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

Intisar Al Alawi[1, 2*], MaryamAlShehhi[2,3], Mohammed S Al Riyami[5], Naifain Al Kalbani[4,5], Aliya Al Hosni[2], Ashwaq Al Mimani[2], Issa Al Salmi[4,6] and John A Sayer[1,7,8]

[1]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, UK

[2]National Genetic Centre, Royal Hospital, Muscat, Oman

[3]Clinical Genetics Unit, Department of Child Health, Royal Hospital, Muscat, Oman

[4]Internal Medicine Residency Training Program, Oman Medical Specialty Board, Muscat, Oman

[5]Pediatric Nephrology Unit, Department of Child Health, Royal Hospital, Muscat, Oman

[6]Renal Medicine Department, Royal Hospital, Muscat, Oman

[7]Renal Services, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK

[8]Newcastle Biomedical Research Centre, Newcastle Upon Tyne, UK

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***Corresponding author:**intisarhs2012@gmail.com

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Abstract

Autosomal recessive polycystic kidney disease (ARPKD) is one of the most prevalent inherited cystic kidney diseases in infants and children, common in highly consanguineous societies such as in Oman. Karyomegalic interstitial nephritis (KIN) is a rare cause of hereditary chronic kidney disease (CKD) presenting with progressive renal impairment and hematoproteinuria. We report a rare case of concurrent KIN and ARPKD in a two-year-old boy from a highly consanguineous Omani family. He presented with failure to thrive, developmental delay, hypotonia and recurrent urinary tract infection, proteinuria, and hematuria. Abdominal ultrasonography showed bilateral enlarged kidneys with distorted parenchyma, loss of corticomedullary differentiation, and multiple small cysts in addition to an enlarged liver. Whole exome sequencing (WES)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*PKHD1*(NM_138694.3:c.406A>G, p.T136A). Familial carrier testing in parents and a similarly affected brother revealed segregation of the *PKHD1* 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 CKD within a highly consanguineous family, mimicking an autosomal dominant pattern of inheritance of cystic kidney disease. We recommend WES as a routine molecular diagnostic tool for children with cystic kidney disease, especially those from consanguineous families.

Keywords: Autosomal Recessive Polycystic Kidney Disease; Karyomegalic Interstitial Nephritis; Chronic Kidney Disease; Whole Exome Sequencing; Oman

Introduction

KIN is a rare inherited kidney disease that frequently present in the second decade of life with hematoproteinuria, recurring respiratory infections, and progressive 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, but these can also be found in the liver, lungs, skin, gastrointestinal tract, heart, and brain. KIN is associated with a chronic tubulointerstitial nephritis with expansion of tubular nuclei on electron microscopy.[2]

ARPKD is one of the most prevalent inherited polycystic kidney diseases 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 autosomal recessive polycystic kidney disease (ARPKD), and a concurrent homozygous *Fanconi anaemia-associated nuclease 1* (*FAN1*) variant causing karyomegalic interstitial nephritis (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* homozygous allele was also present in the proband's father, mimicking an autosomal dominant pattern of inheritance of polycystic kidney disease.

Case Report

A 4-month-oldboy 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 bilateral 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 3 years of age. Urine dipsticks showed proteinuria and hematuria. 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 polycystic kidney disease from childhood, which had now advanced to CKD stage II. An uncle also had polycystic kidney disease. The patient's younger brother had also presented when six months old 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 (VUS) 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 his brother were heterozygous carriers of the *FAN1* (NM_014967.4:c.2854C>T, p.R952*) variant.

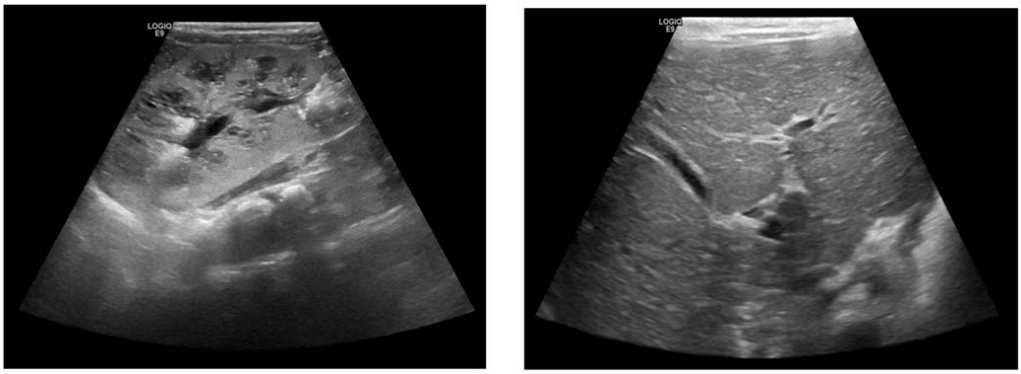

Figure 1: Ultrasound abdomen results of the proband. Kidney ultrasonography showing enlarged kidneys (right kidney 8.2 cm in length) (left panel). Liver ultrasonography shows mild dilatation of intrahepatic ducts (duct diameter 3 mm) but no cystic dilatation of biliary tree (right panel).

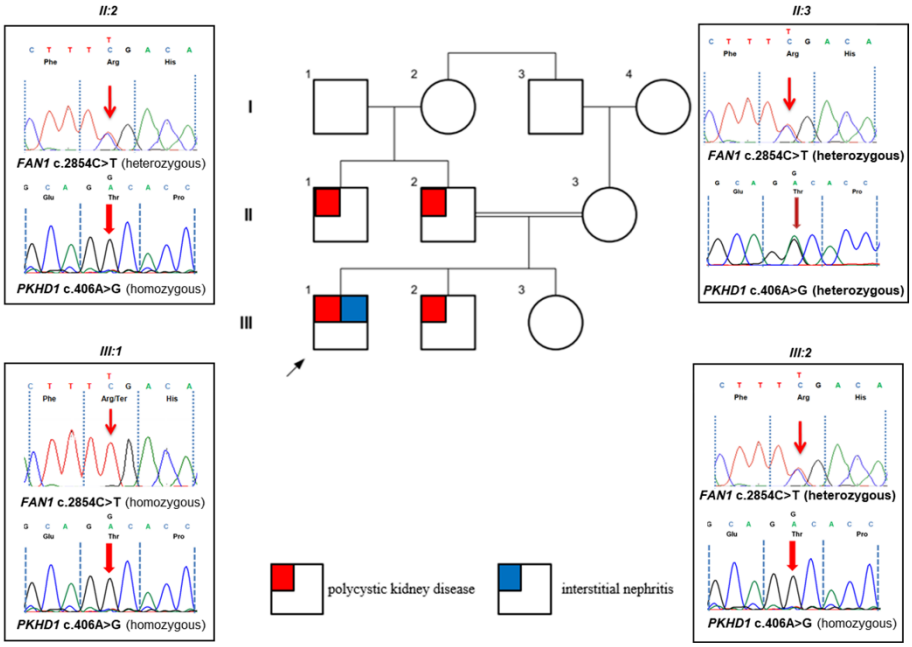

Figure 2: Pedigree diagram and Sanger sequencing chromatograms. A heterozygous nonsense *FAN1* c.2854C>T, p.(R952*) change in father (II:2) and a homozygous *FAN1* c.2854C>T, p.(R952*) in the affected proband (III:1) seen, which may have led to interstitial nephritis. Familial segregation of the *PKHD1* 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.

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]

Here, our patient (the proband) 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 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 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 (ALECT2), the third most common cause of amyloid nephropathy presenting with CKD.[9]

The classic clinical presentation of ARPKD is characterized by bilateral 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 polycystic kidney disease that presented in the adolescence of the father and uncle mimicked autosomal dominant polycystic kidney disease, 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 positive family history for a hereditary disorder.

Conclusion

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

Data availability

Additional data pertaining to this study can be provided upon request.

Disclosure

The authors declare no conflicts of interest. The case was referred for WES through 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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