Annals of Pediatric Research

Case Report
Published: 28 Feb, 2022

A Novel Heterozygous Missense Mutation in UMOD Gene in a Chinese Family with Familial Juvenile Hyperuricemic Nephropathy: A Case Report

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Abstract

Background: Familial Juvenile Hyperuricemic Nephropathy (FJHN) is a rare autosomal dominant disease characterized by hyperuricemia, gout, and chronic renal failure. The UMOD variants are the most common genetic cause of FJHN.

Case Report: We report a novel heterozygous pathogenic UMOD mutations c.296G>A (p.Arg99His) in a 5-year-old boy who presented with hyperuricemia and gouty arthritis. This UMOD mutation was also carried by the proband's elder sister, father, uncle, cousin and grandfather, who had similar clinical signs. The family members were treated with allopurinol and controlled diet to maintain the serum uric acid levels. None of them developed end stage renal disease. The mutation segregated in the family and was the cause of the disease in the proband. c.296G>A (p.Arg99His) mutation was not described in the ExAC, gnomAD and 1000 Genomes Project databases. The mutated amino acids were located in a highly conserved region of the UMOD protein. This mutation was predicted to be damaging and deleterious. A phenotype-genotype correlation analysis of UMOD variants was consistent with those clinical signs.

Conclusion: Our finding suggests that genetic test for specific mutation in UMOD gene should be included in the diagnosis for patients with hyperuricemia, gout, or unexplained chronic kidney disease.

Keywords: Hyperuricemia; Gout; UMOD; Mutation

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Received Date: *27 Jan 2022*
Accepted Date: *19 Feb 2022*
Published Date: *28 Feb 2022*

Citation:
Zeng H, Xie M, Zou X, Chen Y, Chen W, Zhang Z, et al. A Novel Heterozygous Missense Mutation in UMOD Gene in a Chinese Family with Familial Juvenile Hyperuricemic Nephropathy: A Case Report. Ann Pediatr Res. 2022; 6(1): 1063.

Abbreviations

FJHN: Familial Juvenile Hyperuricemic Nephropathy; ACMG: American College of Medical Genetics; eGFR: estimated Glomerular Filtration Rate; EGF: Epidermal Growth Factor

Introduction

Familial Juvenile Hyperuricemic Nephropathy (FJHN) is a rare autosomal dominant disease characterized by hyperuricemia, gout, and chronic renal insufficiency [1]. FJHN was first described in 1960 [2]. In general, affected family members show a sign of impairment of urate secretion before puberty and develop hyperuricemia and gout after adolescence [3]. Renal function gradually deteriorates from ages 15 to 40 years, eventually developing into end-stage renal disease within 10 to 20 years [4]. Renal histopathology exhibits interstitial fibrosis and tubular atrophy [5].

UMOD is located on 16p12.3 and encodes uromodulin, which is markedly increased in renal tubular cells. Uromodulin, also known as Tamm-Horsfall protein, is synthesized exclusively in the thick ascending limb of the loop of Henle and then excreted into the urine [6]. UMOD variants are the most common genetic cause of FJHN.

Mutations in UMOD lead to decreased expression of the gene in renal tubular cells, causing tubulointerstitial damage [7,8]. No established genotype-phenotype correlations between tubulointerstitial kidney disease and UMOD mutations have been described.

In this study, we found a novel heterozygous UMOD variant (c.296G>A, p.Arg99His) in a family member with FJHN. The proband was diagnosed with hyperuricemia and gout. His sister,

father, uncle and grandfather carrying the same variant showed hyperuricemia physical examination, but none developed renal failure.

Case Presentation

A 5-year-old boy was referred to our institution as an inpatient because of arthralgia of the limbs. On admission, he had stable vital signs and no symptoms associated with azotemia. A medical examination showed tenderness in the bilateral knee, wrist, ankle and finger joints. No redness or swelling was observed in the joints. The child had no fever, upper respiratory tract infection or skin infection in the last three months. His serum uric acid level was 499 μmol/L, with a fractional excretion of uric acid of 3.6% (Reference: 10% to 20%). Laboratory tests showed a normal complete blood count, electrolytes and liver function, a serum creatinine level of 40 μmol/L, an estimated Glomerular Filtration Rate (eGFR) of 128.6 mL/(min 1.73 m^2), and a serum albumin level of 41.5 g/L. Routine urinary tests showed no proteinuria, hematuria or pyuria. Blood sedimentation, rheumatoid factor, Anti-Streptococcus hemolysin O (ASO) and antinuclear antibody were normal. Renal ultrasonography revealed normal kidneys without cysts. The child was clinically diagnosed with hyperuricemia and gouty arthritis. His 16-year-old sister had hyperuricemia with a serum uric acid level of 525 μmol/L but no symptoms associated with gout. The child's father also had hyperuricemia and gout, with a serum uric acid level of 502 μmol/L at age 22, a serum creatinine level of 96 μmol/L and eGFR of 129.5 mL/(min 1.73 m^2). The patient's grandfather, aged 73, was diagnosed with hyperuricemia and gout at age 20; his highest serum uric acid level was 723 μmol/L, but he had been under controlled diet and allopurinol treatment. His grandfather's physical examination showed that uric acid was under control, ranging between 300 and 428 μmol/L, with normal serum creatinine levels. The child's uncle and cousin were found to have hyperuricemia (Figure 1). None of the family members underwent dialysis treatment. None of them had any other chronic disease, such as hypertension or diabetes.

Materials and Methods

Genomic DNA of the family members was extracted from peripheral blood samples using the SolPure Blood DNA kit (Magen) following the manufacturer's protocol. The DNA was fragmented by a Q800R Sonicator (Qsonica) to generate 300-bp to 500-bp fragments. The enriched DNA samples were indexed and sequenced using a NextSeq500 sequencer (Illumina, San Diego, CA, USA), with 100,150 cycles of single-end read according to the manufacturer's protocols.

DNA from the patient's parents, uncles, cousins and grandparents was examined by Sanger sequencing and compared with the proband's sequencing results better conveys the intended meaning.

Sequencing reads were mapped to the reference human genome version hg19 (2009–02 release, http://genome.ucsc.edu/). Nucleotide changes observed in the aligned reads were called and reviewed using NextGENe software (Soft Genetics, State College, PA, USA). Sequence variants were annotated using population and literature databases, including 1000 Genomes (http://www.1000genomes.org/), dbSNP (http://www.ncbi.nlm.nih.gov/), GnomAD (http://gnomad.broadinstitute.org/), Clinvar (https://www.st-va.ncbi.nlm.nih.gov/clinvar/), HGMD (http://www.hgmd.cf.ac.uk/ac/index.php) and OMIM (https://www.omim.org/). Online software (https://www.UniProt.org/) was used to analyze the protein structure, predict conserved and functional domains and perform a multiple sequence alignment. Variant interpretation was performed according to American College of Medical Genetics (ACMG) guidelines [9]. Possible pathogenicity was predicted according to the online tools PolyPhen-2 and ClinPred.

Results

Sequence analysis

Genetic analysis revealed a novel heterozygous missense mutation (c.296G>A, p.Arg99His) that altered evolutionarily conserved residues in the gene encoding uromodulin. The c.296G>A (p.Arg99His) mutation is not described in the ExaC, GNomAD and 1000 Genomes Project databases; the frequency of c.296G>A (p.Arg99His) is <0.001 in these gene databases. Based on Sanger sequencing, the proband's sister, cousin, two uncles and grandfather also carried the same mutation in UMOD.

The missense mutation c.296G>A (p.Arg99His) is located in Epidermal Growth Factor (EGF) III domain. We also analyzed this amino acid region in different species (Figure 2). The results indicated that c.296G>A (p.Arg99His) is located in a highly conserved region of the protein. The variant c.296G>A (p.Arg99His) is predicted to be "probably damaging" by PolyPhen-2, with a score of 0.903 (sensitivity: 0.82; specificity: 0.94), and "pathogenic >0.5" by ClinPred.

Discussion

The UMOD gene contains Epidermal Growth Factor (EGF) 1, EGF 2, EGF 3 domains, a cysteine-rich region and a zona pellucida domain (Figure 3). The uromodulin protein consists of 640 amino acids, including 48 cysteine residues (7.5%) required for the formation of disulfide bonds. Mutations in the UMOD gene are known to cause

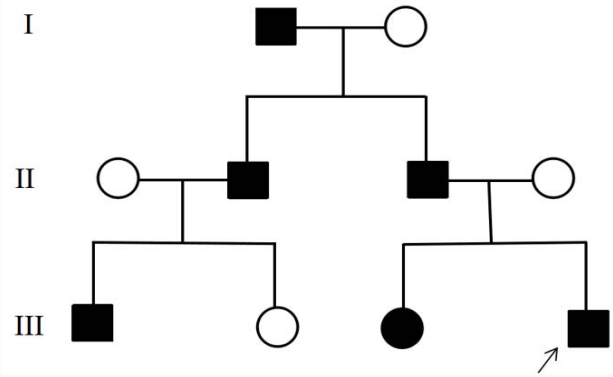

Figure 1: Family pedigree showing individuals with FJHN.

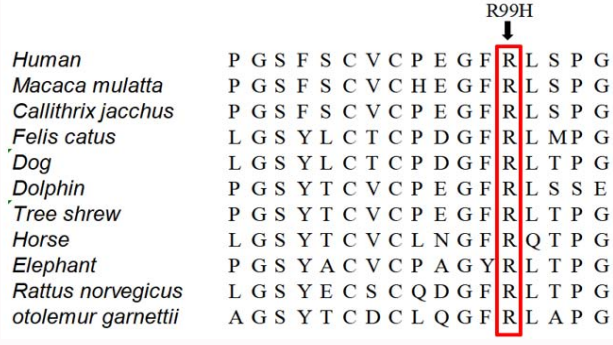

Figure 2: UMOD sequence alignment among representative species around the sites of the missense mutations (c.296G>A, p.Rrg99His).

Figure 3: Schematic representation of the UMOD protein. The novel heterozygous mutation reported herein coincides with the EGF-like 2 domain.

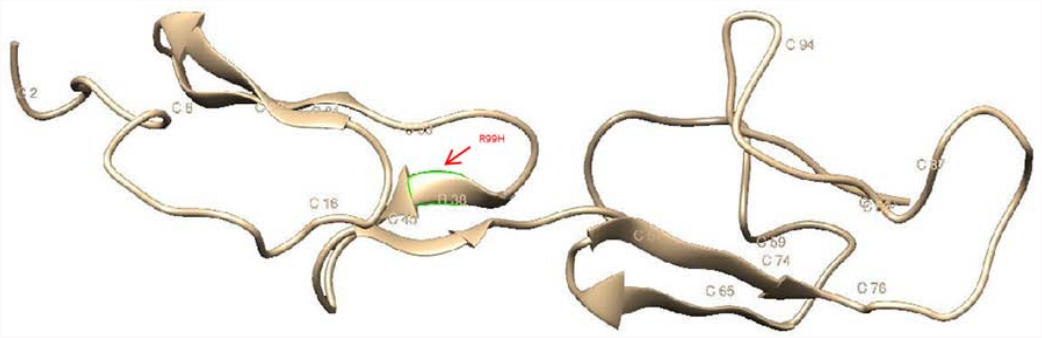

Figure 4: Homology model of UMOD (partial amino acids from positions 62 to 162), the p.R120H mutation resides in EGF-like domain II.

autosomal dominant kidney diseases such as FJHN, medullary cystic kidney disease type 2, and glomerulocystic disease [7]. FJHN is the common clinical manifestation of UMOD mutations, characterized by hyperuricemia, gout tubulointerstitial nephropathy, and end-stage renal disease [1]. Approximately 200 mutations in the UMOD gene (>95% missense, >50% targeting cysteines) have been described [7,8]. Ninety-four percent of the variants are clustered in exons 3 and 4; fewer mutations occur in exons 5 and 7, affecting residues within the ZP domain [10]. The phenotype-genotype of UMOD variants is unclear, and most reports of mutations in UMOD that give rise to poor prognosis are mostly located in the D8C domain [10-12]. However, in the present study, the 73-year-old grandfather with the UMOD variant (c.296G>A, p.Arg99His) only developed hyperuricemia without end-stage renal disease. The proband and other affected family members were under diet control and allopurinol treatment. A similar family manifesting hyperuricemia and/or gout has been reported, involving a novel heterozygous missense mutation (c.1382C>A, p.Ala461Glu) in the UMOD gene, by Lee HD et al. [13]. The family members in that previous study were treated with allopurinol, and serum uric acid levels were well maintained. None developed end-stage renal disease. Although no study has indicated a correlation between age of onset in FJHN and prognosis of the disease, our study reports the youngest proband to date, with a very early onset of hyperuricemia, and good prognosis of older members of the family with FJHN, suggesting that it is possible to maintain proper kidney function through diet control and allopurinol treatment. Interestingly, Zaucke F et al. [11] reported that a 36-year-old man with the UMOD mutation c.688 T>C (p.Trp230Arg) manifested stage 3 chronic kidney disease; his sister and father had end-stage renal disease. In addition, Calado J et al. [12] revealed that a 24-year-old female with the UMOD mutation c.920 A>C (p.K307T) showed gout and hyperuricemia and developed renal failure at age 27. Nakayama M et al. [14] described an 18-year-old patient with a heterozygous missense mutation (c.688 T>C, p.Trp230Arg) who had FIHN, whereas his father had a nephrarctia with some cysts and end-stage renal disease. The clinical symptoms in patients with UMOD mutations are quite diverse. Gout and/or hyperuricemia are not found in all families harboring UMOD mutations. Lopes LB et al. [15] reported that some families with UMOD mutations (c.163G>A, p.Gly55Ser) exhibit a decreased glomerular filtration rate, urinary tract infections, tubular atrophy and interstitial inflammation.

The mechanism by which UMOD mutation causes FIHN and end-stage renal disease remains unclear (Figure 4). A previous study using UMOD knock-out mice showed that UMOD has a protective role against urinary tract infections and calcium oxalate crystal damage [16,17]. *In vitro* studies have indicated that different UMOD variants lead to variable defects. Willian et al. [18] reported that UMOD mutations are associated with endoplasmic reticulum retention and delayed maturation and trafficking of abnormal uromodulin, which is probably due to protein misfolding. Lopes LB et al. [15] reported 11 members with UMOD mutations (c.163G>A, p.Gly55Ser) in a large family. Three members experienced progression to end-stage renal disease between 40 and 60 years, whereas two family members had well-preserved kidney function at ages 59 and 62. This suggests that modifier genes or environmental factors have an effect on clinical phenotypes. At present, there is no specific therapy for FJHN. Most patients under treatment with allopurinol and colchicine have reduced serum uric acid levels. Patients with end-stage renal disease need dialysis or renal replacement therapy.

Conclusion

We identified a novel mutation in the UMOD gene responsible for FIHN. The c.296G>A, p.Arg99His mutation may confer mild clinical phenotypes. Early genetic diagnosis is recommended for family members with hyperuricemia, gout, or unexplained chronic kidney disease.

Funding

The study was supported by the Key Projects of Science and Technology Plan of Dongguan (Project Numbers: 20185071501001628).

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Dongguan Children's Hospital in agreement with the Declaration of Helsinki.

Informed consent was obtained from the parents, cousin, uncles and grandfather of the study subject.

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