A novel heterozygous missense mutation in uromodulin gene in an Indian family with familial juvenile hyperuricemic nephropathy

D. Saxena, P. Srivastava, S. R. Phadke

Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

ABSTRACT

Familial juvenile hyperuricemic nephropathy (FJHN), characterized by early-onset hyperuricemia, reduced fractional excretion of uric acid, and chronic renal failure is caused due to mutation in uromodulin (UMOD) gene. We identified a novel mutation in a family with multiple members affected with FJHN. Ten coding exons of UMOD gene in three family members with clinical and biochemical features of FJHN and one unaffected family member were sequenced, and sequence variants were analyzed for the pathogenicity by bioinformatics studies. A heterozygous novel missense mutation (c. 949 T >G) in exon 5 leading to the replacement of cysteine by glycine at position 317 was identified in all three affected family members. This mutation has not been reported earlier in Human Gene Mutation Database, Human Genome Variation, Clinvar, and 1000 Genome. The mutation lies in the cysteine-rich 2 domain of the protein, and the affected residue is evolutionary conserved in other species. To our knowledge, this is the first report of the identification of UMOD mutation in an Indian family.

Key words: Chronic renal failure, familial juvenile hyperuricemic nephropathy, gout, hyperuricemia, uromodulin

Introduction

Familial juvenile hyperuricemic nephropathy (FJHN1; MIM 162000) is an autosomal dominant condition characterized by defective urinary concentrating ability, gouty arthritis, interstitial nephritis, and chronic renal failure. It is a genetically heterogeneous condition, caused due to mutation in three genes: Uromodulin (UMOD) (40%), renin (2.5%), and hepatocyte nuclear factor-1 beta (2.5%). Biochemical hallmarks of the disease are hyperuricemia out of proportion to the degree of renal failure and reduced fractional uric acid excretion.[1]

Address for correspondence:
Dr. S. R. Phadke,
Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow - 226 014, Uttar Pradesh, India.
E-mail: shubharaophadke@gmail.com

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Here, we describe an Indian family with multiple members affected with FJHN1 due to a novel heterozygous missense mutation in exon 5 of UMOD gene.

Case Report

A 17-year-old male presented with pain and swelling in small joints of hands, feet, knees, ankles, elbows, and wrists for 2 years along with the presence of nodules on the right little finger and the left ear lobe. On examination, swellings were present on second and third metacarpophalangeal joints and third proximal interphalangeal joints. There were tophi of size 2–3 cm with whitish discharge on the right little finger and of 0.5 cm on the left ear lobule [Figure 1]. His blood pressure was normal. The serum uric acid level was

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13.9 mg/dl, and serum creatinine 1.4 mg/dl (normal uric acid level in >18 years old: 6.2 ± 0.8 mg/dl).[2] The fractional excretion of uric acid was reduced (2.93%). Ultrasonography showed normal-sized kidneys with normal echogenicity. There were multiple family members affected with the same disorder; some had only gouty arthropathy and others had both gouty arthropathy and renal disease [Tables 1 and 2]. His father had died at the age of 42 years due to chronic kidney disease and had gouty arthritis. One of his elder brothers and one paternal uncle's son has gout along with kidney disease, and one brother has only gouty arthritis [Figure 2].

Informed consent was obtained from the three affected individuals for deoxyribonucleic acid analysis, collection of clinical data, and publication of photographs. The 10 coding exons of UMOD gene were amplified by polymerase chain reaction and cycle sequenced by capillary electrophoresis using an ABI 310 sequencer (Applied Biosystems Foster City, CA, USA). The pathogenicity of the variant found was analyzed using various bioinformatics tools.

A heterozygous missense variant (c. 949 T >G) in exon 5 [Figure 3] was identified in the proband and two affected brothers causing substitution of cysteine by glycine at codon position 317 (p.C317G). This particular amino acid change was not present in the unaffected sister. It is a novel variant, not reported in 1000 genomes, Clinvar, Human Genome Mutation Database, and Human Genome Variation. The affected residue locates within the cysteine-rich 2 domain and is immediately preceded by a highly conserved cysteine residue. Various bioinformatics tools such as mutation taster, PolyPhen and Sorting Intolerant from Tolerant also predicted it to be pathogenic. This amino acid residue is conserved across other animal species. Based on the above evidence, we concluded that this novel variant is very likely the causal pathogenic mutation.

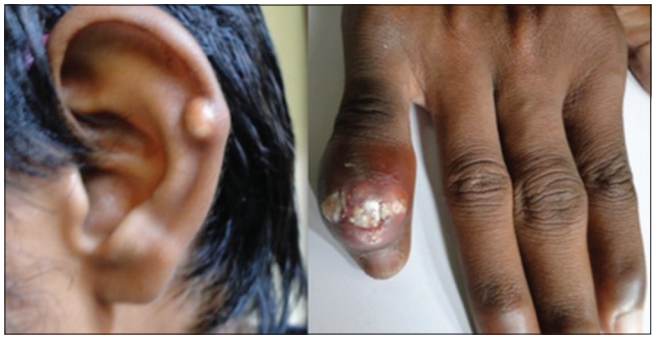

Figure 1: Proband showing a nodule on left ear lobe and another on right little finger with whitish discharge

Discussion

UMOD also called as Tamm–Horsfall protein is a polymeric protein located on the tubular cells lining the thick ascending limb of the loop of Henle and early distal convoluted tubules. From the apical membrane, it is secreted into the tubular lumen where it polymerizes into a water impermeable gel-like structure that modulates salt transport, urine concentration, and urate metabolism.[3] UMOD prevents interstitial cystitis, urinary tract infections, and formation of urinary stones.[4] Common genetic variants in UMOD gene have been found to be associated with hypertension, reduced renal function, and increased risk of chronic renal failure.[5,6] UMOD is the most common of the three genes known to cause FJHN. Other disorders caused by mutation in UMOD are medullary cystic kidney disease type 2 (MIM 603860) and glomerulocystic kidney disease (MIM 609886).[7]

Until date, more than 70 mutations have been described in UMOD and most of them are clustered in exon

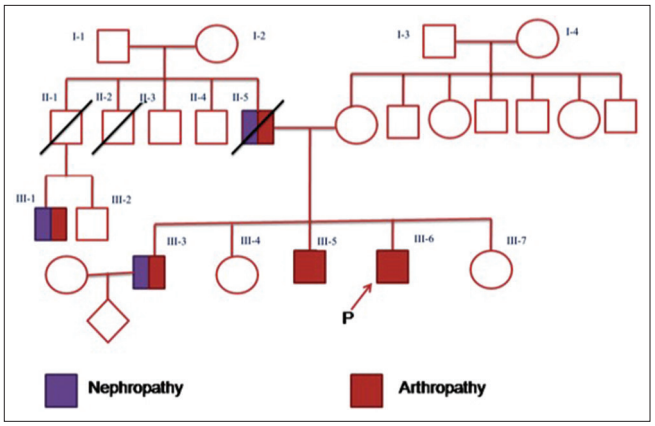

Figure 2: Family pedigree showing multiple affected members

Table 1: Clinical features of proband and his family members

Clinical features	II-5	III-1	III-3*	III-5*	III-6* (proband)
Age (years)	Died at 42	33	25	22	17
Age of onset of gout (years)	~18	~18	17-18	17	15
Presentation	JP[$]	JP	JP	JP	JP
Age at diagnosis of renal disease	35 years	31	22	-	-
Presentation	Anemia	Anemia	Anemia, headache	-	-
Dialysis	Started at 40 years	Not yet required	Not yet required	-	-

*Mutation: Confirmed cases, [$]JP: Pain and swelling in small joints of hands and feet

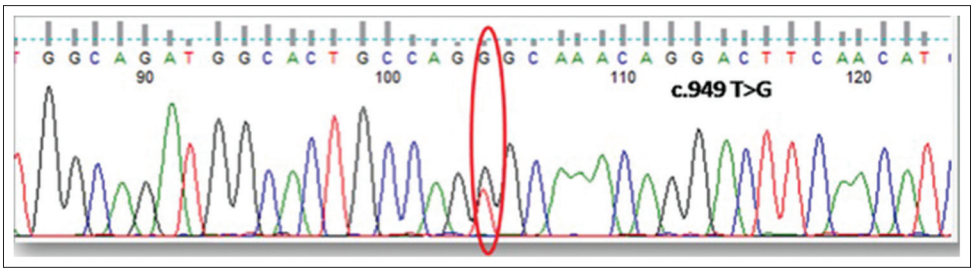

Figure 3: Proband showing heterozygous mutation c.949 T>G in exon 5 of uromodulin gene causing substitution of cysteine by glycine at position 317

Table 2: Investigations of the proband and his brother

Investigations	III-3	III-6
Hemoglobin	7.3 g/dl, 12.3 g/dl (after erythropoeitin)	12.1 g/dl
Serum creatinine	3.57 mg/dl	1.37 mg/dl
Blood urea nitrogen	68 mg/dl	29 mg/dl
Serum uric acid	16.7 mg/dl	13.9 mg/dl
Urine examination	No proteinuria, no hematuria	No proteinuria, no hematuria
Fractional excretion of uric acid	2.85%	2.93%
USG abdomen	Bilateral small kidneys, no cysts	Normal-sized kidneys, no cyst

USG: Ultrasonography

4 (83.8%), 5 (8%), and 8 (8%) of UMOD gene. Two-thirds of these mutations cause substitution of cysteine residues or highly conserved polar amino acids. In the present family, the mutation c. 949 T >G replaces cysteine with glycine at position 317. Substitution of cysteine residue can alter the disulfide bond formation that interferes with correct folding of the UMOD protein. The misfolded protein accumulates in the endoplasmic reticulum of tubular cells that elicits an adaptive response called as "unfolded protein response" causing cell death.[8] Rampoldi *et al*. have shown that substitution of cysteine by tyrosine (Cys317Tyr) at the same position leads to delay in export of UMOD to plasma membrane due to longer retention time in endoplasmic reticulum.[7] The co-segregation of the mutation in affected sibs supports the pathogenic nature. There is marked interfamilial and intrafamilial variability that was also seen in the present family. Hyperuricemia is present in 83.3% of the cases and gout in 45% of mutation – positive cases. Median age of onset of end-stage renal disease (ESRD) was earlier in cases with mutation in epidermal growth factor (EGF)-2 and EGF3 domains and later in cases with mutation in domain of 8 cysteine (D8C) and cysteine – rich regions 1 and 2. However, there is no correlation between the presence of hyperuricemia or gout and development of ESRD.[9]

Definitive treatment is renal transplantation. Use of uricosuric drugs such as allopurinol has a definite role in decreasing hyperuricemia and features related to gout. However, the efficacy of these medications in slowing the progression of renal disease is still not clear.[10] Mutation detection helps in confirmation of the diagnosis of this rare and underdiagnosed condition. This is the first report of a case of FJHN from Indian population. Mutation analysis can be used for presymptomatic diagnosis of relatives. This is especially of importance when the relatives are screened as kidney donors.

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Conflicts of interest

There are no conflicts of interest.

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