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**Autosomal dominant tubulointerstitial kidney disease with a novel heterozygous missense mutation in the uromodulin gene: A case report**

Zhang LL *et al*. Novel heterozygous mutation in the UMOD

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**Abstract**

BACKGROUND

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a progressive chronic disease that is inherited in an autosomal dominant fashion. Symptoms include hyperuricemia, gout, interstitial nephritis, renal cysts, and progressive renal damage that can lead to end-stage renal disease. Mutations in the uromodulin gene (UMOD) characterize the ADTKD-UMOD clinical subtype of this disease. Till now, more than 100 UMOD mutations have been identified. Early diagnosis of ADTKD-UMOD is important to treat the disease, slow down disease progression, and facilitate the identification of potentially affected family members.

CASE SUMMARY

A 40-year-old male harboring a novel heterozygous missense mutation in UMOD (c.554G>T; p. Arg185Leu). The person was suffering from hyperuricemia, gout, and chronic kidney disease. The same mutation was detected in his daughter, aunt, and cousin.

CONCLUSION

In the family affected by ADTKD-UMOD in the present report, a single nucleotide substitution in the exon 3 of UMOD was responsible for the heterozygous missense mutation (c.554G>T, p.Arg185Leu) in this gene.

**Key Words:** Autosomal dominant tubulointerstitial kidney disease; Hyperuricemia; Uromodulin gene; Mutation; Case report

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**Core Tip:** Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a progressive chronic disease that is inherited in an autosomal dominant fashion. It can cause multiple organ damage, and even end-stage renal disease. Mutations in the uromodulin gene (UMOD) characterize the ADTKD-UMOD clinical subtype of this disease. We report a novel heterozygous missense mutation in UMOD (c.554G>T; p. Arg185Leu). This mutation has not been previously reported, it can help facilitate the presymptomatic diagnosis of this rare condition, in addition to helping guide genetic counseling and family planning for relatives of affected individuals.

**INTRODUCTION**

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a set of heritable renal disorders that are characterized by autosomal dominant inheritance and clinical findings of tubulointerstitial disease in affected individuals. Most patients present with hyperuricemia, gout, arthritis, interstitial nephritis, and progressive renal damage, whereas some patients develop end-stage renal disease (ESRD) within 10–20 years[[1](#_edn1)]. Renal biopsy of patients with ADTKD often indicates interstitial fibrosis, tubular atrophy, and renal cysts[[2](#_edn2)]. Pathogenic mutations associated with ADTKD are present in the uromodulin gene (UMOD) in 40% of cases, whereas mutations in either renin or hepatocyte nuclear factor-1β genes are detected in 2.5% of cases[3,4]. UMOD mutations are considered under the clinical ADTKD-UMOD disease subtype, and most UMOD mutations are localized to exons 3, 4, and 5 of this gene in the chromosome 16p11–p13 region[5-8].

Uromodulin is the most abundant protein in urine and is released from epithelial cells *via* proteolytic cleavage within the loop of Henle[9,10]. Missense mutations in this gene lead to misfolding of this protein and its accumulation within the endoplasmic reticulum of affected cells, thereby impairing urinary excretion[11]. These mutations also lead to disrupted trafficking of Na+-K+-2Cl− cotransporters in the luminal membrane of affected cells[12]. This ultimately leads to impaired urine concentration, increased rates of proximal tubular sodium and urate reabsorption, hyperuricemia, and gout, which are the clinical characteristics of ADTKD.

Owing to changes in diets and other factors, the rates of hyperuricemia are increasing annually and the age of ADTKD onset is decreasing continuously, similar to ADTKD-UMOD. However, the risk factors, pathogenesis, and prognosis of these two disease isoforms differ considerably. Early diagnosis of ADTKD-UMOD is important to treat the disease, slow down disease progression, and facilitate the identification of potentially affected family members. Identification of potentially affected family members can facilitate decision-making about donors and family planning. In the present study, we report the case of a 40-year-old Chinese male harboring a novel heterozygous missense mutation in UMOD, which was also detected in his seven family members.

**CASE PRESENTATION**

***Chief complaints***

The patient was a 40-year-old male who was admitted to the hospital because of an increased pain in the metatarsal joints and renal impairment.

***History of present illness***

Of 15 years previously, the patient was diagnosed with gout.

***History of past illness***

The patient had a free previous medical history.

***Personal and family history***

The pro-band had a family history of hyperuricemia as his grandmother, father, two of his aunts, and two of his female cousins were diagnosed with hyperuricemia and gout. The grandmother, father, one aunt, and one female cousin had been undergoing hemodialysis and died between the ages of 30 and 50 years. In addition, the patient’s 9-year-old daughter had also been diagnosed with hyperuricemia based on her 5.6 mg/dL serum uric acid level (normal range for children between the ages of 1 and 10: Less than 5.3 mg/dL)[13] (Figure 1).

***Physical examination***

The patient’s temperature was 36.7 ºC, her heart rate was 88 bpm, respiratory rate was 14 breaths per minute, blood pressure was 132/78 mmHg, and oxygen saturation in room air was 100%. Physical examination indicated the presence of a mildly painful nodule behind the auricle, slight pain and swelling of the knee joints, serious pain and deformity of the interphalangeal joints, and gout stones on the 1 s metatarsal joints in the feet of the patient (Figure 2).

***Laboratory examinations***

The patient had respective blood urea nitrogen and serum creatinine levels of 50.5 mg/dL and 6.2 mg/dL (normal ranges: 7.30–21.06 mg/dL and 0.46–0.82 mg/dL, respectively). The patient had a serum uric acid level of 13.2 mg/dL (normal range: 2.6–6.0 mg/dL), whereas fractional uric acid excretion was reduced by 3.43%. Other laboratory test results were within normal ranges.

***Imaging examinations***

Renal ultrasonography showed that the patient’s kidneys were relatively atrophic (longitudinal image; 8.1 and 8.7 cm in the major axis of right and left kidneys), indicating the presence of cysts and suggestive of ESRD (Figure 3). Analysis of the knee joints by computed tomography showed high bone density, the presence of high-density shadows, narrowing of the joint space, and soft tissue swelling, which were consistent with the patient’s gout/arthritic symptoms (Figure 4).

***Further diagnostic work-up***

Considering the family history of kidney disease, juvenile-onset of hyperuricemia, symptoms of gout/arthritis, and progressive renal impairment beginning at an early age, ADTKD-UMOD was considered highly probable.

After receiving written informed consent from the four affected living members of the patient’s family, DNA analyses, clinical data collection, and image publication were performed for these individuals. The peripheral blood was sent to *CIPHER* gene to perform the whole exome sequencing by Illumina HiSeq (the specific method can be consulted in the Supplementary material). Genetic analyses revealed the presence of a novel heterozygous missense mutation in UMOD exon 3 of the patient, his daughter, aunt, and younger female cousin (Figure 5). The conclusion of the genetic test is “Variants of unknown clinical significance” according to ACMG genetic variation classification standards and guidelines, the variation site is heterozygous, and the zygote type can explain the patient’s disease. Furthermore, this missense mutation was the result of nucleotide exchange at position c.554 (c.554G>T), in which leucine was replaced by arginine at position 185 in the final protein (p.Arg185Leu). This resulted in abnormal folding of the uromodulin protein, leading to its accumulation within the ER and impaired trafficking through the cell.

**FINAL DIAGNOSIS**

The final diagnosis of the presented case is autosomal dominant tubulointerstitial kidney disease with a mutation in the UMOD.

**TREATMENT**

Medications aimed at controlling uric acid levels were administered to the patient but these medications were not efficacious in controlling the gradually increasing serum creatinine and uric acid levels. Recently, the glomerular filtration rate for this patient decreased to 6.3 mL/min/1.73 m2. Hence, we recommended arteriovenous fistula surgery for hemodialysis preparation. Moreover, his affected family members do not currently require dialysis but should maintain a healthy lifestyle and preventatively take uric acid medications to control the onset of hyperuricemia.

**OUTCOME AND FOLLOW-UP**

The patient received regular blood dialysis and medications, and gout is controlled.

**DISCUSSION**

ADTMD is a condition also referred to as medullary cystic kidney disease, familial juvenile hyperuricemic nephropathy, and UMOD-associated kidney disease. Recently, ADTKD has been proposed as a collective term to refer to the aforementioned progressive kidney diseases[3]. Most cases of ADTKD present with mutations in the *UMOD*, *REN*, *MUC1*, *TCF2*, or *SEC51A1* genes[14,15]. ADTKD-UMOD disease subtype is the most common, and the clinical features of all disease subtypes differ based on the mutated gene.

Uromodulin is the most abundant protein in urine and is the primary component of urinary casts that are encoded by chromosome 16p11-p13[7]. Mutations in this gene can result in defective sodium transport in the thick ascending limb, leading to natriuresis that results in secondary proximal tubular sodium and urate uptake. This abnormal sodium and urate uptake further leads to hyperuricemia and gout. In addition, misfolded uromodulin deposits accumulate in the endoplasmic reticulum of affected epithelial cells[11]. Owing to these molecular mechanisms, UMOD mutations can result in conditions such as progressive distal tubular dysfunction, hyperuricemia[11,16], hyperuricemic nephropathy[17], urinary tract stone formation[18], salt-sensitive hypertension, and kidney damage[19]. However, uromodulin excretion is reduced even in ADTKD patients without UMOD mutations[20], and UMOD-knockout mice are not hyperuricemia[21]. In addition, other recent studies have suggested that mutated uromodulin in the kidneys may elicit an immune response that is specific to this protein, ultimately leading to the observed tubular injury and interstitial fibrosis[22]. Hence, that further work is needed to elucidate the underlying mechanisms of ADTKD-UMOD in detail.

ADTKD-UMOD can be diagnosed based on UMOD sequence analyses or immunostaining for misfolded uromodulin protein. However, misfolded uromodulin staining is not routinely performed in pathology laboratories, and only a limited number of institutions can perform this specialized test. In addition, many patients are not eligible for a kidney biopsy at the time of diagnosis, similar to the case reported in this study.

Currently, whether treatment of this condition with allopurinol or febuxostat can effectively reduce blood uric acid levels, relieve gout symptoms, and slow down progressive kidney impairment is unclear. The patient in the present report did not achieve disease remission after receiving medicines aimed at uric acid treatment, and eventually developed ESRD at an early age. However, whether dialysis or renal transplantation can help patients achieve long-term remission will require further study.

**CONCLUSION**

When a young adult individual presents with hyperuricemia and having a family history of hyperuricemia, ADTKD-UMOD should be considered and UMOD DNA analyses are necessary. Identification of the pathogenic mutations governing this condition can help facilitate the presymptomatic diagnosis of this rare condition, in addition to genetic counseling and family planning for relatives of affected individuals.

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**Footnotes**

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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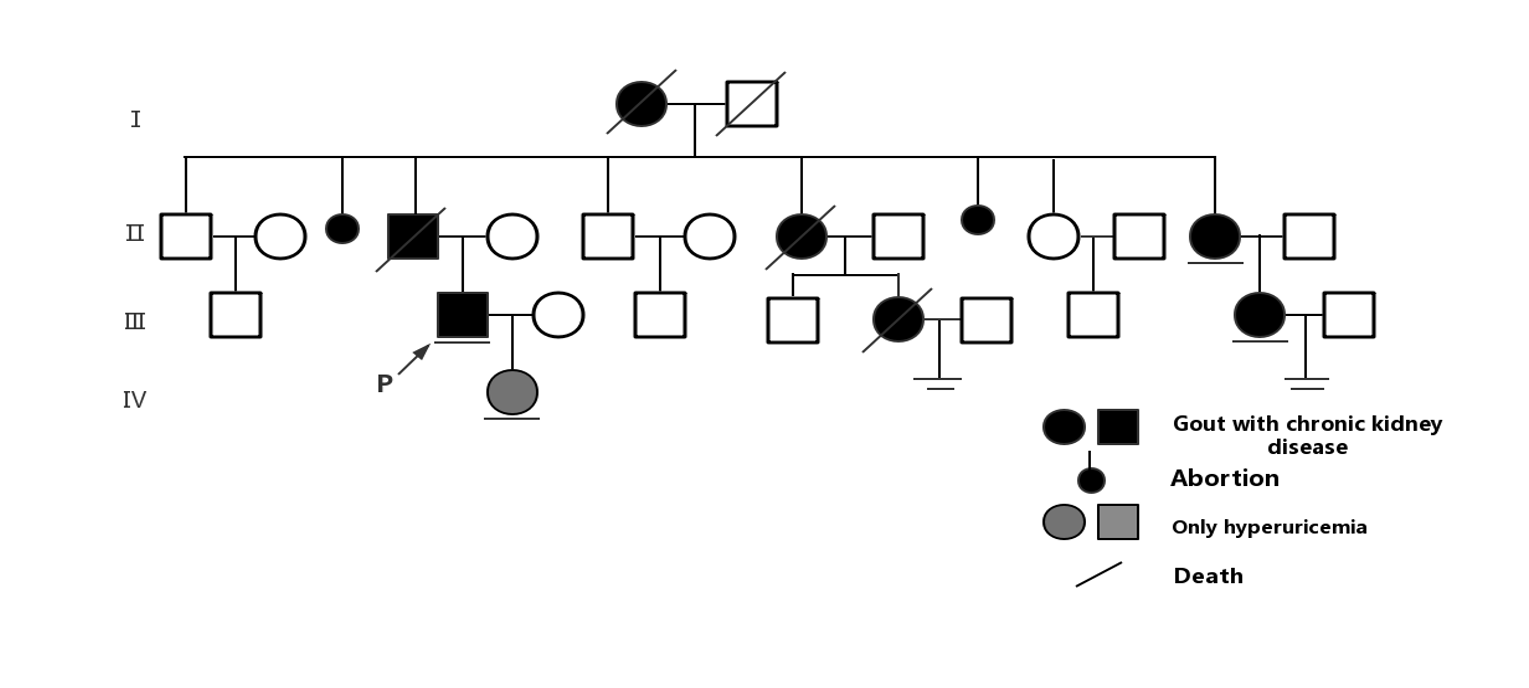
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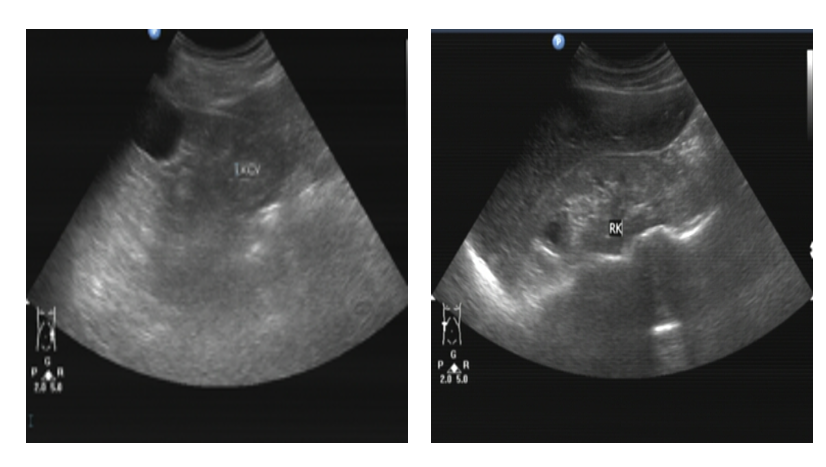
**Figure Legends**



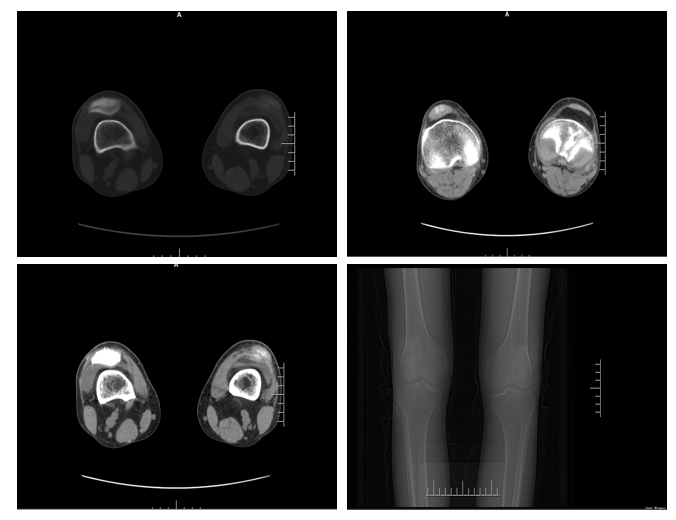
**Figure 1** **Pedigree for the family of the patient, indicating individuals affected by familial hyperuricemia and chronic kidney diseases.** (1) Black and gray symbols corresponding to the affected individuals, with the patient described in this case report marked with an arrow; and (2) Lines under individuals indicate people who provided DNA samples, while the two underlines denote couples with no children.



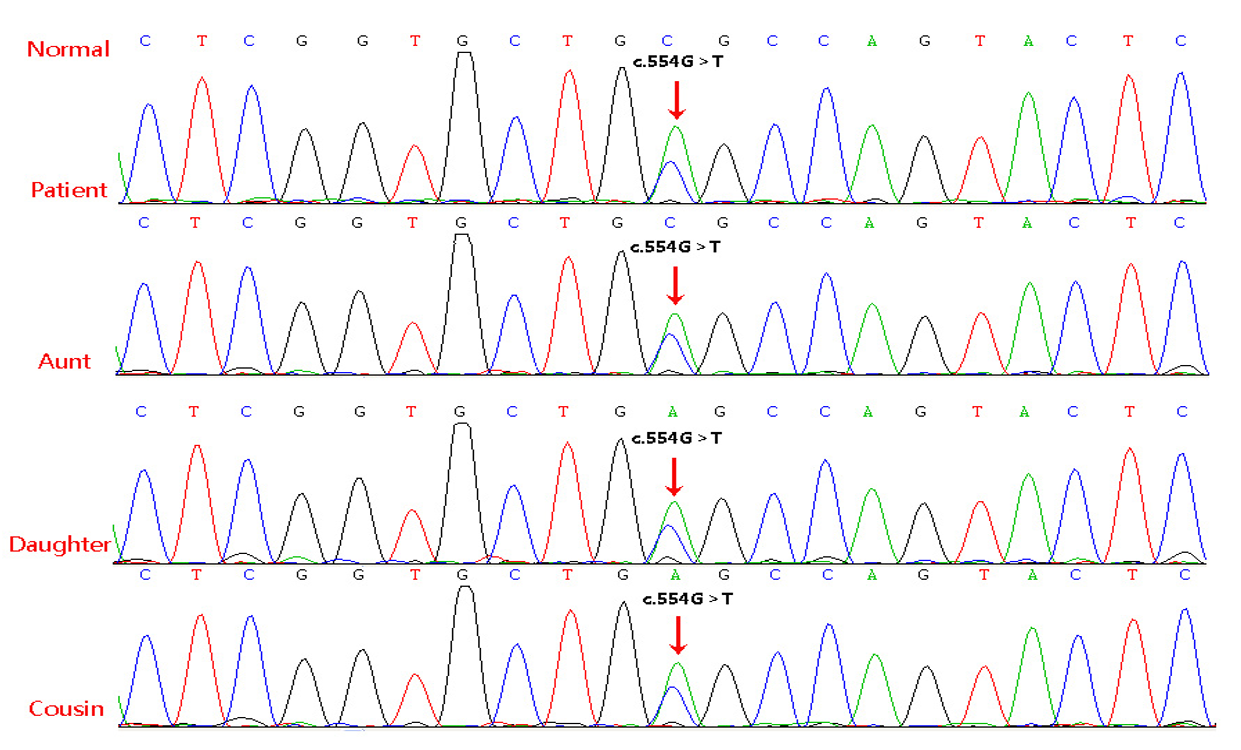
**Figure 2** **Swelling, gout stones, and deformity of the interphalangeal joints, with two large gout stones affecting the 1s metatarsal joints of the feet in the patient.**



**Figure 3** **Renal ultrasound findings of the patient, revealing relatively atrophic kidneys with multiple secondary cysts.**



**Figure 4** **Computed tomography scans demonstrating joint space narrowing, soft tissue swelling, and high density urate crystal deposition in the patient.**



**Figure 5** **Genomic DNA sequence electropherograms for the proband, affected family members, and normal DNA.** The arrow corresponds to a G>T transversion at position 554 of the uromodulin in chr16 (GenBank accession number NM\_003361.3). This mutation was heterozygous in the proband, his daughter, his aunt, and his younger female cousin, respectively.