New PAX2 Mutation Associated with Polycystic Kidney Disease: A Case Report

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ABSTRACT

BACKGROUND: Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of end stage renal disease in children. Diagnosis by genetic testing has proven challenging due to its genetic and phenotypic heterogeneity, as well as incomplete penetrance. We report a case on a 16-months old female with a history of renal cysts and a *PAX2* mutation.

CASE PRESENTATION: The patient presented with a prenatal diagnosis of Potter sequence and a postnatal diagnosis of renal cysts. An ultrasound at 20 weeks gestation revealed right renal agenesis and possible left renal dysplasia. Post natal genetic analyses identified a novel mutation in *PAX2*.

CONCLUSION: Cystic kidney disease is often underdiagnosed due to its variable expressivity and wide range of clinical manifestations; *PAX2* genetic screening should be considered for all patients with CAKUT.

KEYWORDS: PAX2, congenital anomalies of the kidney and urinary tract, CAKUT, children, papillorenal syndrome, case report

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Background

Congenital renal and urinary tract abnormalities (CAKUT) are the most common cause of pediatric end stage renal disease (ESRD) and affect 1 to 5 out of 1000 newborns.[1-3] Almost 30% of these are characterized by renal cysts and ciliopathies, and mutations in proteins essential for proper formation of renal tubules. Conditions arising as a result include autosomal dominant (ADPKD) and recessive (ARPKD) polycystic kidney diseases (caused by mutations in polycystin 1 and 2, and fibrocystin/polyductin and DAZ interacting zinc finger protein 1, respectively), nephronophthisis (caused by mutations in nephrocystin 1-2-4 and invertin) and medullary cystic disease (caused by mutations in uromodulin and mucin).[4-6]

Paired box 2 gene (*PAX2*), located on chromosome 10q24, encodes transcription factors that assist in the development of the eyes, ears, genital tract, midbrain, and kidneys.[7] For the renal system, in particular, it governs the assembly of the mesonephric duct and ureteric bud.[8] To date, mutations in *PAX2* have chiefly been associated with optic coloboma or renal coloboma syndrome (RCS) or papillorenal syndrome, afflicting a total of 230 individuals worldwide.[5,6,9,10] More than 3-quarters (77%) of patients have experienced optic dysplasia and/or the development of colobomas, the vast majority (92%) have presented with renal dysfunction to varying degrees and only 7% have had hearing loss.[11] In a report by Negrisolo et al, investigators noted that *PAX2* mutations may be associated only with renal manifestations due to the role of this gene in nephrogenesis. They propose that a variant in the *PAX2* sequence could cause renal malformations without impacting vision, although more evidence is needed to substantiate this claim.[10] Hildebrandt et al also have reported in non CAKUT patients, the close relationship between PAX2 and different expressions of Steroid Resistant Nephrotic Syndrome-SRNS which can be expressed as FSGS.[12]

In this report, we present a patient with a prenatal diagnosis of Potter sequence and a postnatal diagnosis of renal cysts, similar to those observed in ARPKD. Genetic testing identified a mutation in the *PAX2* gene that has not previously been reported in the literature.

Case Presentation

A 19-month old female is in follow up at our hospital with a history of renal cysts. She was delivered at 38 weeks gestation and her parents had no related kidney dysfunction or consanguinity to each other. Results from maternal laboratory testing for toxoplasma, rubella, cytomegalovirus and herpes were negative—simply showing a normal karyotype in the amniotic fluid, and a fetal echocardiogram indicated no structural abnormalities. An ultrasound at 20 weeks of gestation detected oligohydramnios, right renal agenesis, and

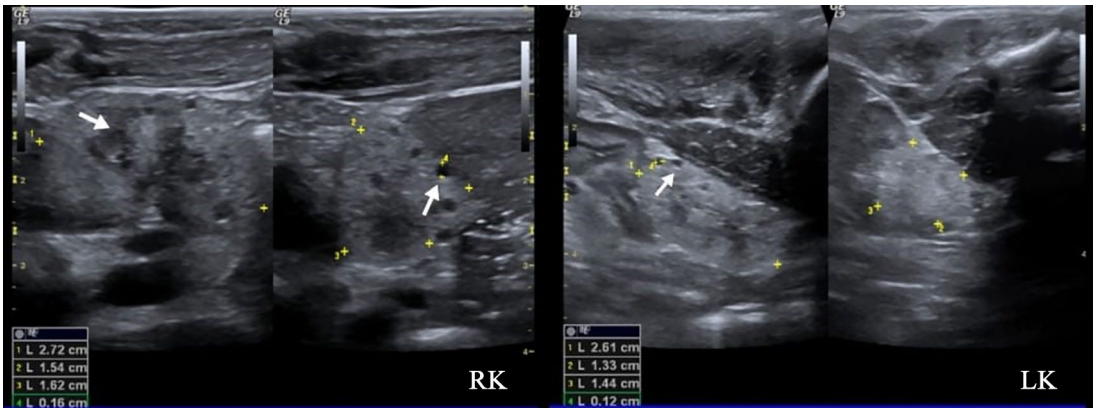

Figure 1. Renal ultrasound showing with multiple cysts.
Abbreviations: RK: Right kidney; LK: Left kidney.

possible left renal dysplasia; therefore we suspected Potter sequence.

The patient's birth weight was 2.859 g, height was 49 cm, and the score for appearance, pulse, grimace, activity, and respiration was 9-9. At one day old, a renal ultrasound revealed increased renal echogenicity with cortical peripheral millimeter cysts, a right kidney size of 34 × 13 × 18 mm and a left kidney size of 37 × 13 × 18 mm, so a possible diagnosis of ARPKD was done (Figure 1). Laboratory tests at 2 days of age showed a serum creatinine level of 1.31 mg/dL with a glomerular filtration rate (GFR) of 16.16 mL/min/1.73 m^2. While in the neonatal intensive care unit (NICU), she had hypertension that was adequately managed with angiotensin II receptor antagonists, and electrolytic disorder (hyperkalemia) that was controlled without compromising urinary output. Upon discharge from the NICU, her serum creatinine level progressively rose to 2.7 mg/dL (TFG 10 mL/min/1.73 m^2).

The patient was followed up by the pediatric nephrology department, requiring treatment with vitamin D, ferrous sulfate, folic acid, and oral bicarbonate due to metabolic problems. At 6 months of age, whole exome sequencing (WES) was performed in triplicate, which identified a *de novo* c.94C > T variation in *PAX2* (p.Pro32Ser). This variant was not found in either of the parents. Sanger sequencing confirmed that this variant has not been reported previously in population databases or current medical literature. Bioinformatic analysis of the variant was performed; SIFT and FATHMM classified the variant as "damaging," while MutationTaster classified it as "causing disease" and Polyphen as "possibly damaging" (score 1.0). Currently, it is classified as "probably pathogenic" according to the guidelines by the American College of Medical Genetics and Genomics (PM1, PM2, PP2, PP3).[13]

Additional examinations were performed. Results from vision and hearing tests were normal; psychomotor development was adequate. An olichocephaly, prominent forehead, micrognathia, and hands with a bilateral fifth finger clinodactyly were recorded. Anthropometric measurements at 1 year of age were a weight of 8 kg, height of 69 cm, and head circumference of 44.5 cm (W/A <1 and <2 SD, L/W <3 SD, HC/A <1 and 0 SD). The last laboratory test at 19 months showed a serum creatinine level of 1.44 mg/dL (GFR 21 mL/min/1.73 m^2). No anomalies in other organs were found.

Discussion

CAKUT is the most common cause of CKD and ESRD in children. In this case study, our patient has at present a CKD stage IV, GFR of 21 mL/min/1.73 m^2. As a result of her prenatal history of oligohydramnios, radiological findings, and the potential need of a kidney transplant, an underlying genetic cause was suspected. Thus, genetic testing was requested and a mutation in *PAX2* was discovered.

WES has become an important clinical test for defining both recognized and previously undefined genes and potential variant susceptibilities to establish molecular diagnoses for birth defects. Also, can be used to identify molecular etiology (SNVs, CNVs) in a subset of individuals with CAKUT or novel CAKUT genes. Nearly 5% of individuals with CAKUT have pathogenic SNVs in known key genes that can be uncovered by WES. In addition, 6.5% of these patients have pathogenic CNVs that were extracted from WES data.[14] In this case, WES was carried out on a massive sequencing platform with Ion ProtonTM technology. Library preparation was performed with Ion AmpliSeq Exome technology (Life Technologies, Carlsbad, CA, USA), which captures >97% of consensus coding sequences (>19 000 genes and >198 000 exons) and terminal intronic regions (20 base pairs). Only variants in the coding and flanking intronic regions with a Minor Allele Frequency (MAF) of 1.5% were evaluated. The MAFs were identified using the following databases: 1000 Genomes, dbSNP, the Exome Variant Server (ESV or inhouse) and the Exome Aggregation Consortium (ExAc).

Papillorenal syndrome, a type of CAKUT, is primarily identified by the presence of renal hypoplasia–dysplasia, but it can also include a multicystic dysplastic kidney, oligomeganephronia, vesicoureteral reflux, ureteropelvic junction obstruction, horseshoe kidney, pyeloureteral duplication, abnormal renal rotation, medullary sponge kidney, and nephrolithiasis. Multicystic renal dysplasia has also been described in 6% to

10% of patients, and ours presented with multiple cortical cysts (1 mm in diameter) along the periphery of her both kidneys.[7] Multicystic renal dysplasia was ruled out properly, because it represents a Solitary Functioning Kidney (SFK) demonstrated by nuclear medicine, and the patient has both kidneys in function. In regard of multiple cysts observed in both kidneys in this case, the appearance of them could be as seen in Glomerulocystic Kidney Disease (GCKD), which consists of histopathological disorders with pathology Bowman space dilatation in the absence of tubular cysts. Cystic glomeruli are evident in different clinical scenarios, one of them is in dysplastic kidneys or urinary tract obstruction. Glomerular cysts can be distributed from the subcapsular zone to the inner cortex with an ultrasound pattern which involves increased echogenicity of the renal cortex with minute cysts, smaller than those evident in ADPKD. Up to the present we couldn't get a histopathologic tissue in order to support the presence of glomerular cysts. The genetic exam – WES, also ruled out an ARPKD. She remains in observation with renal ultrasound twice a year, looking for the distribution of the cysts in the follow up.

Histologically pathogenic variants in *PAX2* have been associated with focal segmental glomerulosclerosis as we described previously[12]; however, our patient did not have proteinuria neither hematuria and she didn´t go to renal biopsy.

Numerous mutations, including insertions, deletions, nucleotide substitutions, and a single incident of a *de novo* translocation have been reported for *PAX2*.[15] Curiously though, there is no consistent correlation between any of these and a person's phenotype, as individuals with identical mutations have presented with a diversity of clinical manifestations ranging from renal hypodysplasia, sensorineural hearing loss, seizures, Arnold–Chiari malformation, fourth metatarsal microsomia, ovarian teratoma, ventricular septal defects and including healthy newborns.[1,8,11,16-18] Moreover, there is no clear evidence to suggest that the location of a pathogenic variant (paired domain, octapeptide domain, partial homeodomain, or transactivation domain) or the type of pathogenic variant (nonsense variant, variant with a sense range, or deletion) is a constant predictor of one's phenotype.[7,19]

Collectively, these findings showcase the wide intrafamilial variability in the severity of pathologies caused by *PAX2* mutations and suggest epigenetic, environmental factors, and other genes are likely to be involved.[20] Our patient did not have any of the abovementioned conditions, warranting further investigation into additional factors influencing her phenotype.

Nevertheless, we also believe that it should be important to establish a Renal Genetics Clinic (RGC). In our practice, as a growing number of genes become implicated in kidney diseases associated with a variety of renal phenotypes that present at all ages, an RGC may become increasingly relevant. An RGC that includes genetic counseling enhances care of renal patients by improving diagnosis, directing management, affording presymptomatic family focused genetic counseling, and assisting patients and kidney donors to make informed decisions.[21]

Limitations and strengths: The limitation of this approach is that a renal biopsy was not performed, due the absence of proteinuria and hematuria. Another limitation was the difficulty to extend the analysis to her grandparents, who couldn´t do it.

As a strength, the patient has had a tight follow up since the prenatal period, which has allowed have a very good adherence to the treatment and to be involved in all studies required.

Conclusion

Cystic kidney disease is rare and underdiagnosed disease due to its variable expressivity and wide range of clinical manifestations. In our case, despite the patient doesn't have coloboma, there are reports from current literature which gives evidence that this PAX2 mutation provides different clinical manifestations, without eye involved as the present case, to be part of the syndrome renal coloboma syndrome (RCS).

We must look for PAX2 mutations in patients with CKD secondary to hypo- dysplasia, in order to search for a genetic related condition, by partial genetic factors as RCS with or without eye involved, in order to benefit the follow up after kidney transplantation.

Authors' Contributions

HP, FJM, DN collected the clinical information and wrote the manuscript. PH and NCJA carried out the genetic testing and evaluated the mutant using expression and functional analyses. RJM, LH and OV were involved in critically revising the article. All authors read and approved the final manuscript.

Consent for Publication

Written informed consent was obtained from the parents of the patient; a copy of this form is available for review by the editor of this journal upon request.

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Data Availability

The datasets are available from the corresponding author, per reasonable request.

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