CASE REPORT

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Rare Combination of Phenotypes of Karyomegalic Interstitial Nephritis and Autosomal Recessive Polycystic Kidney Disease in an Omani Child

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ABSTRACT

Autosomal recessive polycystic kidney disease is one of the most prevalent inherited cystic kidney diseases in infants and children, common in highly consanguineous societies such as Oman. Karyomegalic interstitial nephritis is a rare cause of hereditary chronic kidney disease presenting with progressive renal impairment and hematoproteinuria. We report a rare case of concurrent karyomegalic interstitial nephritis and autosomal recessive polycystic kidney disease in a two-year-old Omani boy. He presented with failure to thrive, developmental delay, hypotonia, recurrent urinary tract infection, proteinuria, and hematuria. Abdominal ultrasonography showed bilaterally enlarged kidneys with distorted parenchyma, loss of corticomedullary differentiation, and multiple small cysts in addition to an enlarged liver. Whole exome sequencing of the patient DNA revealed a homozygous likely-pathogenic variant in *FAN1*(NM_014967.4:c.2854C>T, p.R952*) segregating from each parent, in addition to a homozygous missense variantin *polycystic kidney and hepatic disease 1* (NM_138694.3:c.406A>G, p.T136A). Familial carrier testing in parents and a similarly affected brother revealed segregation of the *polycystic kidney and hepatic disease 1* variant in a homozygous state in the father and brother, and in a heterozygous state in the mother. This case demonstrates two rare genetic causes of chronic kidney disease within a highly consanguineous family, mimicking an autosomal dominant pattern of inheritance of cystic kidney disease. We recommend whole exome sequencing as a routine molecular diagnostic tool for children with cystic kidney disease, especially those from consanguineous families.

Karyomegalic interstitial nephritis (KIN) is a rare inherited kidney disease that is frequently present in the second decade of life with hematoproteinuria, recurring respiratory infections, and progressive chronic kidney disease (CKD), leading to end-stage kidney disease before 50 years of age.[1] There is no obvious sex or ethnic bias. Renal biopsy commonly reveals karyomegalic cells, which can also be found in the liver, lungs, skin, gastrointestinal tract, heart, and brain. KIN is associated with chronic tubulointerstitial nephritis with expansion of tubular nuclei on electron microscopy.[2]

Autosomal recessive polycystic kidney disease (ARPKD) is one of the most prevalent inherited polycystic kidney diseases (PKDs) in infants and children with an estimated incidence of 1:20 000 to 1:40 000 live births, and predictably higher in isolated or inbred populations.[3–5]

Here, we present the case of a pediatric patient with a homozygous *polycystic kidney and hepatic disease 1 (PKHD1)* variant causing ARPKD, and a concurrent homozygous *Fanconi anemia-associated nuclease 1 (FAN1)* variant causing KIN. To our knowledge, this is the first report of these two rare causes of chronic kidney disease found in a single patient. Due to multiple consanguinity, the *PKHD1*

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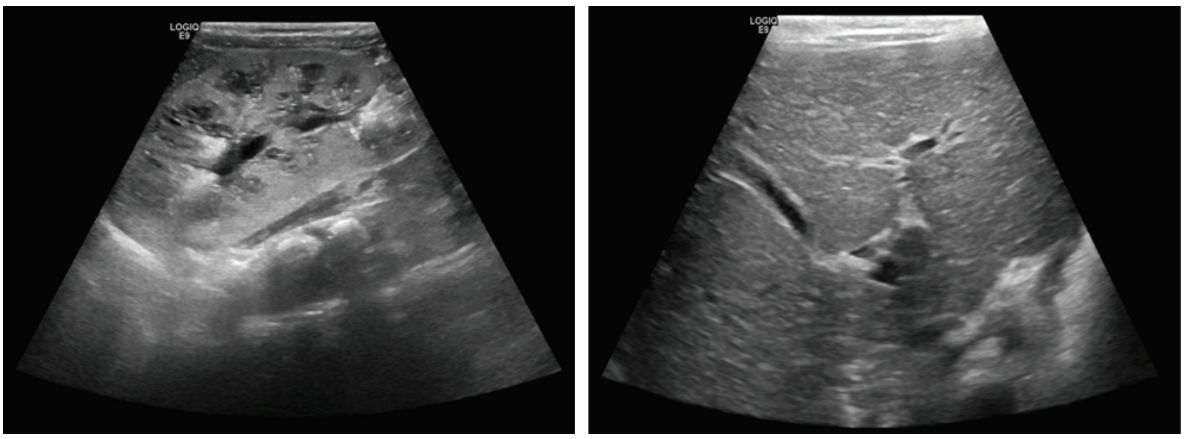

Figure 1: The abdominal ultrasound results of the proband. Kidney ultrasonography showing enlarged kidneys (right kidney 8.2 cm in length) (left panel). Liver ultrasonography showing mild dilatation of intrahepatic ducts (duct diameter 3 mm) but no cystic dilatation of the biliary tree (right panel).

homozygous allele was also present in the proband's father, mimicking an autosomal dominant pattern of inheritance of PKD.

CASE REPORT

A four-month-old boy was referred to our tertiary referral hospital. He was born at 35 weeks gestation weighing 1.92 kg. Antenatally, he had intrauterine growth restriction and large echogenic kidneys with oligohydramnios.

An abdominal ultrasound scan showed bilaterally enlarged kidneys (right = 8.2 cm, left = 7.2 cm) with an increase in cortical echogenicity, hypoechoic pyramids with cystic changes, and echogenic calcific areas [Figure 1]. He was noted to have hypertension, which was treated with propranolol. His kidney function was initially normal but gradually deteriorated over time reaching CKD stage III by three years of age. Urine dipsticks showed proteinuria and hematuria. The urine protein creatinine ratio was 99.7 mg/mmol (reference range < 20 mg/mmol). He had an enlarged liver (3 cm below the costal margin), but liver function tests showed normal results.

The patient's parents were first cousins, and his father had PKD from childhood, which had now advanced to CKD stage II. An uncle also had PKD. The patient's younger brother when six months old had also presented with failure to thrive, anemia, and hypertension. His abdomen ultrasound scan showed soft, palpable bilateral enlarged kidneys with multiple cysts and an enlarged liver (4 cm below the costal margin).

Whole exome sequencing (WES) in the proband (our patient) identified a homozygous likely pathogenic variant in *FAN1* (NM_014967.4: c.2854C>T, p.R952*) in addition to a homozygous nonsense variant of uncertain significance in *PKHD1* (NM_138694.3: c.406A>G, p.T136A) [Figure 2]. Both variants were confirmed with bi-directional Sanger sequencing, and family segregation analysis was performed. Familial carrier testing in parents and the affected sibling confirmed segregation of the *PKHD1* variant in a homozygous state in the patient's father and brother and in a heterozygous state in the mother. It also confirmed that both his parents and brother were heterozygous

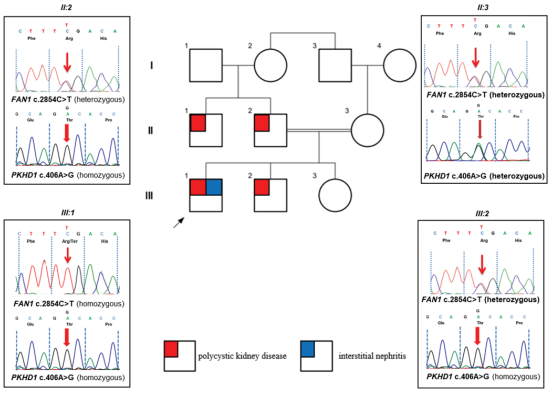

Figure 2: Pedigree diagram and Sanger sequencing chromatograms. A heterozygous nonsense *FAN1* c.2854C>T, p.(R952*) change in father (II:2) and a homozygous *FAN1* c.2854C>T, p.(R952*) in the affected proband (III:1) seen, which may have led to interstitial nephritis. Familial segregation of the *PKHD1* missense variant c.406A>G, p.T136A, which is homozygous in father (II:2) and proband (III:1) and his sibling (III:2), all with polycystic kidney disease phenotypes.

carriers of the *FAN1* (NM_014967.4:c.2854C>T, p.R952*) variant.

A diagnosis of ARPKD secondary to the *PKHD1* pathogenic variant with concurrent KIN secondary to a pathogenic *FAN1* variant was made. The proband, father, and sibling are currently being managed for progressive CKD.

DISCUSSION

KIN is a rare genetic renal disease that has an autosomal recessive mode of inheritance, where an association between mutations in the *FAN1* gene and KIN was recently made.[6] *FAN1* is located on chromosome 15 and encodes a DNA endo- and exonuclease, which acts to repair DNA, a key step in the Fanconi anemia DNA damage response pathway.[6]

Our patient was found to be homozygous for a nonsense variant in *FAN1* which produced a premature stop codon at position 2856. This variant has been reported in the Human Genome Mutation Database (HGMD ID: CM158612) and was previously reported as a germline mutation causing hereditary colorectal cancer.[7] The same variant had previously been submitted to the ClinVar database (ID: 24413339) as a germline mutation associated with KIN.[8] There is no specific treatment for KIN at present but genetic counseling for affected families should be considered. KIN has been reported recently in conjugation with leukocyte chemotactic factor 2 amyloidosis, the third most common cause of amyloid nephropathy presenting with CKD.[9]

The classic clinical presentation of ARPKD is characterized by bilaterally enlarged kidneys with multiple cysts mostly developing in distal tubules and collecting ducts. Congenital hepatic fibrosis due to ductal plate malformation is another typical feature of ARPKD.[4]

In this consanguineous family, the pattern of PKD that presented in the adolescence of the father and uncle mimicked autosomal dominant PKD, highlighting the importance of obtaining a molecular diagnosis of cystic kidney diseases due to phenotypic overlaps. A 1998 study reported 13 members of a consanguineous family with different features of Alport syndrome. They carried homozygous or compound heterozygous splicing variants in *COL4A3*, creating a pseudodominant transmission pattern.[10]

In another study, two inherited kidney disorders were reported in a patient with both ADPKD and Alport syndrome.[11] The coexistence of such severe, inherited kidney disorders is very rare, illustrating the significance of considering WES as a method of choice for genetic diagnosis in the setting of a positive family history for a hereditary disorder.

CONCLUSION

We have presented a case in which two rare genetic causes of CKD (KIN and ARPKD) were present within a highly consanguineous Omani family. This case highlighted the critical level of a homozygosity underlying inherited kidney disease in the Omani population and the importance of undertaking precision molecular diagnosis to guide treatment. Genetic counseling is also necessary for such families. We recommend WES as a routine genetic diagnostic tool for children with CKD, especially in consanguineous families.

Disclosure

The authors declare no conflicts of interest. Informed consent was obtained from the patient's father. The case was referred for WES through the MOH genetic referral committee (Royal Hospital, Oman). John A. Sayer is funded by Kidney Research UK and the Northern Counties Kidney Research Fund.

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