



## LETTER TO THE EDITOR

## Novel pathogenic MAPKBP1 variant in a family with nephronophthisis

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Nephronophthisis (NPHP), an autosomal recessive ciliopathic disease that leads to end-stage kidney disease (ESKD) in childhood or adolescence, is characterized by reduced urinary concentrating ability, chronic tubulointerstitial nephritis and cystic kidney disease [1]. Around 10–20% of patients with NPHP have additional features that can include liver fibrosis, retinal degeneration, heart abnormalities or situs inversus [2, 3]. NPHP is considered to be the most common genetic cause of ESKD in children and young adults [2] and is found in populations worldwide. NPHP clinical subtypes can be classified into three categories based on the age of onset: infantile NPHP, before 3 years of age; juvenile NPHP, before 13 years of age; and adolescent/adult NPHP, before 19 years of age [4].

There are ~25 genes related to NPHP and their encoded proteins localize to the primary cilia, basal body or centrosomes. MAPKBP1 variants were reported recently to be implicated in NPHP [5]. MAPKBP1 encodes a scaffold protein MAPKBP1 that regulates the c-Jun N-terminal kinase and nucleotide-binding oligomerization domain-containing protein 2 signalling pathways [6, 7]. Interestingly, MAPKBP1 is absent from the primary cilia and basal body complex, which may represent a new form of NPHP [5].

Here we report a Saudi Arabian consanguineous family with NPHP caused by a nonsense variant in MAPKBP1.

The index case (IV-1) was first discovered to have chronic kidney disease (CKD) at the age of 19 years, when he presented with flank pain following exertion. Family history was notable for consanguinity in the parents and two maternal uncles who reached ESKD before 30 years of age, as well as a younger brother with CKD and cystic kidney disease.

On examination, he was documented to be normotensive and underweight [body mass index (BMI) 14.7 kg/m<sup>2</sup>]. Retinal examination was normal and physical examination was otherwise unremarkable. Initial investigations revealed a low urinary-specific gravity of 1.003. Serum creatinine was 121 µmol/L [estimated glomerular filtration rate (eGFR) 71 mL/min/1.73 m<sup>2</sup>, Chronic Kidney Disease Epidemiology Collaboration equation]. A renal ultrasound scan revealed increased parenchymal echogenicity with bilateral cysts, confirmed on CT scanning (Figure 1).

There was progressive CKD with minimal proteinuria progressing to ESKD at 24 years.

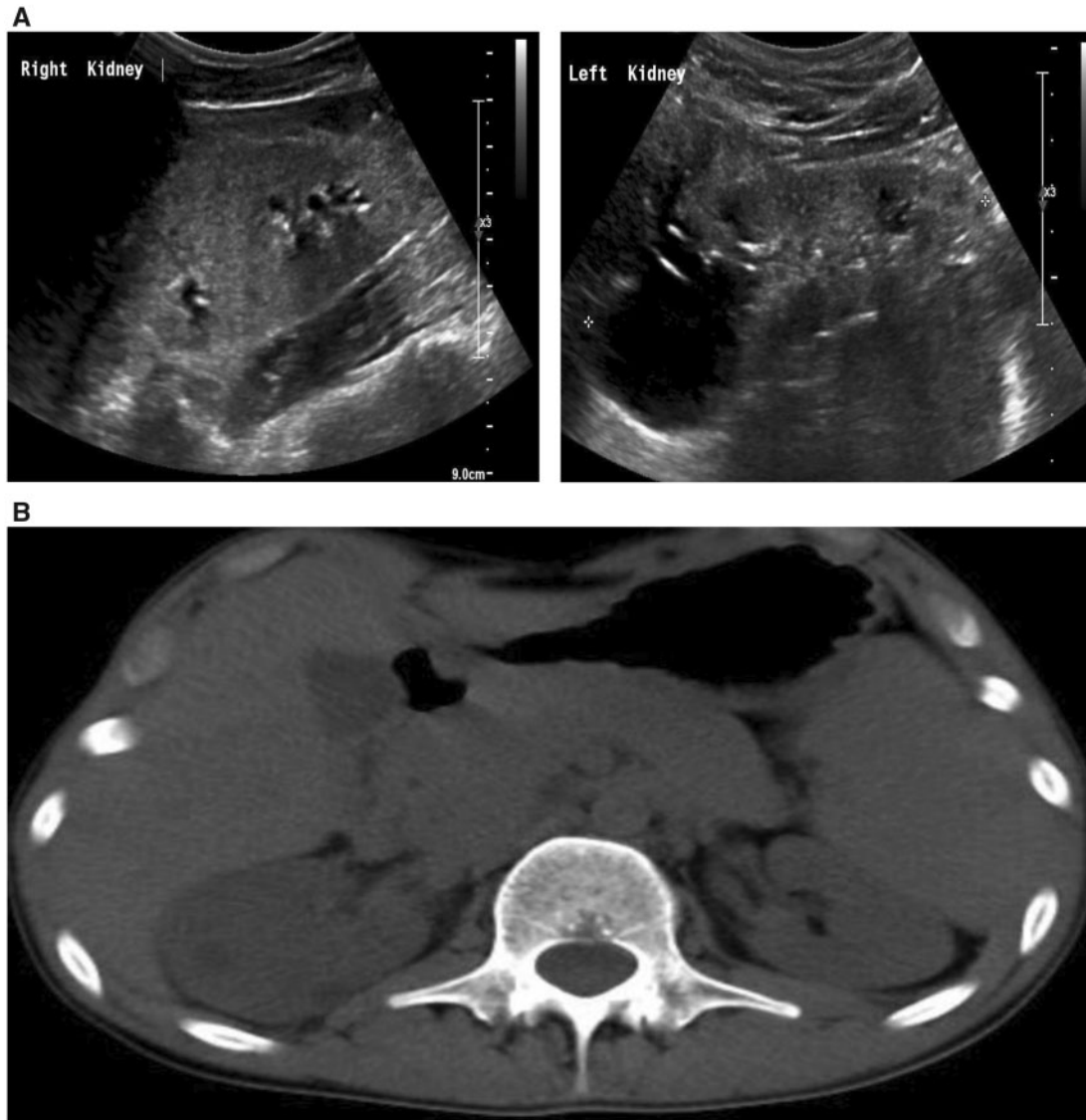
The affected younger sibling, age 9 years (IV:7) (Figure 2) underwent a renal biopsy in another hospital, which was consistent with a diagnosis of NPHP.

Genetic investigations in both affected patients revealed no chromosomal abnormalities (array comparative genomic hybridization). Genome-wide human single-nucleotide polymorphism

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**FIGURE 1:** (A) Renal ultrasound reveals echogenic parenchyma with numerous small parenchymal cysts as well as multiple larger cysts bilaterally. (B) CT scan without contrast showing numerous small cysts bilaterally as well as two larger cysts in the right kidney.

array 6.0 was used to identify regions of homozygosity and whole-exome sequencing detected a novel homozygous nonsense mutation in *MAPKBP1* (NM\_001128608:c.952C>T:p. Arg318\*) within a region of homozygosity (Figure 2). Sanger confirmation for all family members detected heterozygous status in both unaffected parents and two unaffected siblings, and two unaffected siblings were wild-type for the allele. The nonsense variant detected in the *MAPKBP1* gene here increases the number of known disease alleles to seven, with six of them leading to a predicted loss of function (Figure 2).

The diagnosis of NPHP relies on the presence of characteristic clinical, histological and imaging findings, while a molecular genetic diagnosis is possible in ~30–40% of cases [8, 9]. Approximately 80–90% of NPHP cases are isolated and have no extrarenal features, while the remainder have extrarenal manifestations that constitute a ciliopathy syndrome. Detection of the molecular cause of NPHP is an important step for clinicians and for the family in terms of definitive diagnosis, prognosis

and cascade screening and diagnostics and will prevent unnecessary invasive investigations.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was obtained from the family and approved by the Research Advisory Council at King Faisal Specialist Hospital and Research Centre (RAC 2160 022).

### CONSENT TO PUBLISH

The Research Advisory Council at King Faisal Specialist Hospital and Research Centre approved the waiver.

### AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this published article.

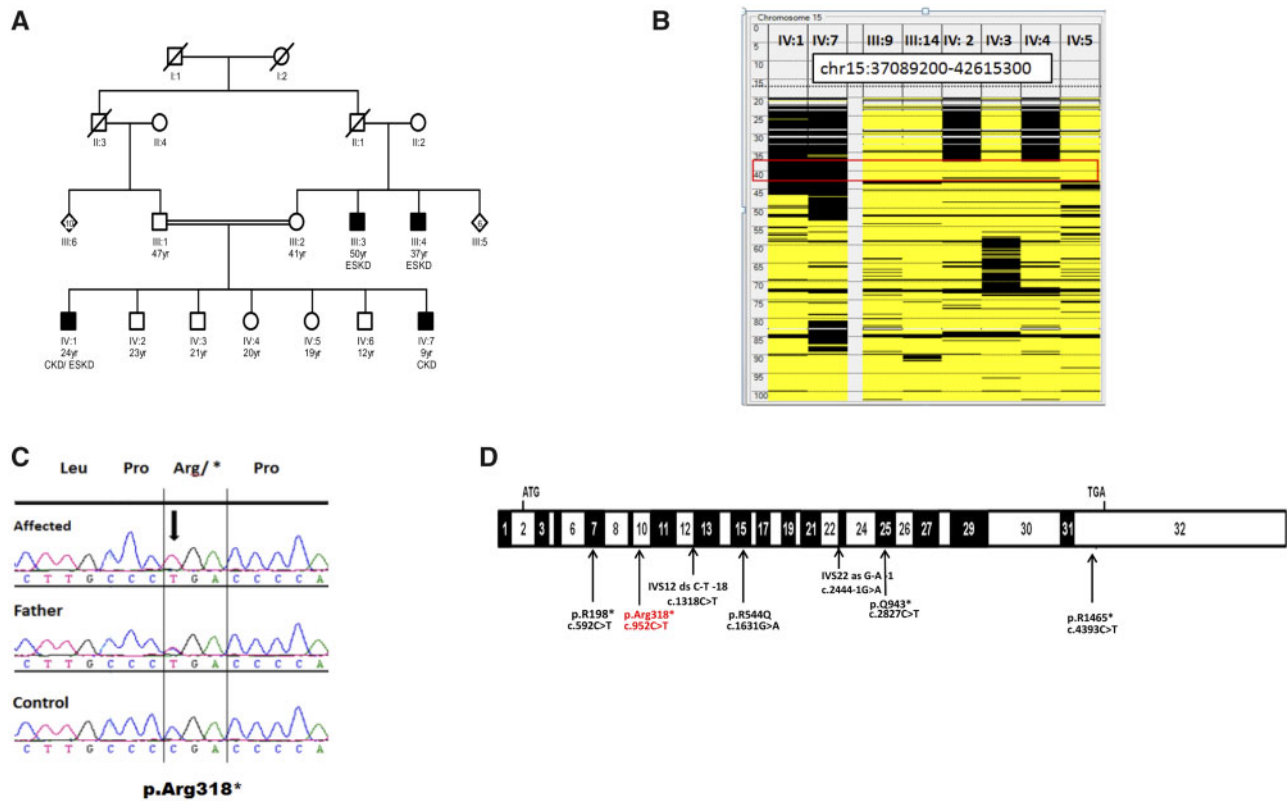


FIGURE 2: (A) Pedigree of the Saudi Arabian family. Affected individuals are shown with shaded symbols. (B) AutoSNPa homozygosity mapping in the family showing the region of homozygosity in black in the affected individuals in chromosome 15. (C) DNA chromatograms of the affected, father and unaffected control of exon 10 in MAPKBP1 gene (reference sequence NM\_001128608.2). (D) Schematic representation of the exon structure of the MAPKBP1 gene, showing identified mutations. The p.Arg318\* mutation is shown in red.

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## AUTHORS' CONTRIBUTIONS

M.H.A-H., J.A.S. and F.I. conceived the study and participated in its design and coordination and drafted and revised the manuscript. H.Z., M.H. and A.Q. participated in the clinical diagnosis of the patients. L.A. carried out all technical aspects of molecular diagnosis. J.A.S. revised the manuscript. All authors read and approved the final manuscript.

## CONFLICT OF INTEREST STATEMENT

None declared.

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