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

Rasmussen, Maria; Nielsen, Marlene Louise; Manak, J Robert; Mogensen, Helle; Lildballe, Dorte Launtoft

Published in:
Clinical Kidney Journal

DOI:
10.1093/ckj/sfaa013

Publication date:
2021

Document version:
Final published version

Document license:
CC BY-NC

Citation for published version (APA):
Rasmussen, M., Nielsen, M. L., Manak, J. R., Mogensen, H., & Lildballe, D. L. (2021). PAX2 variant associated with bilateral kidney agenesis and broad intrafamilial disease variability. Clinical Kidney Journal, 14(2), 704-706. https://doi.org/10.1093/ckj/sfaa013

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:
• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain.
• You may freely distribute the URL identifying this open access version.
If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to: puresupport@bib.sdu.dk
EXCEPTIONAL CASE

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

Maria Rasmussen1, Marlene Louise Nielsen2, J. Robert Manak3,4, Helle Mogensen5 and Dorte L. Lildballe1

1Department of Clinical Genetics, Vejle Hospital, Vejle, Denmark, 2Department of Clinical Genetics, Aarhus University, Aarhus N, Denmark, 3Department of Paediatrics, Carver College of Medicine, University of Iowa, Iowa City, IA, USA, 4Department of Biology, University of Iowa, Iowa City, IA, USA and 5Department of Gynecology and Obstetrics, Kolding Hospital, Kolding, Denmark

Correspondence to: Maria Rasmussen; E-mail: maria.rasmussen5@rsyd.dk

**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

Received: 11.9.2019; Editorial decision: 26.12.2019

© The Author(s) 2020. Published by Oxford University Press on behalf of ERA-EDTA. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
copy number variants were identified. Subsequently, a gene panel (including CAKUT genes BMP7, CDSCI, 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 deletions/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).

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.

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 post-mortem 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.

**ACKNOWLEDGEMENTS**

We wish to thank the family for their contribution to the report.

**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**

1. Bower M, Salomon R, Allanson J et al. Update of PAX2 mutations in renal coloboma syndrome and establishment of a locus specific database. *Hum Mutat* 2012; 33: 457–466
2. Barua M, Stellacci E, Stella L et al. Mutations in PAX2 associate with adult-onset FSGS. *J Am Soc Nephrol* 2014; 25: 1942–1953
3. Negrisolo S, Carraro A, Fregonese G et al. Could the interaction between LMX1B and PAX2 influence the severity of renal symptoms? *Eur J Hum Genet* 2018; 26: 1708–1712
4. Madariaga L., Morinière V, Jeanpierre C et al. Severe prenatal renal anomalies associated with mutations in HNF1B or PAX2 genes. *Clin J Am Soc Nephrol* 2013; 8: 1179–1187
5. Ford B, Rupps R, Lirenman D et al. Renal-coloboma syndrome: prenatal detection and clinical spectrum in a large family. *Am J Med Genet* 2001; 99: 137–141