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Exceptional Case

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PAX2 variant associated with bilateral kidney agenesis and broad intrafamilial disease variability

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ABSTRACT

Pathogenic variants in *PAX2* have previously been associated with renal coloboma syndrome. Here we present a novel variant c.68T>C associated with bilateral kidney agenesis, minimal change nephropathy, ureteropelvic junction obstruction, duplex kidney with hydronephrosis of upper pole system and bilateral kidney hypoplasia within the same family. Additionally, two family members were found to have optic nerve abnormalities further supporting the impact of the *PAX2* variant. This is the first report of a *PAX2* variant associated with bilateral kidney agenesis.

Keywords: intrafamilial disease variability, kidney agenesis, kidney hypoplasia, *PAX2*, renal coloboma syndrome

BACKGROUND

Pathogenic variants in *PAX2* have previously been associated with renal coloboma syndrome, isolated congenital anomalies of the kidney and urinary tract (CAKUT) and focal segmental glomerulosclerosis. The most common CAKUT phenotypes seen with *PAX2* variants are kidney hypoplasia, vesicoureteral reflux, kidney cysts and multicystic dysplastic kidneys [1, 2]. Up to now, variants in *PAX2* have not been associated with the most severe form of CAKUT, namely bilateral kidney agenesis. Here, we present genetic data from a family revealing that *PAX2* plays a role not only in a diverse array of kidney disease, but also in bilateral kidney agenesis.

CASE REPORT

Post-mortem examination of a 15 + 2 deceased female foetus born to a 39-year-old healthy woman revealed isolated bilateral kidney agenesis. The father of the foetus was diagnosed with kidney hypoplasia and minimal change nephropathy at the age of 36 years due to persistent proteinuria. Subsequently, he was diagnosed with hypertension and hyperuricaemia, both requiring medical therapy. However, at the age of 53 years, kidney function was only mildly impaired. The father has a strong family history of kidney disease (Figure 1A).

DNA extracted from foetal tissue was analysed using array comparative genomic hybridization. No pathogenic genomic

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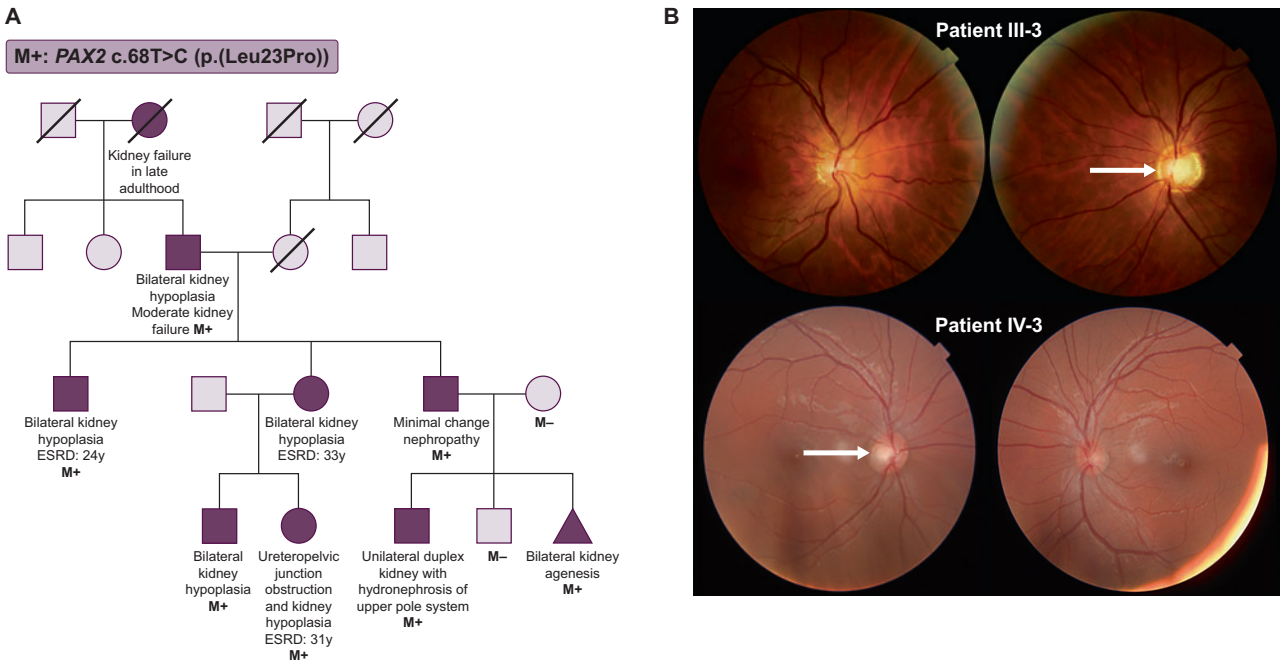

FIGURE 1: **(A)** Pedigree of the family under study. Circles indicate females, squares indicate males and black-shaded symbols indicate family members affected by kidney disease. **(B)** Arrows indicate optic nerve coloboma in Patient III-3 and the unilateral optic pit in Patient IV-3.

copy number variants were identified. Subsequently, a gene panel (including CAKUT genes *BMP7*, *CDC5L*, *CHD1L*, *EYA1*, *FRAS1*, *FREM1*, *FREM2*, *GATA3*, *GREM1*, *GRIP1*, *HNF1B*, *ITGA8*, *PAX2*, *RET*, *ROBO2*, *SALL1*, *SIX2*, *SIX5* and *TBX18*) was targeted for sequencing to identify putative disease-associated variants using next-generation sequencing. Smaller indels, up to 50 bp, were called in the variant analysis pipeline, whereas exon deletion/duplications were analysed using a copy number variation tool. These analyses only identified a heterozygous *PAX2* missense variant c.68T>C [p.(Leu23Pro)].

Subsequently, the *PAX2* candidate variant was assessed for cosegregation with kidney phenotypes in the family under study. The variant was identified in all family members affected by kidney disease for which DNA was available (Figure 1A). The kidney phenotypes seen in the family were remarkably heterogeneous, including bilateral kidney agenesis, minimal change nephropathy, ureteropelvic junction obstruction, duplex kidney with hydronephrosis of upper pole system and bilateral kidney hypoplasia with end-stage renal failure in early adult life or with only moderate chronic kidney failure in late adult life.

To study whether the severe foetal phenotype was exacerbated by additional variants in modifier genes, an additional 138 genes previously associated with kidney disease were analysed, including *GREB1L*, *FGF20* and *LMX1B*. No additional candidate variants were identified.

Retinal examination of Patient III-3 revealed unilateral optic nerve coloboma and retinal examination of Patient IV-3 revealed unilateral optic pit (Figure 1B).

DISCUSSION

We identified a *PAX2* missense variant c.68T>C [p.(Leu23Pro)] in a foetus with bilateral kidney agenesis. This missense variant has not previously been associated with disease nor has it been reported in the variant frequency database gnomAD. Prediction software indicates that the variant is damaging (accessed via www.varsome.com). Along these lines, the variant is located in the evolutionarily conserved Paired domain, as are the majority of pathogenic variants in this gene including missense variants affecting two downstream amino acids (Numbers 24 and 25) previously reported as pathogenic (HGMD2019.2) [1]. Segregation analysis revealed that the *PAX2* variant segregates with kidney phenotypes in eight meioses in the family.

As *PAX2* variants primarily have been associated with renal coloboma syndrome, the finding of unilateral optic nerve coloboma and unilateral optic pit in the father and his son, respectively, further supports the phenotypic influence of the *PAX2* variant.

So far, no genotype–phenotype correlation for *PAX2* variants has been reported, suggesting that missense variants may cause as severe a phenotype as null variants. This is in line with the broad intrafamilial disease variability reported in this and other families. It has been suggested that variants in additional kidney genes may cause the exacerbated kidney phenotype seen in some family members [3]. However, we were unable to identify any additional variants in possible modifier genes in the foetus with bilateral kidney agenesis.

While variants in *FGF20*, *ITGA8*, *GREB1L* and *RET* have been associated with isolated bilateral kidney agenesis, to the best of our knowledge, no such variants have been identified in *PAX2* [4]. However, other foetuses with oligohydramnios and Potter sequence harbouring *PAX2* variants have been reported, indicating severely impaired kidney function in foetal life. Also, one foetus found to have severe kidney hypoplasia and oligohydramnios by prenatal ultrasound examination showed only small nephric buds associated with minuscule ureters at postmortem examination, thereby approximating bilateral kidney agenesis [1, 5].

In conclusion, *PAX2* variants can present with broad intrafamilial disease variability. Here, we present for the first time a

PAX2 variant associated with bilateral kidney agenesis and extend the range of phenotypes associated with *PAX2* variants.

PATIENT CONSENT

Informed consent for publication was obtained from all family members undergoing genetic testing.

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CONFLICT OF INTEREST STATEMENT

None declared.

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