# Autosomic Dominant Tubulo Interstitial Kidney Disease: Case Report of a New Variant of the UMOD Gene

Nefrologo in corsia

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**ABSTRACT**

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a low-prevalence pathology mainly associated with pathogenic variants of the UMOD gene. It is characterized by the progressive deterioration of renal function, associated with hyperuricemia and accompanied by a family history of gout or hyperuricemia. Often, clinical variability and a lack of molecular testing results in diagnostic failure to determine the ADTKD-UMOD association.

**Case presentation:** We describe the case of a 14-year-old male who presented to the nephrology service with hyperuricemia, renal ultrasonographic changes, and progression to chronic kidney disease in 4 years. He had a family history of hyperuricemia. A probable genetic disease with an autosomal dominant inheritance pattern was considered, confirmed by the presence of a probably pathogenic variant of the UMOD gene, not previously reported in the literature.

**Conclusion:** The investigation of this case led to the identification of a new variant in the UMOD gene, broadening the spectrum of known variants for ADTKD-UMOD. In addition, in this case, a comprehensive anamnesis, that takes into account family history, was the key point to carry out genetic tests that confirmed the diagnosis suspicion. Directed Genetic tests are currently an essential diagnostic tool and should be performed as long as they are available and there is an indication to perform them.

**KEYWORDS**: UMOD, Uromodulin, hyperuricemia, Uric acid, Familial Juvenile Hyperuricemic Nephropathy, case report

## Introduction

Interstitial nephropathies (IN) compromise not only the interstitial tissue of the kidney, but also the renal parenchyma, affecting the glomerulus, tubules and blood vessels at the renal level [1, 2]. Autosomal dominant tubulointerstitial kidney disease (ADTKD) was recently introduced in the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines [3], and includes genetic disorders with high penetrance (~100%); however, few cases have been reported in unaffected heterozygous individuals [4]. To date (April 2023), five genes associated with the disease have been described: UMOD (ADTKD-UMOD), REN (ADTKD-REN), MUC1 (ADTKD-MUC1), HNF1B (ADTKD-HNF1B) and SEC61A1, the last one still without clear clinical relevance and defined outcome [1–3, 5].

Regarding frequency, the main cause of ADTKD is secondary to pathogenic variants in the MUC-1 gene (Spain 42.5% and Ireland 64%), followed by the UMOD gene (35%), and in third place HNF1B gene variants (13.9%). So far, only 14 affected families have been reported in the literature with REN gene-related ADTKD [6, 7].

The clinical profile can be heterogeneous according to the variant and age group, even within the same families. Different levels of proteinuria, urinary sediment, and microscopic hematuria could be present [2]; despite this, the progressive decrease in renal function that leads to end-stage chronic kidney disease (ESKD) seems to be a characteristic sign [1, 7], which could be; depending on the genetic variant [3, 7, 8], also accompanied by bilateral renal hypoplasia [1].

Corticomedullary differentiation is compromised, and in severe cases, the presence of cystic lesions can be observed. Some specific pathogenic variants in the UMOD gene (ADTKD-UMOD) are associated with hyperuricemia, which may initially be mild but can progress to severe forms [9]. As renal involvement evolves, it can be associated with high blood pressure (HBP). For patients with the REN gene variant (ADTKD-REN), tubulointerstitial involvement may be more severe, even associated with early anemia [1, 5, 7].

The highly nonspecific symptoms, slow progression, and wide variability in the age of presentation of ADTKD have made this a challenging diagnosis [1]. Chronic kidney disease (CKD) caused by pathogenic variants in the UMOD gene has a low prevalence, although it may be underdiagnosed. The variants in UMOD are closely related to ADTKD and medullary cystic kidney disease type 2 (MCKD2) [1, 7]. Therefore, we suspect that understanding the pathology is crucial to carry out a better follow-up and try to reduce the impact of the disease: diminishing the rapid progression towards CKD and the early identification of relatives at risk [1].

## Case presentation

This is a 14-year-old male patient, asymptomatic, who was referred to the pediatric nephrology clinic due to an incidental finding of renal abnormalities evidenced by renal and urinary tract ultrasonography. With no relevant personal pathological history, but with a history of his father diagnosed with gouty nephropathy, end-stage chronic kidney disease at 22 years of age, and a kidney transplant at 28 years of age. Given the paternal history, the parents of the case performed annual laboratory and imaging surveillance, without findings of renal involvement until the patient was 14 years old. In the annual study, bilateral hyperechogenicity of the renal medulla was reported and confirmed with a second ultrasound. The physical examination revealed a good general condition with vital signs within normal parameters for their age, height, and gender, including blood pressure (below the 95th percentile). The patient had an adequate nutritional status for his height, and body mass index in the normal range and without relevant clinical findings.

Based on the imaging findings, we proceeded to rule out associated pathologies that could be related, such as hyperparathyroidism, hypophosphatasia, hypercalcemia, and hypomagnesemia. There was no evidence of any disorder in the metabolism of calcium, phosphorus, or minerals, nor consumption of vitamin D analogues, hypercalciuria or hyperoxaluria, proximal tubulopathy or loop of Henle involvement. Thyroid function was also normal.

The study showed a serum creatinine of 1.3 mg/dl, which resulted in a calculated glomerular filtration rate by modified Schwartz equation of 58 cc/1.73/min and a serum uric acid of 10.8 mg/dl. Therefore, paraclinical confirmation was established, which reaffirmed the presence of KDIGO 3A1 classification CKD plus hyperuricemia without albuminuria or hyperuricosuria.

Given the clinical context of the patient, the family tree was elaborated (Figure 1). There, other cases of paternal line hyperuricemia were identified. And, due to the inheritance pattern, an autosomal dominant disease was considered as a differential diagnosis.

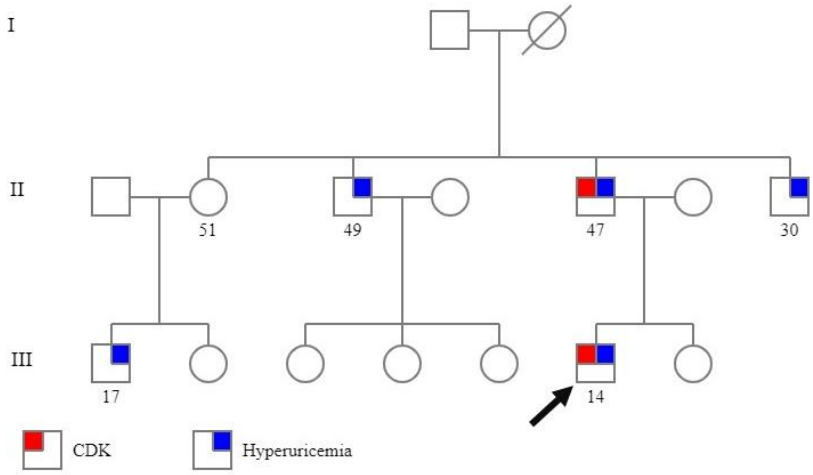


Figure 1. Family tree of the patient described in the clinical case.

A Next Generation Sequencing (NGS) genetic panel was requested for the REN, SEC61A1, and UMOD genes, which reported the presence of a probably pathogenic variant in the UMOD gene: c.287G>C; p.Cys96Ser, which has not been previously described in the literature. A study of the variant was carried out on the patient's father, confirming its presence and the diagnosis in the father. Genetic counseling was carried out on the patient and his parents, and the family variant study was recommended for his sister and all relatives at risk. Simultaneously, while the genetic study was carried out, the medical approach involved initiating treatment with a hypouricemic agent (allopurinol) at 50 mg/m$^2$ every 24 hours. During the patient's follow-up (4 years), the dose was gradually increased, reaching 200 mg/day. At this point, a reduction in hyperuricemia was observed. Despite the progression of the KDIGO stage of chronic kidney disease from 3A1 to 3B1, the treatment dose was stable. Transition to adult nephrology was made as the patient reached 18 years of age. Currently, the patient is clinically and paraclinically stable, without progression of the CKD stage.

## Discussion

ADTKD due to alteration of the UMOD gene (ADTKD-UMOD), was formerly known as familial juvenile hyperuricemic nephropathy type 1 (FJHN1), medullary cystic kidney disease type 2 (MCKD2), or UMOD-associated kidney disease [2, 10]. This is a disease caused by pathogenic or probably pathogenic variants in uromodulin, which is considered rare, but is the second cause of ADTKD-gen-associated disease [8].

Importantly, although ADTKD-UMOD is related to a high percentage of family history of hyperuricemia and kidney disease, in some cases there may be an apparent lack of family history due to incomplete penetrance and variable expressivity of the disease [8]. Therefore, in patients with hyperuricemia or renal disease with no known family history, the possibility of pathogenic variants in the UMOD gene should be considered and genetic studies should be tracked into account for accurate diagnosis and appropriate management [5, 11].

The clinical characteristics of ADTKD-UMOD are determined by the presence of hyperuricemia with progressive deterioration of renal function at an early age [8]. Hyperuricemia is generally associated with hyperuricosuria, which promotes uric acid adherence at the level of tubular epithelial cells [3]. The formation of uric acid crystals in the renal tubules causes a local inflammatory response and histological changes, not only related to these deposits, but also due to hemodynamic disturbances and changes in the vascular structure, leading to glomerular arterial disease [1, 12–14].

Hyperuricemia stimulates the renin-angiotensin system and affects endothelial nitric oxide release and action, leading to magnification of vasoconstriction of the renal vasculature and increased glomerular pressure, followed by glomerulosclerosis and tubulointerstitial fibrosis [3, 12–15].

It's important to remember that ADTKD is one of the causes of ESRD and is associated with the UMOD, MUC, HNF1B, REN, and SEC61A1 genes [1, 7, 15], with UMOD being the most frequent [1, 5].

The UMOD gene encodes uromodulin, also known as the Tamm-Horsfall glycoprotein. This protein is highly glycosylated and contains four epidermal growth factor (EGF) like domains, a cysteine-rich (D8C) domain, and a zona pellucida bipartite domain, allowing for protein polymerization [4]. Uromodulin binds to glycosylphosphatidylinositol and promotes the integrity and impermeability of the thick ascending limb of the loop of Henle [15–17]; it is also expressed in the initial part of the distal convoluted tubule [2].

Patients with disease-causing variants have low urinary uromodulin excretion due to impaired uromodulin retention in the endoplasmic reticulum of the tubular cells of the ascending limb of the loop of Henle [18–21]. Consequently, the abnormal expression of the protein in the thick ascending branch of the loop of Henle generates a decrease in the reabsorption of Na+K+-2Cl, generating alterations in the urinary concentration capacity, promoting the reabsorption of sodium and urate at the proximal contouring tubule level [16]. All these actions cause local inflammatory processes that generate atrophy and cell death, which leads to an impact on the urinary excretion of uric acid, determining hyperuricemia and progressive CKD [18, 20, 22].

In our patient and his father, the presence of the variant c.287G>C, p.Cys96Ser in heterozygosity, classified as probably pathogenic, located in the exon 4 of the UMOD gene was evidenced. To date, this variant has not been reported in the literature; variants in the same codon have been classified as probably pathogenic, which suggests that this change can generate a deleterious effect on uromodulin. Furthermore, we analyzed fifteen in silico predictors, all of which classified the variant as pathogenetic. It has been described that approximately 95% of the UMOD gene variants are located in exons 3 and 4, which correspond to the N-terminal portion of the protein and encode the four domains similar to EGF and D8C [23].

We would like to highlight that the mutations associated with the ADTKD generate early-onset progressive CKD [3, 10], even in adolescence [2]. Our patient presented hyperuricemia at the age of 14. He also had changes in the renal parenchyma and in the end, the result of a genetic study revealed a probably pathogenic variant in the UMOD gene, which was inherited from his father, who also had renal pathology. The initial findings were incidental and were discovered as part of the active search for renal pathology due to his family history.

In a retrospective study that included 109 patients belonging to 45 families with variants in the UMOD gene and variable degrees of CKD, the presence of 37 different variants was determined; of these, 19 were de novo. Hyperuricemia was found in 80% of the cases [24].

In our case, the early presentation of hyperuricemia in both the patient and his father, and the progressive evolution to CKD are noteworthy. These findings are consistent with what was described in an international cohort study of 726 patients belonging to 585 families, in which a prevalence of hyperuricemia of 66% was reported and a family history of CKD or hyperuricemia was reported in 92% of all cases. In this study, 84% of patients had kidney disease and 43% progressed to CKD [25]. It is important to consider that the diagnosis of ADTKD is purely genetic, which represents a great limitation for an early diagnosis in countries with limited resources (like Colombia), due to regulatory and resource barriers [2]. In Colombia, currently, it is feasible to carry out genetic studies, but there are still difficulties in access and in family screening processes.

To date, there is no specific treatment standardization for ADTKD. Basically, the management of this disease focuses on the control of symptoms, such as hyperuricemia, and on slowing the progression of renal insufficiency [3, 26]. In a retrospective follow-up study, the cases of 27 patients with ADTKD belonging to 8 families were analyzed. All of them were treated with allopurinol when the disease was suspected. In 83.3% of the patients who started treatment with allopurinol and had a serum creatinine greater than 1.35 mg/dl, progression to end-stage CKD occurred between 2 and 10 years later. In contrast, patients with a serum creatinine lower than 1.35 mg/dl who started treatment early showed slower progression, reaching end-stage CKD in a period of 10 to 34 years of follow-up. On the other hand, patients who did not present CKD when starting treatment with allopurinol maintained disease stability for up to 20 years of follow-up [27].

In our patient, the use of xanthine oxidase inhibitors (allopurinol) was considered the initial treatment; however, there was a fast progression of CKD, and treatment follow-up was short, which did not allow evaluation of long-term effects and outcomes.

## Conclusions

We report the case of an adolescent with signs of CKD and the presence of a probably pathogenic variant in the UMOD gene, inherited from his father; this variant was not previously reported in the literature.

Our findings highlight the importance of the family history during the anamnesis in order to guide the diagnosis. Genetic confirmation makes it possible to provide a clear aetiology that will further allow specific guidelines for prompt treatment and follow-up, as well as genetic counseling and identification of relatives at risk.

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