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## Autosomal Recessive Trait of *UMOD* Gene in Consanguineous Family Presented with End Stage Renal Disease

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### Abstract

We report a consanguineous family with Uromodulin mutation with autosomal recessive pattern which is not reported before in the literature. Twenty six years of male diagnosed with end stage renal disease of unknown etiology had a history of dialysis in his mother, maternal aunt and his maternal grandfather. In genetic analysis by Sanger sequencing a homozygous missense variation, c.263G>A/p.Gly88Asp in *UMOD* (NM\_003361) gene has been detected. In summary, we report a novel *UMOD* mutation in a Turkish family with autosomal recessive trait.

**Keywords:** End stage renal disease; Sanger sequencing; Genetic disorders

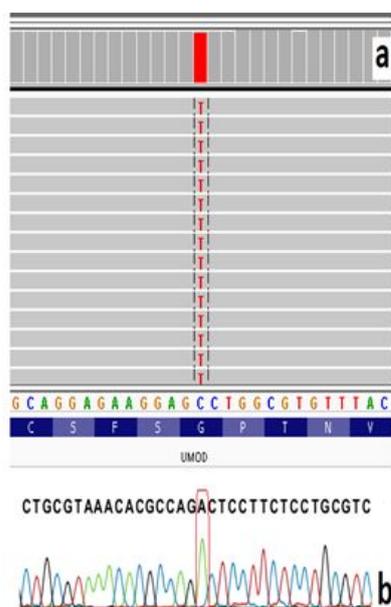
### Introduction

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of genetic disorders leading end stage renal disease (ESRD). Mutations in *Uromodulin* (*UMOD*) gene encoding uromodulin cause ADTKD also known as uromodulin kidney disease (UKD). Uromodulin is produced in the thick ascending limb (TAL) of the loop of Henle and regulate salt transport. *UMOD* mutations are generally in autosomal dominant inheritance pattern and almost located on exon 3, 4 or 5. The main alteration is the reduction of the fractional excretion of uric acid due to increased uric acid absorption in the proximal tubule [1,2]. As a result, the clinical features of the disease generally consist of a slowly progressive chronic kidney disease with bland urine and gout history that ended up with ESRD at the 2<sup>th</sup>-5<sup>th</sup> decades. Herein we presented a Turkish family with early onset of ESRD at the age of 26 in all affected members as a consequence of an autosomal recessive (OR) mutation in *UMOD* gene that was not reported before.

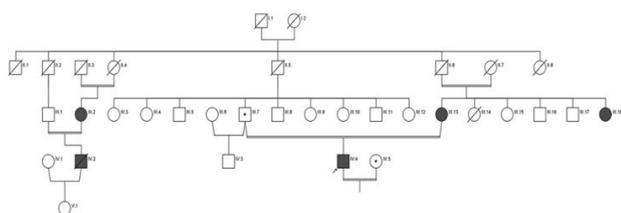
### Case Report

A 26-year-old male was admitted to our hospital because of severe headache. On his initial examination, a blood pressure of 200/110 mmHg was detected. His initial laboratory tests revealed hemoglobin 10.4 g/dL, serum glucose 103 mg/dL, blood urea nitrogen 200 mg/dL, creatinine 8 mg/dL, uric acid 8.8 mg/dL, sodium 142 mEq/L, potassium 4.6 mEq/L, calcium 7.8 mg/dL, phosphorus 6.4 mg/dL, and PTH 775 pg/mL. He had no history of gout or kidney stone diseases. The kidney ultrasonography showed chronic changes in the renal parenchyma, indicating ESRD. Peritoneal dialysis was planned and after catheter insertion, PD treatment was started. Remarkably, the patient had a family history of dialysis commencing at 26 years of age in all affected family members due to ESRD (Figure 1). There was no clinical, laboratory or imaging finding which consistent with monogenic familial kidney diseases like polycystic kidney disease, Alport's disease or Fabry disease. Therefore, genomic DNA was extracted from peripheral venous blood using the QIAamp® DNA Mini Kit (QIAGEN, Ankara, Turkey). The Custom Panel, Nephropathies Solution (SOPHiA GENETICS), was used to targeted gene enrichments. All procedures were carried out according to the manufacturer's protocols. It was a capture-based target enrichment kit and covers 44 selected genes related to a broad range of nephropathies. Paired-end sequencing was performed on an Illumina NextSeq 500 system with a read length of 150x2. Base calling and image analysis were conducted using Illumina's Real-Time Analysis software. The BCL (base calls) binary was converted into FASTQ utilizing Illumina package bcl2fastq. All bioinformatics analysis performed on Sophia DDMTM platform which includes algorithms for alignment, calling SNPs and small indels (Pepper), calling copy number variations (Muskat) and functional annotation (Moka). Raw reads were aligned to the human reference genome (GRCh37/hg19). Variant filtering and interpretation performed on Sophia DDMTM. Integrative Genomics Viewer (IGV) was used to bam file visualization. Next generation sequencing showed a homozygous missense

variation, c.263G>A/p.Gly88Asp in *UMOD* (NM\_003361) gene. The variation was confirmed by Sanger sequencing (Figure 2). Sanger sequencing was also applied to relatives of the patient. The variation was homozygous in patients and heterozygous in healthy individuals (Figure 1). This condition showed that the inheritance pattern of the disease was autosomal recessive (OR) [3].



**Figure 1:** Integrative Genomics Viewer (IGV) and chromatogram views of the variation. (a) Excerpt of next generation sequencing data visualized with IGV. (b) Result of DNA sequencing. A novel homozygous germline mutation, c.263G>A, p.Gly88Asp in *UMOD* gene of the patient (indicated by red frame).



**Figure 2:** Pedigree of the family showing the identified *UMOD* variant (c.263G>A, p.Gly88Asp). The arrow indicates the proband. Black symbols indicate the affected individuals. Sanger sequencing analysis performed for proband, IV.5, III.7, and III.18. Proband and III.18 are homozygous; his father and IV.5 are heterozygous for the variant.

## Discussion

This variant has not been previously reported in the Human Gene Mutation Database (HGMD; <http://www.hgmd.cf.ac.uk/ac/index.php>) and in population studies (ExAC: Exome Aggregation Consortium and 1000 Genomes

Project). In silico analysis programs (VarSome; DANN Score: 0.9977 and ACMG; Likely Pathogenic) showed that this change could be the cause of the disease. *UMOD* is located on chromosome 16p12.3-16p13.11 and is composed of 11 exons. Knockout mice models proposed that *UMOD* has extremely important role in regulation of renal outer medullary potassium (ROMK) channel and of sodium-potassium-chloride (NKCC2) transporter in the TAL cells of the kidney. *UMOD* is also involved in host defense against *Escherichia coli* [1,2]. Mutation in the *UMOD* gene causes autosomal dominant tubulointerstitial kidney disease, medullary cystic kidney disease type 2 (MCKD2; MIM 603860) and familial juvenile hyperuricemic nephropathy (FJHN; MIM 162000) [4]. Main inheritance of aforementioned *UMOD* mutations are autosomal dominant pattern, however in our family the inheritance pattern was OR which was not reported before in *UMOD* related genetic diseases. In *UMOD* related diseases, hyperuricemia and gout were reported to commonly accompany CKD and renal imaging generally shows cortico medullary cysts. The families carrying this mutation in the literature reach ESRD between the ages of 25 and 70 years or older [5]. Opposite of these findings in our family, none of the affected members had a history of gout and USG revealed only chronic changings without renal cysts. Furthermore, renal replacement treatment initiation age was remarkable younger in all the affected members of our family. Main similarities of our patients with other *UMOD* related diseases are onset of diseases. Probably concentration defects and decreased secretion of UA were prominent but not reported by patient and his family. Until now to our knowledge autosomal recessive *UMOD* related disease is not reported.

## Conflict of Interest

The authors have declared that no conflict of interest exists.

## Informed Consent

A written informed consent was obtained from the patient included in this case study.

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