

The Role of Genetic Testing in Diagnosing ADTKD-HNF1B in a Pregnant Woman

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Abstract

Autosomal dominant tubulointerstitial kidney disease (ADTKD) accounts for approximately 2%-5% of monogenic causes of chronic kidney disease (CKD) and remains frequently underrecognized due to its heterogeneous clinical presentation. We report the case of a 37-year-old pregnant woman diagnosed with CKD, initially attributed to chronic pyelonephritis. She presented with bilateral renal cysts, electrolyte abnormalities, uterine malformation, and a family history of CKD. Genetic testing was pursued based on the phenotypic features, identifying a novel heterozygous *HNF1B* variant, c.785_786dup p.(Ala263Argfs*3), classified as likely pathogenic. Subsequent familial screening revealed that the patient's mother, who was on hemodialysis for CKD of unknown etiology, carried the same mutation, leading to the reclassification of her CKD etiology as ADTKD related to *HNF1B*. This case highlights the clinical variability and diagnostic challenges of *HNF1B*-related ADTKD, emphasizing the crucial role of genetic testing in identifying the etiology and improving disease understanding among nephrologists.

Keywords: Genetic Diseases, Inborn; Genetic Testing; Hepatocyte Nuclear Factor 1-beta; Polycystic Kidney, Autosomal Dominant; Pregnancy

INTRODUCTION

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is an underrecognized condition that accounts for approximately 2%-5% of monogenic causes of chronic kidney disease (CKD).¹ It is characterized by tubular damage and interstitial fibrosis, typically in the absence of significant glomerular involvement.² Disease-causing mutations have been identified in four genes encoding uromodulin (*UMOD*), renin (*REN*), mucin-1 (*MUC*) and hepatocyte nuclear factor-1B (*HNF1B*).³ More recently, mutations in α 1 subunit of the SEC61 translocon (*SEC61A1*) and DNAJ/HSP40 homolog, subfamily B, member 11 (*DNAJB11*) have also been implicated in ADTKD, further expanding the genetic spectrum of the disease.⁴ *HNF1B* is a transcription factor essential for the embryonic development of kidneys, liver, pancreas, and urogenital tract. Mutations in *HNF1B* gene can lead to a multisystemic disorder encompassing CKD, congenital anomalies of the kidney and urinary tract (CAKUT), maturity-onset diabetes of the young (MODY5), hypomagnesemia and hyperuricemia.^{5,6} Here, we present the case of a pregnant woman with CKD,

renal cysts, electrolyte abnormalities, a uterine malformation, and a positive family history of CKD, in whom genetic testing revealed a novel heterozygous mutation in *HNF1B*.

CASE REPORT

A 37-year-old pregnant woman at 26 weeks of gestation, with stable CKD stage G3a (estimated glomerular filtration rate of 54 mL/min/1.73 m²) previously attributed to chronic pyelonephritis, presented to the emergency department with acute pyelonephritis. Her medical history was significant for gestational diabetes, hyperuricemia disproportionate to her CKD stage, and two prior urinary tract infections. Notably, her mother had been diagnosed with CKD of unknown etiology and had been on hemodialysis since the age of 50. No other family members were known to have CKD (Fig. 1). On presentation, laboratory findings included a serum creatinine of 1.23 mg/dL, normal liver function tests, hyperuricemia of 7.3 mg/dL (despite treatment with 100 mg allopurinol), hypomagnesemia of 0.93 mEq/L, and renal tubular acidosis with serum bicarbonate of 18.5 mmol/L. Urinalysis revealed an

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unremarkable urine sediment and absence of proteinuria. A renal ultrasound demonstrated bilateral renal dysplasia, with normal-sized kidneys displaying increased

echogenicity and multiple bilateral cortical cysts. An abdominal ultrasound identified a septate uterus.

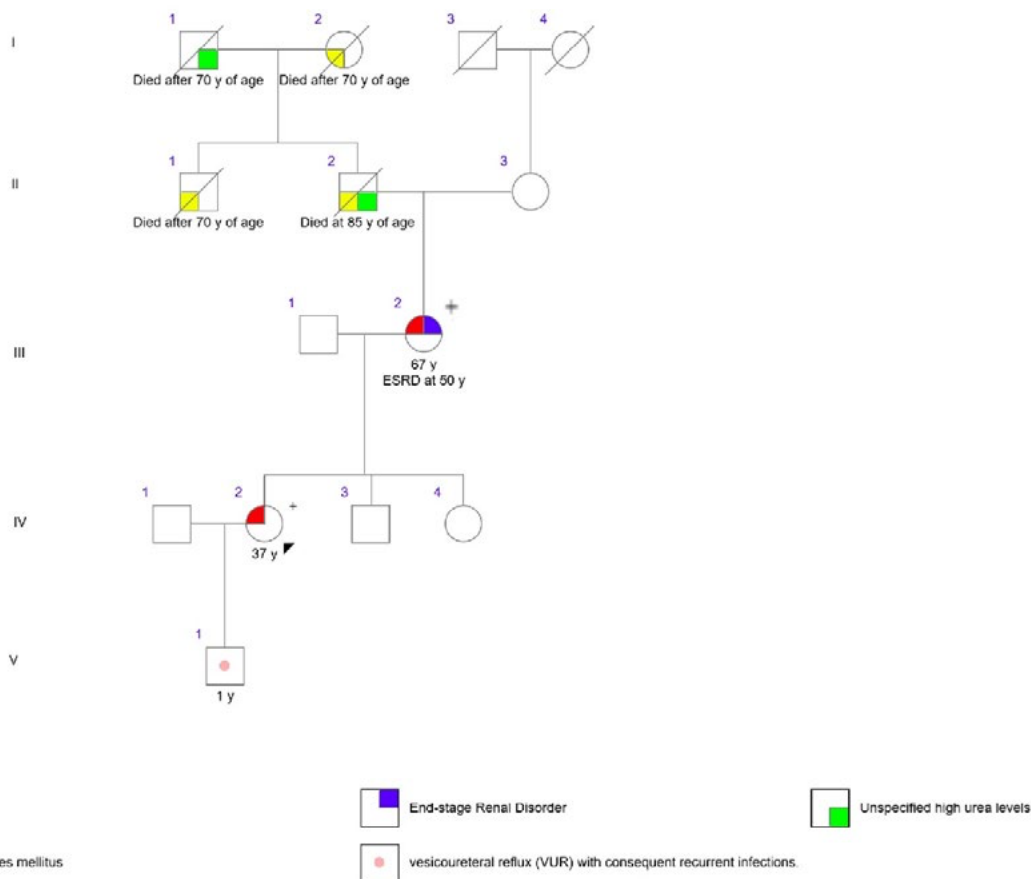


Figure 1. Pedigree of the family, showing the main clinical characteristics. No family members besides the mother's proband (III-2) had end-stage renal disorder (ESRD) and none died at a young age. The + sign refers to the presence of the heterozygous *HNF1B* c.785_786dup p.(Ala263Argfs*3) variant in DNA obtained from leucocytes in the peripheral blood.

Given these findings, *HNF1B*-related nephropathy with predominant features of ADTKD (ADTKD-*HNF1B*) was suspected. Genetic testing was performed on leucocytes obtained from peripheral blood using a targeted next-generation sequencing (NGS) panel on the Illumina NovaSeq6000 platform (Macrogen). The panel included the genes *HNF1B*, *MUC1*, *REN*, *UMOD*, *COL4A3*, *COL4A4*, *COL4A5*, *SEC61A1*, and *SLC8A1*. This analysis identified a previously undescribed heterozygous variant in *HNF1B*, c.785_786dup p.(Ala263Argfs*3), classified as likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) criteria.⁷ Subsequent genetic testing of the patient's mother identified the same mutation, supporting the diagnosis of ADTKD-*HNF1B* in this family.

Despite the episode of pyelonephritis and a diagnosis of gestational diabetes, the remainder of the pregnancy was

uneventful. The patient underwent spontaneous labor at 37 weeks and 1 day, following spontaneous rupture of membranes, and delivered a healthy male infant. During the first months of life, the newborn experienced urinary tract infections due to vesicoureteral reflux; however, genetic testing for the familial *HNF1B* mutation was negative.

DISCUSSION

We present a case of a young woman with CKD previously attributed to chronic pyelonephritis, who was diagnosed during pregnancy with ADTKD-*HNF1B* due to a novel heterozygous variant c.785_786dup p.(Ala263Argfs*3) at *HNF1B* gene. Subsequent familial screening revealed that the patient's mother, who was on hemodialysis for CKD of unknown etiology, carried the same mutation, leading to the recognition of familial ADTKD-*HNF1B*.

Mutations at *HNF1B* can result in multisystemic manifestations, including renal, hepatic, neurological, pancreatic and genital anomalies. As a key transcription factor in

nephron development, *HNF1B* variants are a recognized monogenic cause of CAKUT, often presenting with bilateral kidney cysts, resembling autosomal dominant polycystic kidney disease. In addition to CAKUT, patients may present with isolated hypomagnesemia, ADTKD, or extra-renal manifestations, making *HNF1B*-related disease a preferred term.^{5,6,8} This phenotypic variability that cannot be predicted by the genotype, aided by its variable penetrance, high intra-/interfamilial heterogeneity, contributes to diagnostic challenges and may lead to an underestimation of disease prevalence.⁹ Moreover, molecular diagnosis is further complicated by a high frequency of *de novo* mutations (>50%), which can discourage genetic testing, and copy number variations, which may not be detected using next-generation sequencing techniques.¹⁰

Despite not being previously described, the c.785_786dup (Ala263Argfs*3) frameshift mutation identified in this case results in a premature termination codon, likely leading to

the absence or truncation of the HNF1B protein, which explains the patient's phenotype. This supports its classification as a likely pathogenic variant.⁷ Our patient was referred for genetic counselling, given the 50% risk of transmission in future pregnancies. She continues to receive CKD management following established guidelines, with special attention to diabetes and electrolyte imbalances. If kidney transplantation is considered in the future, disease recurrence in the allograft is not expected. However, related living donors should undergo genetic testing to assess for potential disease transmission.

In conclusion, this case underscores the clinical spectrum of ADTKD-HNF1B and highlights the importance of genetic testing in diagnosing monogenic kidney diseases. By identifying pathogenic variants, genetic testing enhances disease awareness among nephrologists, facilitates familial screening, and enables genetic counselling, ultimately improving patient care.

Ethical Disclosures

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