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The Varied Clinical Presentation of Autosomal Dominant Tubulointerstitial Kidney Disease Due to *HNF1β* Mutations

Anthony J. Bleyer[1,2] and Stanislav Kmoch[1,2]

[1]Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC, USA; and [2]Research Unit of Rare Diseases, Department of Pediatric and Adolescent Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic

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Although mutations in *HNF1β* were first identified as a cause of maturity onset diabetes of youth,[1] it has become increasingly clear over time that the predominant clinical manifestations of this condition involve the kidney. HNF1β is a master transcription factor regulating the expression of several kidney-specific genes from the first steps of nephrogenesis. Thus, mutations in *HNF1β* can affect kidney development, maintenance of the tubular architecture, cyst formation, and ion transport. Mutations in *HNF1β* comprise whole-gene deletions, missense, non–sense, frameshift, and splice-site mutations with ∼50% of them occurring *de novo*. The allelic heterogeneity is reflected by the varied clinical presentation, making diagnosis difficult. In this month's *Kidney International Reports*, Izzi and colleagues[2] present a case series showing the many presentations of *HNF1β* mutations, including a newly described manifestation: medullary sponge kidney.

HNF1β is an integral factor in the embryogenesis of the genitourinary tract. Kaminski and colleagues[3] have shown that the combination of HNF1β with transcription factors Emx-2, HNF-4alpha, and Pax-8 can transform fibroblasts into renal tubular epithelial cells. Expression of HNF1β occurs early in life in the branching ureteric bud.[4] Thus, mutations in *HNF1β* involving only 1 allele can significantly affect kidney development. In a study of 80 children with structural abnormalities of the kidney on their first postnatal ultrasound, 25 (31%) had *HNF1β* mutations.[5] The clinical manifestations can be diverse, including solitary kidney, dysplastic kidney, and congenital anomalies of the kidney and urinary tract, as well as genitourinary abnormalities, including bicornuate uterus.[6]

HNF1β is also important in the maintenance of renal tubular architecture. HNF1β regulates *PKHD1* (mutations of which cause autosomal recessive polycystic kidney disease), *PKD2*, and *GLIS2* (associated with nephronophthisis).[7] Thus, it is unsurprising that the development of kidney cysts is a frequent presentation in patients with *HNF1β* mutations. As with developmental anomalies, the presentation can be diverse. Patients may present with no cysts, a few cysts, or many cysts in the kidney, as in Family 1 in the article by Izzi *et al*.[2]

Finally, *HNF1β* is also important in tubular transport. *HNF1β* modulates *UMOD*, important in urate transport, and *FXDY2*, which is integral in magnesium transport.[8] Thus, a significant proportion of patients with *HNF1β* mutations have both gout and hypomagnesemia. Hypokalemia and a Gitelman-like syndrome have also been found in this disorder.[6]

Although *HNF1β* mutations can adversely affect kidney formation and cause cystic kidney disease, hyperuricemia, hypokalemia, and hypomagnesemia, there is incomplete penetrance of all of these conditions. Thus, patients may have all, some, or none of these clinical findings. The variable presentation of patients, even within a family, makes diagnosis of *HNF1β* mutations incredibly difficult. Clinicians may not recognize the autosomal dominant inheritance due to the absence of clinical signs or symptoms in some affected patients and the varied clinical presentations. As described by Izzi *et al*.,[2] mutations in *HNF1β* are truly a great masquerader, presenting with signs and symptoms that could be ascribed to many other nephrologic conditions. Making diagnosis even more difficult, there are frequently *de novo* mutations.[9]

Correspondence: Anthony J. Bleyer, Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC, USA 27157 USA. E-mail: ableyer@wakehealth.edu

Due to the autosomal dominant nature of the disorder, bland urinary sediment, and a frequent finding of chronic kidney disease, *HNF1β* mutations have been included in the group of autosomal dominant tubulointerstitial kidney diseases. These conditions include primarily ADTKD-*UMOD* and ADTKD-*MUC1*. As with other forms of ADTKD, patients can progress to end-stage kidney disease.[9]

It is difficult to determine the prevalence of *HNF1β* mutations due to their rarity and difficult detection. Izzi and colleagues performed genetic testing on individuals with tubulointerstitial kidney disease who presented after age 50 years or had a positive family history of kidney disease. Of 92 probands, they identified 9 families with pathogenic mutations in *HNF1β*. Thus, mutations in *HNF1β* can be viewed as a common cause of tubulointerstitial kidney disease in this population.

The cases presented in the article by Izzi *et al*. show the tremendous variation in presentation of ADTKD-*HNF1β*. For example, in Family 1, a 73-year-old man presented with bilateral polycystic kidney disease. In contrast, his son had presented 35 years earlier at 2 years of age with polyuria and concerns of nephronophthisis. In Family 4, an affected member presented at 38 and was found incidentally to have a serum creatinine of 1.32 mg/dl, with ultrasound showing a few cortical cysts. The authors describe for the first time a patient with an *HNF1β* mutation who suffered from medullary sponge kidney. Although one cannot prove the causal nature of the mutation, this finding would be consistent with the effects of *HNF1β* on tubular transport and tubular architecture.

With no treatments for ADTKD and the difficulties in diagnosis, one may wonder why making a genetic diagnosis should be pursued. As with other rare genetic conditions, patients and their families have a strong desire to know the cause of a disease that has often affected multiple family members for several generations.[S1] An *HNF1β* mutation provides a unifying diagnosis for many mysterious and seemingly unrelated conditions. For example, in Family 1,[2] polycystic kidneys, hypomagnesemia, hypokalemia, diabetes, and pancreatic hypoplasia were all found due to an *HNF1β* mutation. Diagnoses will help prevent unneeded kidney biopsies. In addition, family members can be tested to see whether they could be potential living related kidney donors.

How, then, can a nephrologist make a diagnosis of ADTKD-*HNF1β*? Although kidney cysts, gout, and chronic kidney disease are common findings in chronic kidney disease, one should be alert for clinical findings in ADTKD-*HNF1β* that are less common in other disorders, including hypomagnesemia, maturity onset diabetes of youth, unexplained liver function test abnormalities, and congenital anomalies of the kidney and urinary tract.

The development of kidney disease gene panels is a major step forward in the diagnosis of ADTKD-*HNF1β* as well as other difficult-to-diagnose disorders. These panels screen for mutations in several different genes. Panels usually target exons and can screen for single nucleotide variants, small insertions and deletions, and large copy number variant. Given recent investigations showing that genetic causes are present in more than 10% of advanced chronic kidney disease,[S2] we believe that genetic panels will soon become routine in all individuals with chronic kidney disease. Gene panels can also identify other rare causes of genetic kidney disease, including nephronophthisis and ADTKD-*UMOD* and ADTKD-*REN*. Unfortunately, gene panels are unable to identify mutations in ADTKD-*MUC1*, which requires specialized genetic testing.

In summary, the recent study of Izzi and colleagues displays the varied symptomatology that can be found in ADTKD-*HNF1β*. The use of kidney disease genetic panels will be helpful in the diagnosis of ADTKD-*HNF1β* and many related conditions.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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