFHR5 nephropathy secondary to intragenic duplications, which predominantly presented with hematuria and/or proteinuria. Together, these findings highlight the value of maintaining suspicion of CFHR5 nephropathy in non-Cypriot patients presenting with nephrotic syndrome.

This case study reports the first diagnosed and confirmed case of CHFR5 nephropathy in an Australian Greek-Cypriot family (Table 3). It highlights the value of obtaining detailed family medical and ethnic history for the diagnosis of rare genetic diseases in everyday nephrology clinical practice. This case also highlights the benefits of a multidisciplinary team approach, along with genetic testing, for identifying and confirming a genetic renal diagnosis.

DISCLOSURE

All the authors declared no competing interests.

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