A Novel *UMOD* Gene Mutation Associated with Uromodulin-associated Kidney Disease in a Young Woman with Moderate Kidney Dysfunction

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**Abstract**

Uromodulin-associated kidney disease (UAKD) is an autosomal dominant disease caused by a mutation in the *uromodulin* (*UMOD*) gene, leading to end-stage renal disease. We herein report the case of a family with UAKD caused by a novel mutation (C135G) in the *UMOD* gene. A 31-year-old woman had a low estimated glomerular filtration rate (59.7 mL/min per 1.73 m²). Her father, grandfather and paternal aunt had received maintenance hemodialysis therapy since their 40’s. This case underscores the importance of performing genetic testing in young patients even in cases involving only moderate abnormalities in the kidney function.

**Key words:** medullary cystic kidney disease type 2, familial juvenile hyperuricemic nephropathy, uromodulin, UMOD, hyperuricemia, chronic kidney disease

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**Introduction**

Uromodulin, also called the Tamm-Horsfall protein, is produced in the kidneys by cells of the thick ascending limb of the loop of Henle (TALH) and distal tubules. Healthy individuals excrete approximately 20-70 mg of uromodulin per day (1). Mutations within the *uromodulin* (*UMOD*) gene cause uromodulin storage diseases and chronic kidney disease (CKD) (2-5). *UMOD* gene mutations in chromosome 16p12 result in uromodulin-associated kidney disease (UAKD), including medullary cystic kidney disease (MCKD) type 2 and familial juvenile hyperuricemic nephropathy (FJHN) (6). A distinct clinical entity from MCKD type 1 is associated with a mutation in chromosome 1q21 (7). MCKD type 2 follows a pattern of autosomal-dominant inheritance, with end-stage renal disease (ESRD) occurring in the fourth decade of life or later (8).

In most CKD patients, the disease is detected based on routine laboratory tests, such as urinalyses. However, a small number of patients exhibit mild abnormalities (e.g., a low glomerular filtration rate) of unknown cause without proteinuria or other common sequelae of CKD. We herein report the case of a family with UAKD, which caused early-onset CKD without evident proteinuria when the members were young adults.

**Case Report**

The patient was a 31-year-old Japanese woman who had not been previously diagnosed with organ abnormalities or taken conventional or traditional Chinese medications. Laboratory results showed CKD stage 3 (estimated glomerular filtration rate 59.7 mL/min per 1.73 m²), mild hyperuricemia...
(6.9 mg/dL), protein excretion of urinalysis within the normal limits (0.02 g per day) and the absence of microscopic hematuria or casts. On presentation, she had a normal blood pressure and body mass index (20.9 kg/m²). There were no electrolyte imbalances or immune markers irregularities. Magnetic resonance imaging of the kidneys showed no medullary cysts or abnormalities of the urinary tract. On echographic images, the patient’s kidneys were smaller than those of healthy individuals (right: 87×44 mm, left: 85×37 mm), although no other structural abnormalities were apparent. A histological analysis showed diffuse tubulointerstitial fibrosis with inflammatory cell infiltration and tubular atrophy; however, no cystic formations were observed in the kidney biopsy specimens (Fig. 1). Of the 40 glomeruli examined, 25% showed global sclerosis. There was no evidence of segmental sclerosis, crescent formation or mesangial increases in the other glomeruli. The immunofluorescence results did not indicate immunoglobulin or complement deposition in the glomeruli.

The patient’s grandfather, father and paternal aunt had developed ESRD of unknown cause, without proteinuria, and started maintenance hemodialysis while in their 40’s (Fig. 2). Her grandfather and father also had hyperuricemia and gout as young adults before starting maintenance hemodialysis therapy. Based on her family history of kidney dysfunction, we speculated that the patient and her family carried a UMOD gene mutation and subsequently performed a DNA analysis of the patient and her father after obtaining their consent. The DNA analysis was approved by the Ethics Committee of Kobe University Graduate School of Medicine. Briefly, genomic DNA was extracted from peripheral blood mononuclear cells using the Quick Gene DNA whole blood kit S (Fuji Film, Tokyo, Japan). All 10 coding exons of UMOD were amplified via polymerase chain reaction (PCR), and the PCR products were analyzed using direct sequencing (3100 Genetic Analyzer, Life Technologies Japan, Tokyo, Japan). A mutation analysis of UMOD showed that both the patient and her father harbored a novel T403G substitution in exon 4 that resulted in a C135G amino acid ex-
change (Fig. 3). Therefore, the patient was diagnosed as having UAKD and treated with allopurinol for hyperuricemia.

**Discussion**

In order to predict the functional effects of missense mutations in this study, we used the Polyphen 2 (Polymorphism Phenotyping v2, http://genetics.bwh.harvard.edu/pph2/) and Sorting Intolerant From Tolerant (SIFT, http://sift.jcvi.org/) systems. The Polyphen 2 score for the mutation was 0.958 (sensitivity: 0.63 and specificity: 0.92) and the SIFT score was 0.006 (9). We found no UMOD mutations in the DNA samples obtained from 100 healthy Japanese individuals using the same techniques, indicating that the T403G substitution is the likely cause of the current patient’s pathogenic condition.

UAKD is characterized by several features of hereditary nephropathy associated with UMOD gene mutations. MCKD type 2 and FJHN are considered forms of UAKD. However, UAKD is distinguished by its variable severity of symptoms, including hyperuricemia, gout and CKD (10, 11). Meanwhile, MCKD type 2 is a rare type of progressive tubulointerstitial nephropathy with autosomal dominant inheritance that results in the development of ESRD in adulthood. Compared to MCKD type 1, MCKD type 2 is associated with a more severe phenotype involving hyperuricemia and gout (12). Moreover, MCKD type 2 exhibits a younger median age at onset (32 years for MCKD type 2 versus 62 years for MCKD type 1) (7).

The uromodulin protein contains three epidermal growth factor (EGF) domains, a cysteine-rich region and a zona pellucida domain (10). The entire protein consists of 640 amino acids, including 48 cysteine residues (7.5%) required for the formation of disulfide bonds (12). To date, 76 distinct UMOD mutations have been identified (Table 1), many of which are missense changes in one of the conserved cysteine residues clustered in exon 4 encoding the first EGF domain. Furthermore, of the 74 known nucleotide polymorphisms, 38 involve cysteine residues (51.4%), and cysteine residues clustered in exon 4 encoding the first EGF domain.

### Table 1. Mutations in the *UMOD* Gene

| No. | Exon | NC | ECS | Ref |
|-----|------|----|-----|-----|
| 1   | 4    | 95 G>A | C132Y | 14 |
| 2   | 4    | 96 C>G | C131W | 22 |
| 3   | 4    | 100 G>A | E34K | 12 |
| 4   | 4    | 149 G>C | C50S | 23 |
| 5   | 4    | 156 T>G | C52W | 21 |
| 6   | 4    | 172 G>T | G58C | 24 |
| 7   | 4    | 176 A>C | D50A | 5 |
| 8   | 4    | 187 T>C | C63R | 25 |
| 9   | 4    | 205 T>C | C69R | 12 |
| 10  | 4    | 206 G>A | C69Y | 24 |
| 11  | 4    | 229 T>G | C77G | 10 |
| 12  | 4    | 230 G>A | C77Y | 4 |
| 13  | 4    | 307 G>T | G103C | 3 |
| 14  | 4    | 317 G>A | C106Y | 24 |
| 15  | 4    | 334 T>C | C112R | 5 |
| 16  | 4    | 376 T>C | C126R | 5 |
| 17  | 4    | 383 A>G | N128S | 4 |
| 18  | 4    | 403 T>G | C135G | present |
| 19  | 4    | 403 T>A | C135S | 21 |
| 20  | 4    | 442 T>C | C149R | 12 |
| 21  | 4    | 443 G>A | C149Y | 3 |
| 22  | 4    | 444 T>G | C148W | 26 |
| 23  | 4    | 449 G>C | C150S | 26 |
| 24  | 4    | 509 G>A | C170Y | 5 |
| 25  | 4    | 514 G>C | C172R | 12 |
| 26  | 4    | 520 T>C | C174R | 27 |
| 27  | 4    | 529_555 del | 177_185 del | 3 |
| 28  | 4    | 552 G>C | W184C | 12 |
| 29  | 4    | 553 C>T | R185C | 12 |
| 30  | 4    | 553 C>A | R185S | 5 |
| 31  | 4    | 553 C>G | R185G | 22 |
| 32  | 4    | 554 G>A | R185H | 12 |
| 33  | 4    | 563_661 del | 188_221 del | 5 |
| 34  | 4    | 584 G>T | R195F | 21 |
| 35  | 4    | 585_586 CG>TA | D196N | 32 |
| 36  | 4    | 586 G>T | D196Y | 28 |
| 37  | 4    | 586 G>A | D196N | 22 |
| 38  | 4    | 605 G>C | W202S | 21 |
| 39  | 4    | 610 C>G | R204P | 12 |
| 40  | 4    | 610 C>G | R204G | 5 |
| 41  | 4    | 628 G>A | G210S | 12 |
| 42  | 4    | 649 T>G | C217G | 12 |
| 43  | 4    | 649 T>C | C217R | 3 |
| 44  | 4    | 651 C>G | C217W | 22 |
| 45  | 4    | 665 G>C | R222P | 5 |
| 46  | 4    | 667 T>C | C223R | 22 |
| 47  | 4    | 668 C>G | C223Y | 29 |
| 48  | 4    | 674 C>T | T225M | 5 |
| 49  | 4    | 674 C>A | T225K | 30 |
| 50  | 4    | 686 G>T | M229R | 14 |
| 51  | 4    | 688 T>C | W230R | 31 |
| 52  | 4    | 707 C>T | P236L | 21 |
| 53  | 4    | 710 C>G | S237C | 12 |
| 54  | 4    | 743 G>C | C248S | 24 |
| 55  | 4    | 744 C>G | C248W | 10 |
| 56  | 4    | 749 A>T | H250L | 12 |
| 57  | 4    | 764 G>A | C255Y | 4 |
| 58  | 4    | 809 G>T | G270C | 13 |
| 59  | 4    | 817 G>A | V273L | 12 |
| 60  | 4    | 821 A>G | V274C | 24 |
| 61  | 4    | 844 T>C | C282R | 5 |
| 62  | 4    | 855 A>G | A285E | 12 |
| 63  | 5    | 891 T>G | C297W | 32 |
| 64  | 5    | 893 G>A | C297Y | 12 |
| 65  | 5    | 898 T>G | C300G | 4 |
| 66  | 5    | 899 G>A | C300Y | 33 |
| 67  | 5    | 920 A>C | K307T | 34 |
| 68  | 5    | 943 T>C | C315R | 26 |
| 69  | 5    | 944 A>G | A315Y | 12 |
| 70  | 5    | 947 A>C | Q316P | 35 |
| 71  | 5    | 950 G>A | C317Y | 26 |
| 72  | 6    | 1039 T>G | C347G | 36 |
| 73  | 8    | 1382 A>G | A461E | 12 |
| 74  | 8    | 1406 C>T | T469M | 12 |
| 75  | 8    | 1462 G>C | C488R | 22 |
| 76  | 9    | 1815 A>G | T605G | 37 |
residues account for 25 of the 54 known mutation positions (46.3%) (Table 2). Similar to that observed in many previous cases, the UMOD gene mutation detected in our patient and her father was within exon 4 of the EGF domain 3, suggesting that the loss of a cysteine residue in the EGF domain leads to the initiation or progression of UAKD. In fact, the onset of ESRD occurs significantly earlier in individuals with UMOD mutations within EGF domain 2 or 3 (range, 45-52 years) compared to that associated with mutations within the cysteine-rich domains (range, 60-65 years) (10).

The diagnosis of UAKD is made based solely on the presence of UMOD mutations detected on a DNA analysis. Therefore, the clinical and pathologic features of patients with UMOD mutations are well known. For example, the pathologic findings of UAKD patients include tubular atrophy, interstitial fibrosis, tubular basement membrane thickening, lamellation and the presence of fibrillar inclusion bodies in TALH cells on light microscopy (13). The results of immunohistochemical staining for UMOD in our patient showed intense staining of dense and coarse intracytoplasmic aggregates within the cells of the TALH (Fig. 4). In contrast, kidney tissues without UMOD gene mutations exhibit diffuse staining for UMOD within the cells of the TALH (13). UMOD urinary excretion is generally decreased in MCKD type 2/FJHN patients (14). However, the decreased UMOD excretion may occur secondary to renal disease (15). Therefore, urine tests may be not effective for making the diagnosis of UAKD. An in vitro investigation recently revealed that the intracellular accumulation of mutant UMOD in the endoplasmic reticulum induces apoptosis and causes progressive kidney dysfunction (16). However, the pathophysiology of this condition remains unclear in the clinical setting.

Hyperuricemia has been reported to develop in approximately 80% of MCKD type 2/FJHN patients (17). A previous report showed that hyperuricemia is effectively treated with allopurinol (18) or uricosuric drugs such as benzbro-

### Table 2. Numbers of Mutations of Amino Acid  

| Amino acid | Cases (n=74) | Positions (n=54) |
|------------|-------------|-----------------|
| Cys        | 38 (51.4%)  | 25 (46.3%)      |
| Arg        | 7           | 3               |
| Gly        | 5           | 5               |
| Asp        | 5           | 3               |
| Thr        | 4           | 3               |
| Trp        | 3           | 3               |
| Ala        | 2           | 2               |
| Glu        | 1           | 1               |
| His        | 1           | 1               |
| Asn        | 1           | 1               |
| Pro        | 1           | 1               |
| Ser        | 1           | 1               |
| Val        | 1           | 1               |
| Met        | 1           | 1               |
| Tyr        | 1           | 1               |
| Lys        | 1           | 1               |
| Gln        | 1           | 1               |

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