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【 CASE REPORT 】

A Novel Heterozygous and Pathogenic Variant of the *HNF1B* Gene Associated with Autosomal Dominant Tubulointerstitial Kidney Disease with a Broad Spectrum of Extrarenal Phenotypes: A Case Report

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Abstract:

We encountered a family with hereditary renal failure, renal medullary cysts, pancreatic hypoplasia, hypomagnesemia, liver enzyme abnormalities, and diabetes mellitus (DM). We identified a novel heterozygous variant of *HNF1B* (NM_000458.4:c.791dup, p.L264Ffs*30) using whole-exome sequencing of genomic DNA samples from this family. This variant is located in the DNA-binding domain of the HNF1B protein and produces a truncated protein with a *de novo* sequence, suggesting that this variant changes HNF1B binding to genomic DNA or causes nonsense-mediated mRNA decay. Based on the phenotypes and identified gene variants, this family suffers from autosomal dominant tubulointerstitial kidney disease caused by this HNF1B variant.

Key words: autosomal dominant tubulointerstitial kidney disease (ADTKD), HNF1B, whole-exome sequencing

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Introduction

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of autosomal dominant diseases characterized by almost normal kidneys, unremarkable urinary findings, progressive loss of renal function leading to end-stage renal disease (ESRD), and tubulointerstitial fibrosis sometimes associated with medullary cysts (1). Among familial tubulointerstitial kidney diseases, ADTKD is one of the most common forms of polycystic kidney disease, accounting for approximately 5% of monogenic disorders leading to ESRD (2). ADTKD is caused by pathogenic variants of the *UMOD*, *MUC1*, *HNF1B*, *REN*, *SEC61A1*, and *DNAJB11* genes (3). ADTKD cases are now classified based on their causative genes and are described as ADTKD-*UMOD*.

HNF1B, a gene located on chromosome 17q12, encodes hepatocyte nuclear factor 1β, which is a member of the homeodomain-containing family of transcription factors. HNF1B plays a pivotal role in organ morphogenesis and maintenance. It is expressed in multiple organs, including the liver, pancreas, and organs of the genitourinary tract, especially the kidney, which explains why pathogenic variants of HNF1B cause a broad spectrum of phenotypes in these organs, such as renal involvement, mature-onset diabetes of the young type 5, pancreatic hypoplasia, and urogenital tract and liver test abnormalities (4). We herein present an ADTKD-affected family with a broad spectrum of extrarenal phenotypes caused by a completely novel pathological vari-

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ant of HNF1B.

Case Presentation

The pedigree of a Japanese family is shown in Fig. 1. The proband's father (patient II-2) was born weighing 2050 g and was diagnosed with intrauterine growth retardation (IUGR). The patient had normal urine test results at school. At 27 years of age, a reduced renal function (serum Cr 2.0 mg/dL) was noticed during a health check performed upon recruitment by a company. At the same time, kidney hypoplasia (left: 78.4×25.7 mm, right: 61.8×25.3 mm) with medullary cysts was discovered. Type 2 diabetes was confirmed at 32 years of age (HbA1c 6.5%). His blood sugar control was poor (HbA1c, 7.0%-10%). At 43 years of age, he started insulin therapy. The patient's renal function gradually deteriorated. Peritoneal dialysis was initiated at 47 years of age. The patient was confirmed to have pancreatic hypoplasia (agenesis of the pancreatic tail) (Fig. 2a). The blood and urine test results at the time of peritoneal dialysis are shown in Table 1. The proband's sister (patient III-1) was confirmed to have medullary cysts in both kidneys at 29 years of age (Fig. 2b). Her pancreas was normal. The results of blood and urine chemistry tests at the time of referral are shown in Table 1. Patient III-2 (proband) had medullary cysts in both kidneys at 18 years of age (Fig. 2d). He also had pancreatic hypoplasia (agenesis of the pancreatic tail of the pancreas) (Fig. 2c). The results of blood and urine chemistry tests at the time of referral are shown in Table 1.

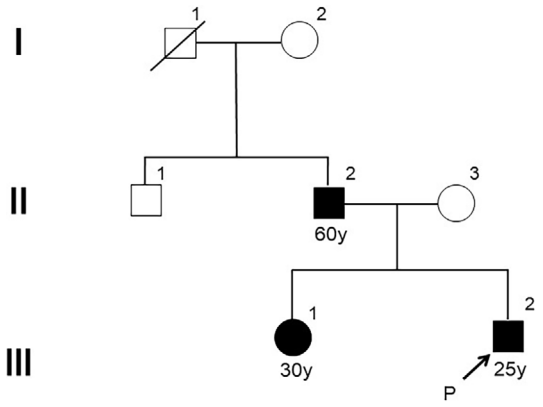

Figure 1. The pedigree of the Japanese family. Black symbols indicate family members with kidney disease.

Genetic analyses

Using genomic DNA samples from some family members (II-2, II-3, III-1, and III-2), we performed whole-exome sequencing and subtraction analyses of rare variants. We identified *HNF1B* (NM_000458.4):c.791dup [p.(Leu264PhefsTer 30)]. This variant was evaluated as pathogenic (PVS1, PM2, PP1) based on the guidelines of the American College of Medical Genetics and Genomics (ACMG) (5). This variant has not been reported in any of the human variant databases that we surveyed [HGVD, ToMMo (4.7KJPN), gnomAD_

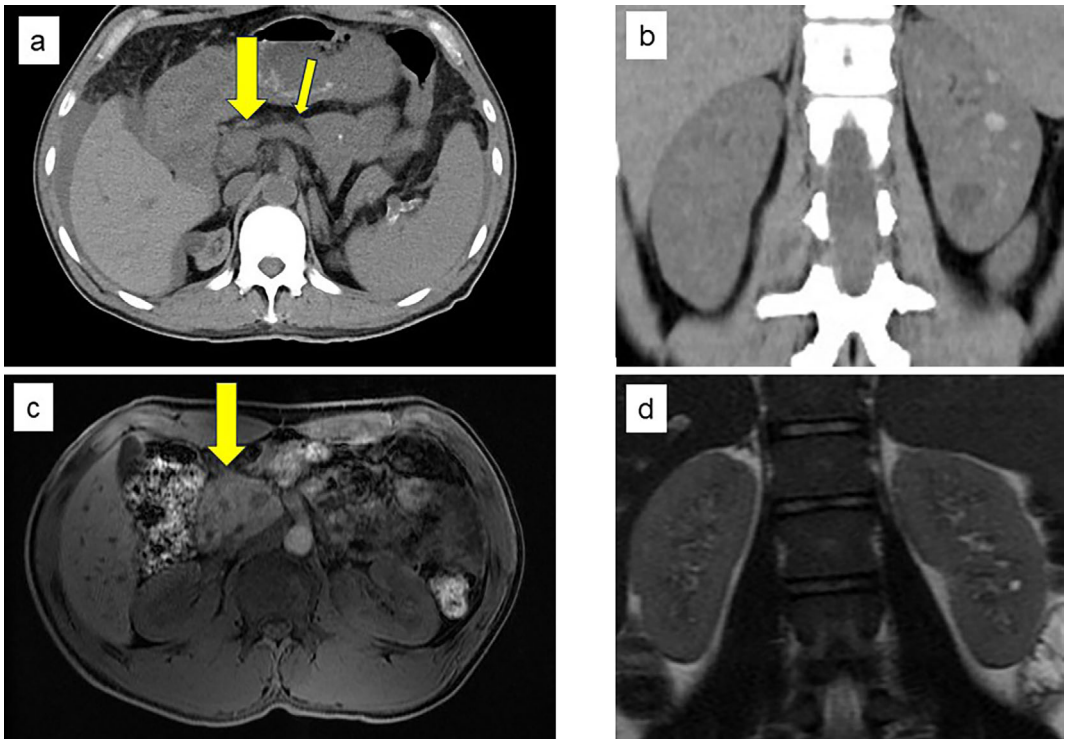

Figure 2. Computed tomography findings. a: Pancreatic head (large arrow) and hypoplasia of the pancreatic body or tail (small arrow) in patient II-2. b: Kidney cysts in patient III-1. Magnetic resonance imaging findings. c: Pancreatic head (arrow) and agenesis of the pancreatic tail in patient III-2 (LAVA-Flex sequence). d: Kidney cysts in patient III-2 (T2-weighted SSFSE sequence).

Table 1. Blood and Urine Data of the Family.

	II-2	III-1	III-2
Total protein level (g/dL)	6.0	7.5	7.3
Albumin (g/dL)	3.9	4.6	4.4
Urea nitrogen (mg/dL)	48.9	10	15.8
Creatinine (mg/dL)	7.76	1.0	1.3
Estimated glomerular filtration rate (mL/min/1.73m^2)	6.8	54.5	63.5
Uric acid(mg/dL)	6.7	5.8	7.0
Magnesium (mg/dL)	1.5	1.5	1.5
Total bilirubin (mg/dL)	0.7	1.7	2.2
Aspartate aminotransferase (IU/L)	13	33	60
Alanine aminotransferase (IU/L)	26	49	92
γ-glutamyl transpeptidase (IU/L)	48	60	150
Alkaline phosphatase (IU/L)	283	88	232
Total cholesterol (mg/dL)	148	242	254
Low-density-lipoprotein cholesterol (mg/dL)	77	150	153
Hemoglobin A1c (%)	6.4	5.3	5.7
Urine protein creatin ratio (g/gCr)	2.37	n.d.	n.d.

Blood and urine chemical data of patient II-2 at the time of PD introduction of peritoneal dialysis are shown. n.d.: not detected.

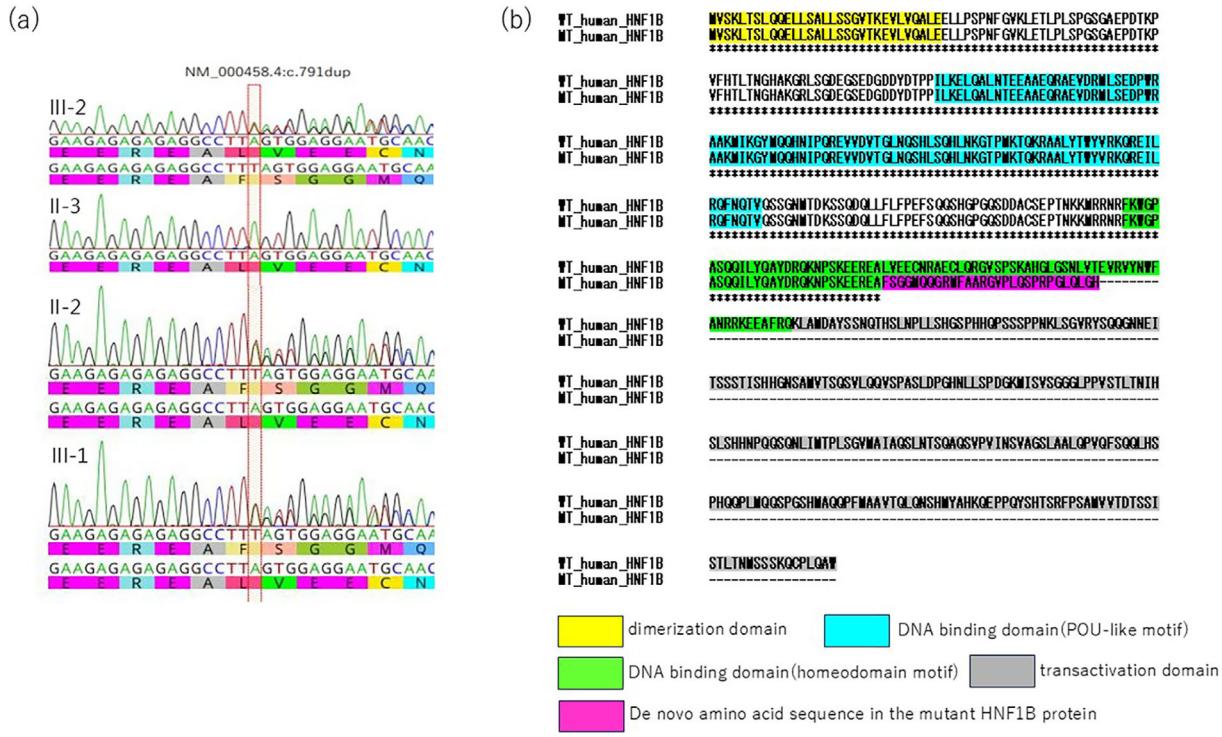

Figure 3. Sanger sequencing of the family members (a) and the hypothetical amino acid sequence derived from the variant cDNA (b). b: Yellow indicates the amino acid sequence of the dimerization domain. Light blue indicates the first DNA binding domain. Light green indicates the second DNA binding domain. Gray indicates the transactivation domain. Purple indicates the *de novo* sequence.

ALL (v4.1.0), HGMD, ClinVar]. Sanger sequencing analyses showed that this variant was present only (in the heterozygous form) in family members with renal disease (Fig. 3a). The variant is located in exon 3, which encodes the second DNA-binding domain of HNF1B. Based on the cDNA sequence of this variant, a truncated mutant protein with a *de novo* amino acid sequence was produced (Fig. 2b). These findings suggest that the mutant protein, if successfully translated, may have an altered association with the genomic DNA. Alternatively, the variant transcript may be degraded via nonsense-mediated mRNA decay (NMD).

Discussion

HNF1B-associated disorders demonstrate a broad spectrum of disease phenotypes, including renal phenotypes,

Table 2. HNF1B-associated Disease Phenotypes in This Family

Typical HNF1B-associated phenotypes	II-2	III-1	III-2
Neurological features	none	none	none
Abnormal liver function	none	yes	yes
Mature-onset diabetes of the young type 5 (MODY5)	yes	none	none
Pancreatic hypoplasia	yes	none	yes
Developmental kidney disease	yes	yes	yes
Genital tract malformations	none	none	none
Hypomagnesemia	yes	yes	yes
Early-onset hyperuricemia	yes	yes	yes
HNF1B score (cutoff value ≥8)	16 (family history, left and right kidney hypoplasia, MODY, Low serum Mg2+)	14 (family history, left and right renal cysts, Low serum Mg2+, liver test abnormalities of unknown origin)	18 (family history, left and right renal cysts, Low serum Mg2+, pancreatic hypoplasia, liver test abnormalities of unknown origin)

type 2 diabetes, pancreatic hypoplasia, liver test abnormalities, early onset gout, and genital tract deformity. This is explained by the fact that *HNF1B* encodes a transcription factor, hepatocyte nuclear factor 1β, which governs tissue-specific gene expression in the epithelial cells of various organs, including kidney, pancreas, liver, and genitourinary tract (4). Carriers of HNF1B variants are known to exhibit an extraordinarily variable phenotype, with no clear evidence of a genotype-phenotype relationship having been obtained (6). In accordance with these features of *HNF1B*-associated disorders, our ADTKD-affected family demonstrated a wide variety of extrarenal phenotypes (Table 2). The phenotypes varied among all affected individuals in this family despite having a similar genetic background. The father of the proband (patient II-2) exhibited IUGR, a rare *HNF1B*-associated phenotype that remains unknown (7). The high HNF1B scores (8) in these patients indicate that this form of ADTKD might be compatible with ADTKD-*HNF1B*.

This family's gene variant affecting the second DNA-binding domain is novel. If the variant HNF1B protein was successfully translated, it would have a truncated form containing a *de novo* sequence composed of 30 amino acids, the function of which is unknown. A previous report revealed that disease-causing *HNF1B* missense and frameshift variants were clustered in the first four exons of the gene, particularly in exons 2 and 4, which encode two different DNA-binding domains (9). The variant in the present family, located in exon 3, was predicted to produce a truncated protein with a *de novo* 30-amino-acid sequence from almost the middle of the second DNA-binding domain (Fig. 3b). Previous case reports have identified truncating pathogenic variants, p.Q275* (10) and p.R276* (11), around the pathogenic variant of this family. If the encoded variant protein is successfully produced, it might exhibit a different affinity for genomic DNA, giving rise to a different pattern of gene expression in the tissues. Interestingly, all patients in this family showed hypomagnesemia (Table 1), suggesting that this variant might affect the expression of *FXYD2*, a gene responsible for autosomal dominant hypomagnesemia (12). Alternatively, the variant transcript could be degraded by NMD. A previous study on the susceptibility of truncating HNF1B variants to NMD revealed that four of the pathogenic variants showed reductions in variant RNA relative to the wild-type allele were as follows: 181X(A), 71%; R181X (B), 45%; Q243fsdelC, 24%; P328 L329fsdelCCTCT, 22%; and A373fsdel, 29, 3%. This suggests that NMD plays an important role in the pathogenesis of HNF1B-associated disease. The same study identified that the position of the variant determines the 5' to 3' polarity (13). Given this context, further studies are needed to clarify the underlying disease mechanisms.

The authors state that they have no Conflict of Interest (COI).

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