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

Anthony J. Bleyer¹,² and Stanislav Kmoch¹,²

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

Kidney Int Rep (2020) 5, 2133–2135; https://doi.org/10.1016/j.ekir.2020.10.008 © 2020 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

See Clinical Research on Page 2341

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 colleagues² 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 colleagues³ 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.⁷ 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
Due to the autosomal dominant nature of the disorder, bland urinary sediment, and a frequent finding of chronic kidney disease, HNF1\(\beta\) 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 HNF1\(\beta\) 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 HNF1\(\beta\). Thus, mutations in HNF1\(\beta\) 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-HNF1\(\beta\). 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 HNF1\(\beta\) 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 HNF1\(\beta\) 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.\(^5\)

An HNF1\(\beta\) 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 HNF1\(\beta\) 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-HNF1\(\beta\)? Although kidney cysts, gout, and chronic kidney disease are common findings in chronic kidney disease, one should be alert for clinical findings in ADTKD-HNF1\(\beta\) 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-HNF1\(\beta\) 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,\(^2\) 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-HNF1\(\beta\). The use of kidney disease genetic panels will be helpful in the diagnosis of ADTKD-HNF1\(\beta\) and many related conditions.

**DISCLOSURE**

All the authors declared no competing interests.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)
Supplementary References.

**REFERENCES**

1. Horikawa Y, Iwasaki N, Hara M, et al. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet*. 1997;17:384–385.
2. Izzi C, Dordoni C, Econimo L, et al. Variable expressivity of HNF1B nephropathy, from renal cysts and diabetes to medullary sponge kidney through tubulo-interstitial kidney disease. *Kidney Int Rep*. 2020;5:2341–2350.
3. Kaminski MM, Tosic J, Kresbach C, et al. Direct reprogramming of fibroblasts into renal tubular epithelial cells by defined transcription factors. *Nat Cell Biol*. 2016;18:1269–1280.
4. Massa F, Garbay S, Bouvier R, et al. Hepatocyte nuclear factor 1beta controls nephron tubular development. *Development*. 2013;140:886–896.
5. Uliński T, Leslure S, Beauvais S, et al. Renal phenotypes related to hepatocyte nuclear factor-1beta (TCF2)
mutations in a pediatric cohort. J Am Soc Nephrol. 2006;17:497–503.
6. Verhave JC, Bech AP, Wetzes JF, Nijenhuis T. Hepatocyte nuclear factor 1beta-associated kidney disease: more than renal cysts and diabetes. J Am Soc Nephrol. 2016;27:345–353.
7. Ferre S, Igarashi P. New insights into the role of HNF-1 beta in kidney (patho)physiology. Pediatr Nephrol. 2019;34:1325–1335.
8. Adalat S, Woolf AS, Johnstone KA, et al. HNF1B mutations associate with hypomagnesemia and renal magnesium wasting. J Am Soc Nephrol. 2009;20:1123–1131.
9. Faguer S, Decramer S, Chassaing N, et al. Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. Kidney Int. 2011;80:768–776.