A novel HNF1B mutation p.R177Q in autosomal dominant tubulointerstitial kidney disease and maturity-onset diabetes of the young type 5
A pedigree-based case report

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Abstract
Rationale: Mutations in the hepatocyte nuclear factor-1-beta (HNF1B) gene result in a very variable presentation, including maturity onset diabetes of the young (MODY), renal cysts, renal dysplasia, and autosomal dominant tubulointerstitial kidney disease (ADTKD), which is characterized by tubular damage, renal fibrosis, and progressive renal dysfunction.

Patient concerns: A 22-year-old man came to the hospital presenting with hyperglycemia, hyperuricemia and elevated serum creatinine. His urine protein was within the normal range. The ultrasound examination revealed shrunken kidneys with renal cysts. The patient’s mother was diagnosed with diabetes mellitus when she was 25 years old. Her laboratory results showed elevated serum creatinine. Her ultrasonography revealed shrunken kidneys with renal cysts and hydronephrosis without kidney stones. The next-generation sequencing revealed that the proband and his mother held the same heterozygous missense mutation (c.530G>A, NM_000458, p.R177Q) in the HNF1B gene. Bioinformatic analyses predicted that the mutation was likely pathogenic.

Diagnosis: The patient and his mother were diagnosed as ADTKD and MODY5 due to HNF1B mutation.

Intervention: The proband was administered metformin at a dose of 500mg/day.

Outcomes: The patient had well-controlled blood glucose levels and a stable renal function at his 12-month follow-up.

Lessons: We should take into account the diagnoses of ADTKD and MODY5 if patients present with early onset diabetes and multiple renal cysts or evidence of renal tubulointerstitial dysplasia, especially those with negative proteinuria results. Genetic testing helps detect the HNF1B gene mutations.

Abbreviations: ADTKD = Autosomal Dominant Tubulointerstitial Kidney Disease, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CREA = serum creatinine, eGFR = estimated glomerular filtration rate, GADA = glutamic acid decarboxylase antibody, GLU = blood glucose, HbA1c = glycated hemoglobin, HNF1B = hepatocyte nuclear factor 1 homeobox B, IAA = anti-insulin autoantibody, ICA = islet cell antibody, KDIGO = Kidney Disease Improving Global Outcomes, MODY5 = Maturity onset Diabetes of the Young Type 5, NGS = Next generation sequencing, PCR = urinary protein creatinine ratio, UA = uric acid.

Keywords: ADTKD, HNF1B, MODY5
1. Introduction

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a recently defined entity characterized by autosomal dominant inheritance, bland urinary sediment with minimal blood and protein, pathological changes of tubulointerstitial fibrosis, and slowly progressive chronic kidney disease.[1] A few genes with disease-causing mutations have been identified in ADTKD, including UMOD, REN, MUC1, SEC61A1, and HNF1B. HNF1B encodes a POU (Pit-1/Oct-1/2-UNC-86) homedomain-containing transcription factor that hepatocyte nuclear factor 1B (HNF1B). HNF1B is essential for the normal development of the kidney, liver, pancreas and other epithelial organs by regulating tissue-specific gene expression in these organs.[2] ADTKD-HNF1B manifests as renal cysts, renal hypoplasia, single kidney, collecting system abnormalities, bilateral hydropnephrosis, and more.[3,4] Since the first HNF1B mutation (p.R177X) was described in a Japanese family in 1997,[5] more than 200 similar mutations have been reported, including missense/nonsense, splicing, deletions, and insertions. The majority of identified mutations are clustered in the first four exons of the gene, among which the POU domains are hot spots for mutations.[6] Here, we report a Chinese family with ADTKD and MODY5. The proband and his mother were carrying a novel missense mutation (c.530G>C) in the POU domain of the HNF1B gene. The detailed clinical features and pathogenesis are discussed below.

2. Case reports

A 22-year-old Chinese man (III:1) came to the hospital complaining of hyperglycemia revealed by a routine examination done 2 months earlier. No polyphagia, polyuria, polydipsia, and emaciation were noticed. The patient’s height was 168 cm, and his weight was 70 kg, the body mass index was 24.8. His blood pressure was 138/75 mmHg. There was no edema of the lower extremities. Laboratory tests revealed that fasting blood glucose was 130 mg/dL. The alanine aminotransferase was 69 IU/L and aspartate aminotransferase was 7 IU/L and aspartate aminotransferase was 7 IU/L. Her urine tested negative for protein. The ultrasonography showed small kidneys (left kidney: 7.5 × 4.3 × 3.1 cm, right kidney: 8.0 × 4.7 × 4.7 cm) with multiple cysts and increased cortical echogenicity. The liver and pancreas were normal. The fundus examination did not show diabetic retinopathy. The glutamic acid decarboxylase antibody (GADA), insulin autoantibody (IAA), and anti-islet cell antibody (ICA) were negative (Table 1).

His mother (II:2), a 47-year-old woman, was diagnosed with diabetes mellitus when she was 25 years old, after which she was put on insulin therapy. Laboratory tests showed that fasting blood glucose was 151 mg/dL and the serum creatinine level was 1.44 mg/dL. The alanine aminotransferase was 7 IU/L and aspartate aminotransferase was 20 IU/L. Her urine tested negative for protein. The ultrasonography showed small kidneys (left kidney: 8.1 × 3.9 × 4.7 cm, right kidney: 7.9 × 4.0 × 3.2 cm) with multiple cysts and hyperechogetic cortical ultrasonography. Besides, bilateral hydropnephrosis without kidney stones was revealed. Her GADA and ICA were negative, IAA was positive (Table 1). The health of the proband’s father (II:1) was sound. The proband’s uncle (II:5) was diagnosed as diabetes mellitus (Fig. 1A).

After written informed consent was obtained, next-generation sequencing (NGS) was performed. A missense mutation, c.530G>A (p.R177Q) in the HNF1B (reference sequence GenBank accession no. NM_000458, p. R177Q) in the POU domain of the HNF1B gene. The detailed clinical features and pathogenesis are discussed below.

3. Discussion

In humans, the HNF1B gene is located on chromosome 17q12. The phenotypic expression of HNF1B is seen in the kidney, liver, pancreas, urogenital tract, gut, and bile ducts. The encoded transcription factor HNF1B contains 557 amino acids with three distinct domains: the dimerization domain, the DNA-binding domain, and the transactivation domain.[9] HNF1B binds to DNA to regulate tissue-specific gene expression in different organs.

### Table 1: Laboratory examination.

| Reference range | The proband (II:1) | His mother (II:2) |
|-----------------|---------------------|------------------|
| FBG (mg/dL)    | 70–105              | 130              | 151              |
| UA (mg/dL)     | 4.0–8.2             | 7.92             | 7.21             |
| CREA (mg/dL)   | 0.64–1.10           | 1.79             | 1.44             |
| eGFR (mL/min per 1.73 m²) | 56–122              | 52.71            | 42.68            |
| ALT (IU/L)     | <50                 | 69               | 7                |
| AST (IU/L)     | <40                 | 40               | 20               |
| HBAlc (%)      | 4.5–6.1             | 8.4              | ND               |
| PRO (g/L)      | (-)                 | (-)              | (-)              |
| PGR (mmol Cr)  | <1.05               | 0.024            | ND               |
| IAA            | (-)                 | (-)              | (+)              |
| ICA            | (-)                 | (-)              | (-)              |
| GADA (U/mL)    | <1.05               | 0.42             | 0.38             |

--- negative, + positive, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CREA=serum creatinine, Cr=estimated glomerular filtration rate, FBG=fasting blood glucose, GADA=glutamic acid decarboxylase antibody, HBAlc=glycated hemoglobin, IAA=anti-insulin autoantibody, ICA=islet cell antibody, ND=no data, PGR=urinary protein creatinine ratio, PRO=urine protein, UA=uric acid.
A total number of 286 HNF1B mutations have been documented in the HGMD (accessed on the May 12, 2020), with approximately 50% of patients having either a missense or nonsense mutation and others having splice site mutations, small insertions/deletions or gross deletions. The highly conserved DNA-binding domain of HNF1B is an essential area for transcription regulation, which is also a hot spot for mutations. The phenotype of HNF1B mutation carriers is extremely variable with autosomal dominant traits. Half of the patients do not have any family history because of spontaneous mutations. The kidney is the most commonly affected organ, with manifestations that include tubulointerstitial disease with cysts, hypoplastic glomerulocystic kidney disease, unilateral multicystic dysplasia, hypodysplasia, unilateral agenesis and hydronephrosis. Electrolyte abnormalities can also occur. About 5% to 31% of congenital abnormalities of the kidney and urinary tract are associated with HNF1B mutations. Clinically HNF1B nephropathy manifests as chronic renal failure with little or no proteinuria (<1 g/day) and no hematuria. HNF1B nephropathy has a slow-progressive phenotype in childhood except for very early onset cases. About 3% to 15% of these patients develop end-stage renal disease. The detailed pathogenic mechanism has not yet been elucidated. In the stage of nephrogenesis, HNF1B gene deficiency causes abnormal ureteric bud branching and deformed S-shaped bodies generating, which finally differentiate into the Bowman’s capsule and tubules. Inactivation of HNF1B in the metanephric mesenchyme leads to the formation of aberrant nephrons. HNF1B gene mutations could directly downregulate the transcription of genes like Pkhd1, Pkd2, Umod, Glis2, and Kif12, which result in the production of kidney cysts.

The pancreas is the most commonly affected extra-renal organ. The patients may present with pancreatic hypoplasia, agenesis (75%) and insulin-dependent diabetes mellitus (~45%). HNF1B-associated diabetes mellitus represents ~1% to 6% of MODY cases in the United Kingdom. Diabetes typically develops during adolescence or early adulthood and the mean age at diagnosis of diabetes is 26 years. HNF1B plays an important role in the early development of the pancreas, participating in the proliferation of pancreatic multipotent progenitor cells, pancreatic duct and islet cells.

Here, we presented a family with ADTKD and MODY5. A novel HNF1B mutation at the guanine-recognizing residue R177 (c.530G>A) was identified in the proband and his mother. The family study revealed the autosomal dominant trait. Interestingly, the first reported HNF1B mutation (c.529C>T, p.R177X) sat in the same locus. The R177X mutation generates a protein of...
176 amino acids with the N-dimerization and POU domains. The truncated protein does not stimulate transcription and seems to be a loss-of-function mutation. As a missense mutation, the R177Q mutation seems to be less pathogenic than the R177X mutation. However, the R177Q mutation also caused ADTKD and MODY5, which suggest the importance of POU-containing domains in HNF1B. The proband’s mother maintained mildly increased serum creatinine and bland urinary sediments 20 years after the onset of MODY, suggesting that the R177Q mutation may lead to a slow-progressive kidney phenotype.

In conclusion, we identified a novel HNF1B mutation (c.530G>A, NM_000458, p.R177Q) in a Chinese family with typical phenotypes of ADTKD and MODY5. This case suggests that a missense mutation in POU-containing domains in HNF1B may be pathogenic. The presentation of the HNF1B mutations is highly variable. Accurate genetic diagnosis is important. The NGS could help in detecting the gene mutations.

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