



## Case report

# Familial juvenile hyperuricemic nephropathy: Revisiting the SLC8A1 gene, in a family with a novel terminal gross deletion in the UMOD gene



Francisco Gonçalves<sup>a,b,◇</sup>, Pedro Lisboa-Gonçalves<sup>a,c,◇</sup>, Rita Quental<sup>d</sup>, Susana Fernandes<sup>e</sup>, Sofia Quental<sup>f</sup>, Laurence Michel-Calemard<sup>g</sup>, Claire Goursaud<sup>g</sup>, Sofia Marques<sup>h</sup>, Joana Santos<sup>a</sup>, Isabel Tavares<sup>a,c,i</sup>, João Paulo Oliveira<sup>d,e,i,\*</sup>

<sup>a</sup> Serviço de Nefrologia, Centro Hospitalar Universitário de São João, Porto, Portugal

<sup>b</sup> Departamento de Cirurgia e Fisiologia, Faculdade de Medicina, Universidade do Porto, Porto, Portugal

<sup>c</sup> Departamento de Medicina, Faculdade de Medicina, Universidade do Porto, Porto, Portugal

<sup>d</sup> Serviço de Genética Médica, Centro Hospitalar Universitário de São João, Porto, Portugal

<sup>e</sup> Unidade de Genética, Departamento de Patologia, Faculdade de Medicina, Universidade do Porto, Porto, Portugal

<sup>f</sup> IPATIMUP - Instituto de Patologia e Imunologia Molecular, i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal

<sup>g</sup> Service Biochimie Biologie Moléculaire Grand Est, UM Pathologies Rénales et Osseuses, LBMMS, Hospices Civils de Lyon, Bron, France

<sup>h</sup> Serviço de Nefrologia, Hospital das Forças Armadas, Pólo do Porto, Porto, Portugal

<sup>i</sup> Grupo de Investigação e Desenvolvimento em Nefrologia e Doenças Infeciosas, i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal

## ARTICLE INFO

### Article history:

Received 22 May 2023

Accepted 13 September 2023

Available online 23 September 2023

### Keywords:

Autosomal dominant tubulointerstitial kidney disease (ADTKD)

Familial juvenile hyperuricemic nephropathy (FJHN)

Chronic kidney disease (CKD)

Hyperuricemia

Uromodulin

UMOD

SLC8A1

## ABSTRACT

Autosomal dominant tubulointerstitial kidney disease (ADTKD) comprises a heterogeneous group of rare hereditary kidney diseases characterized by family history of progressive chronic kidney disease (CKD) with bland urine sediment, absence of significant proteinuria and normal or small-sized kidneys. Current diagnostic criteria require identification of a pathogenic variant in one of five genes – *UMOD*, *MUC1*, *REN*, *HNF1β*, *SEC61A1*. The most prevalent form of ADTKD is uromodulin-associated kidney disease (ADTKD-*UMOD*).

Genetic study of a Portuguese family diagnosed with familial juvenile hyperuricemic nephropathy (FJHN), one of the nosological entities in the spectrum of ADTKD, revealed a previously unreported large deletion in *UMOD* encompassing the entire terminal exon, which strictly cosegregated with CKD and hyperuricemia/gout, establishing the primary diagnosis of ADTKD-*UMOD*; as well as an ultra-rare nonsense *SLC8A1* variant cosegregating with the *UMOD* deletion in patients that consistently exhibited an earlier onset of clinical manifestations.

Since the terminal exon of *UMOD* does not encode for any of the critical structural domains or amino acid residues of mature uromodulin, the molecular mechanisms underlying the pathogenicity of its deletion are unclear and require further research.

\* Corresponding author.

E-mail address: [jpo@med.up.pt](mailto:jpo@med.up.pt) (J.P. Oliveira).

◇ These authors contributed equally to this work as first authors.

<https://doi.org/10.1016/j.nefro.2023.09.007>

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The association of the *SLC8A1* locus with FJHN was first indicated by the results of a genome-wide linkage analysis in several multiplex families, but those data have not been subsequently confirmed. Our findings in this family revive that hypothesis.

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## Nefropatía hiperuricémica juvenil familiar: revisando el gen *SLC8A1*, en una familia con una nueva delección terminal extensa en el gen *UMOD*

### R E S U M E N

#### Palabras clave:

Enfermedad renal  
tubulointersticial autosómica  
dominante  
Nefropatía hiperuricémica  
juvenil familiar  
Enfermedad renal crónica  
Hiperuricemia  
Uromodulina  
*UMOD*  
*SLC8A1*

La enfermedad renal tubulointersticial autosómica dominante (ADTKD) comprende un grupo heterogéneo de enfermedades renales hereditarias raras caracterizadas por historia familiar de enfermedad renal crónica (ERC) progresiva con sedimento urinario blando, ausencia de proteinuria significativa y riñones normales o de tamaño pequeño. Los criterios de diagnóstico actuales requieren la identificación de una variante patogénica en uno de cinco genes: *UMOD*, *MUC1*, *REN*, *HNF1β*, *SEC61A1*. La forma más frecuente de ADTKD es la enfermedad renal asociada a uromodulina (ADTKD-*UMOD*).

El estudio genético de una familia portuguesa diagnosticada con nefropatía hiperuricémica juvenil familiar (FJHN), una de las entidades nosológicas en el espectro de ADTKD, reveló una delección extensa en el gen *UMOD* abarcando todo el exón terminal, no reportada anteriormente, que cosegregaba estrictamente con ERC e hiperuricemia/gota, permitiendo establecer el diagnóstico de ADTKD-*UMOD*; así como una variante sin sentido, ultra rara, en el gen *SLC8A1* que cosegregaba en pacientes que consistentemente exhibieron un inicio más temprano de las manifestaciones clínicas.

Dado que el exón terminal de *UMOD* no codifica ninguno de los dominios estructurales críticos o de los aminoácidos de la uromodulina madura, los mecanismos moleculares subyacentes a la patogenicidad de su eliminación no están claros, requiriendo más investigación.

La asociación del locus *SLC8A1* con la FJHN fue indicada por primera vez por los resultados de un genoma en varias familias multiplexadas, pero esos datos no se han confirmado posteriormente. Nuestros hallazgos en esta familia reavivan esa hipótesis.

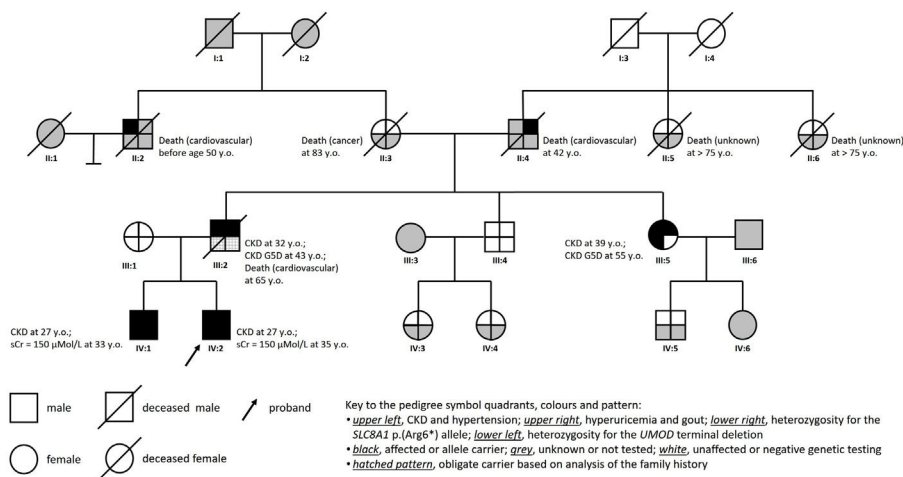
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## Introduction

The term autosomal dominant tubulointerstitial kidney disease (ADTKD) refers to a heterogeneous group of rare hereditary kidney disorders characterized by tubular damage and interstitial fibrosis, in the absence of glomerular lesions.<sup>1–3</sup> Progressive chronic kidney disease (CKD) with bland urine sediment, absence of significant proteinuria, and normal- or small-sized kidneys are the typical clinical features, with a significant proportion of patients also developing hyperuricemia and gout at young ages. The nosology of ADTKD has recently been revised into a gene-based classification system,<sup>1</sup> also encompassing the entities formerly designated “medullary cystic kidney disease (MCKD)” and “familial juvenile hyperuricemic nephropathy (FJHN)”. As a group, ADTKD constitutes the third most common genetic disorder in adults with CKD, after autosomal dominant polycystic disease and the collagen type IV-related kidney diseases.<sup>2,3</sup> Histopathological findings are nonspecific and definitive diagnosis of ADTKD requires identification of a pathogenic variant in one of the underlying genes<sup>1</sup> – i.e. those

encoding uromodulin (*UMOD*), also known as uromucoid or Tamm-Horsfall protein; mucin 1 (*MUC1*); hepatocyte nuclear factor 1β (*HNF1β*); renin (*REN*); or the α1 subunit of *SEC61* translocon (*SEC61A1*).<sup>2,3</sup> The most prevalent form of ADTKD is ADTKD-*UMOD*, which is typically associated with early-onset hyperuricemia and gout.<sup>2–4</sup> More than 225 deleterious *UMOD* variants are reported at The Human Gene Mutation Database (<https://www.hgmd.cf.ac.uk/ac/gene.php?gene=UMOD>; accessed on 15.08.23), of which the large majority (95.3%) are missense single base-pair substitutions, most of them clustered in exons 3 and 4.<sup>3–6</sup>

A possibly distinct form of ADTKD – designated FJHN type 3 (FJHN3) – has been tentatively mapped to chromosome 2p22.1-p21,<sup>7</sup> by genome-wide linkage analysis in 5 multiplex families with ADTKD. The most likely candidate in that genomic interval was the gene encoding solute carrier family 8 member 1 (*SLC8A1*), a sodium/calcium exchanger,<sup>8</sup> but no pathogenic *SLC8A1* sequence variants could be identified in any of the probands<sup>7</sup> – however, with the sequencing methods used to that end, copy number variants (CNVs) might have been missed. So far, FJHN3 remains classified as a “phenotype description or locus, molecular basis unknown” in



**Fig. 1** – Family pedigree. sCr: serum creatinine; y.o.: years old; CKD defined as eGFR <60 ml/min/1.73 m<sup>2</sup> (using the CKD-Epidemiology collaboration equation, version 2009). Deceased subject III:2 was an oblate carrier of both the *UMOD* exon 11 deletion and the *SLC8A1* c.16C>T p.(Arg6\*) allele.

the Online Mendelian Inheritance in Man<sup>®</sup> catalog (OMIM<sup>®</sup>; <https://www.omim.org/entry/614227>; accessed on 15.08.23) and no *SLC8A1* variants have ever been established to cause ADTKD.

We report herein the genotype–phenotype correlation analysis of a Portuguese family with ADTKD/FJHN that suggest a possible novel genetic mechanism underlying uromodulin-associated kidney disease and provide evidence supporting a pathogenic role for *SLC8A1* variants in the development and natural history of ADTKD.

## Clinical report

The proband (IV:2; Fig. 1) was a 27-year-old white Portuguese male, referred to the nephrology clinic for evaluation and treatment of CKD. His medical history was relevant for nocturnal enuresis until age 10; arterial hypertension diagnosed at age 19, well controlled ever since with low dose lisinopril (2.5 mg, QD); and hyperuricemia. On the baseline laboratory workup, the estimated glomerular filtration rate was 49 ml/min/1.73 m<sup>2</sup> (CKD-Epidemiology Collaboration creatinine equation, version 2009), the serum uric acid level (831 μmol/L) was disproportionately increased to kidney function, and the urinalysis was unremarkable. Magnetic resonance imaging showed normal-sized, normal-shaped kidneys containing multiple small cysts in the medulla and at the corticomedullary junction. Despite continued therapy with allopurinol, the patient suffered several gout attacks during clinical follow-up.

The pedigree chart (Fig. 1) illustrates the unequivocal autosomal dominant pattern of inheritance of the hyperuricemic nephropathy and CKD in this family. The typical clinical phenotype was characterized by (i) hypertension, hyperuricemia and gout as presenting manifestations; (ii) progressive CKD diagnosed in the second to the fourth decades of life; (iii) absence of proteinuria or hematuria; and (iv) normal-sized kidneys with medullary cysts seen on imaging studies.

## Genetic diagnosis workup

Genetic testing using a customized next-generation sequencing (NGS)-based diagnostic gene panel targeted to ADTKD/MCKD/FJHN (*Ipatimup Diagnósticos*, i3S – Instituto de Investigação e Inovação em Saúde; University of Porto, Portugal), which includes the *SLC8A1* gene, revealed that both the proband and his affected older brother (pedigree subject IV:1) were heterozygous for an ultra-rare nonsense *SLC8A1* allele – c.16C>T p.(Arg6\*) (Table 1 and Fig. 2A) –, classified as “variant of uncertain significance (VUS)”, according to standard genetic nomenclature guidelines.<sup>9</sup> However, since the *SLC8A1* p.(Arg6\*) allele was not detected in their affected paternal aunt (pedigree subject III:5), it could not explain the segregation of kidney disease in the family.

Coincidentally, the proband’s older brother underwent further genetic testing abroad (*Hospices Civils de Lyon*; Bron, France), where the use of an extended kidney-disease gene panel allowed to identify (i) a previously unreported large terminal deletion in the *UMOD* gene, encompassing the entire exon 11, classified as “likely pathogenic” (Table 1); and (ii) an ultra-rare missense variant in the gene encoding polycystin-1 (*PKD1*) – c.9170T>C p.(Val3057Ala) (Table 1) –, classified as VUS. Since the latter was inherited by the two affected brothers (pedigree subjects IV:1 and IV:2; Fig. 2A) from their healthy mother (pedigree subject III:1; Fig. 2A), who exhibited no kidney cysts on ultrasonography examination at age 63, its pathogenicity could be confidently excluded.<sup>10</sup>

The *UMOD* single-exon deletion had been overlooked in the proband’s original genetic testing, because the bioinformatic algorithm to detect CNVs using the NGS panel data<sup>11</sup> had not yet been validated by the laboratory. Using a quantitative polymerase chain reaction (qPCR) approach, heterozygosity for the *UMOD* exon 11 deletion was subsequently demonstrated in the other two affected family members (pedigree subjects IV:2 and III:5; Fig. 2B), while it was excluded in the healthy relatives available for genotyping (pedigree subjects III:1 and III:4; Fig. 2B).

**Table 1 – Genomic identifiers and population prevalence of the *UMOD*, *SLC8A1* and *PKD1* variants identified in this family.**

Gene name	RefSeq accession <sup>a</sup>	Genomic/coding DNA change	Protein change (predicted)	dbSNP-identifier <sup>b</sup>	gnomAD <sup>c</sup> population frequency data: allele count/total allele number (sequence type)
<i>UMOD</i>	NC_000016.10	g.(20335481_20333375) ? _(20333051..?)del	?	–	Novel
<i>SLC8A1</i>	NM_021097.5 <sup>d</sup>	c.16C>T	p.(Arg6*)	rs767111343 <sup>f</sup>	1/152076 alleles (genomes) <sup>h</sup>
<i>PKD1</i>	NM_001009944.3 <sup>e</sup>	c.9170T>C	p.(Val3057Ala)	rs758627119 <sup>g</sup>	1/160674 alleles (exomes) <sup>i</sup>

<sup>a</sup> Reference sequence database.

<sup>b</sup> Single nucleotide polymorphism database; National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM), at the National Institutes of Health (NIH), Bethesda, MD, USA.

<sup>c</sup> Genome aggregation database; Broad Institute, Cambridge, MA, USA.

<sup>d</sup> [https://www.ncbi.nlm.nih.gov/nucore/NM\\_021097](https://www.ncbi.nlm.nih.gov/nucore/NM_021097).

<sup>e</sup> [https://www.ncbi.nlm.nih.gov/nucore/NM\\_001009944](https://www.ncbi.nlm.nih.gov/nucore/NM_001009944).

<sup>f</sup> <https://www.ncbi.nlm.nih.gov/snp/?term=rs767111343>.

<sup>g</sup> <https://www.ncbi.nlm.nih.gov/snp/?term=rs758627119>;

<sup>h</sup> [https://gnomad.broadinstitute.org/variant/2-40430265-G-A?dataset=gnomad\\_r3](https://gnomad.broadinstitute.org/variant/2-40430265-G-A?dataset=gnomad_r3) [accessed 15.01.23].

<sup>i</sup> [https://gnomad.broadinstitute.org/variant/16-2152413-A-G?dataset=gnomad\\_r2.1](https://gnomad.broadinstitute.org/variant/16-2152413-A-G?dataset=gnomad_r2.1) [accessed on 15.01.23].

Notably, the deceased father of the two affected brothers (pedigree subject III:2), who was an obligate carrier of both the *UMOD* exon 11 deletion and the *SLC8A1* p.(Arg6\*) allele, needed kidney replacement therapy (KRT) at age 43, while his also affected younger sister (pedigree subject III:5) did so only at age 55. The earlier clinical presentations of ADTKD in the double heterozygous individuals (pedigree subjects III-2, IV-1 and IV-2), as compared to the significantly later disease onset observed in their relative who inherited only the *UMOD* variant (III-5), suggest that heterozygosity for the nonsense *SLC8A1* p.(Arg6\*) allele had a pathogenic or disease modifier role, which is in accordance with its predicted protein truncating effect.<sup>9,12</sup>

## Discussion

This study illustrates some of the major challenges that clinicians and molecular geneticists encounter in the diagnostic approach to hereditary kidney disorders and highlights the importance of detailed clinical assessment of affected individuals and the potential usefulness of family segregation analysis for reclassification of VUS.<sup>13</sup>

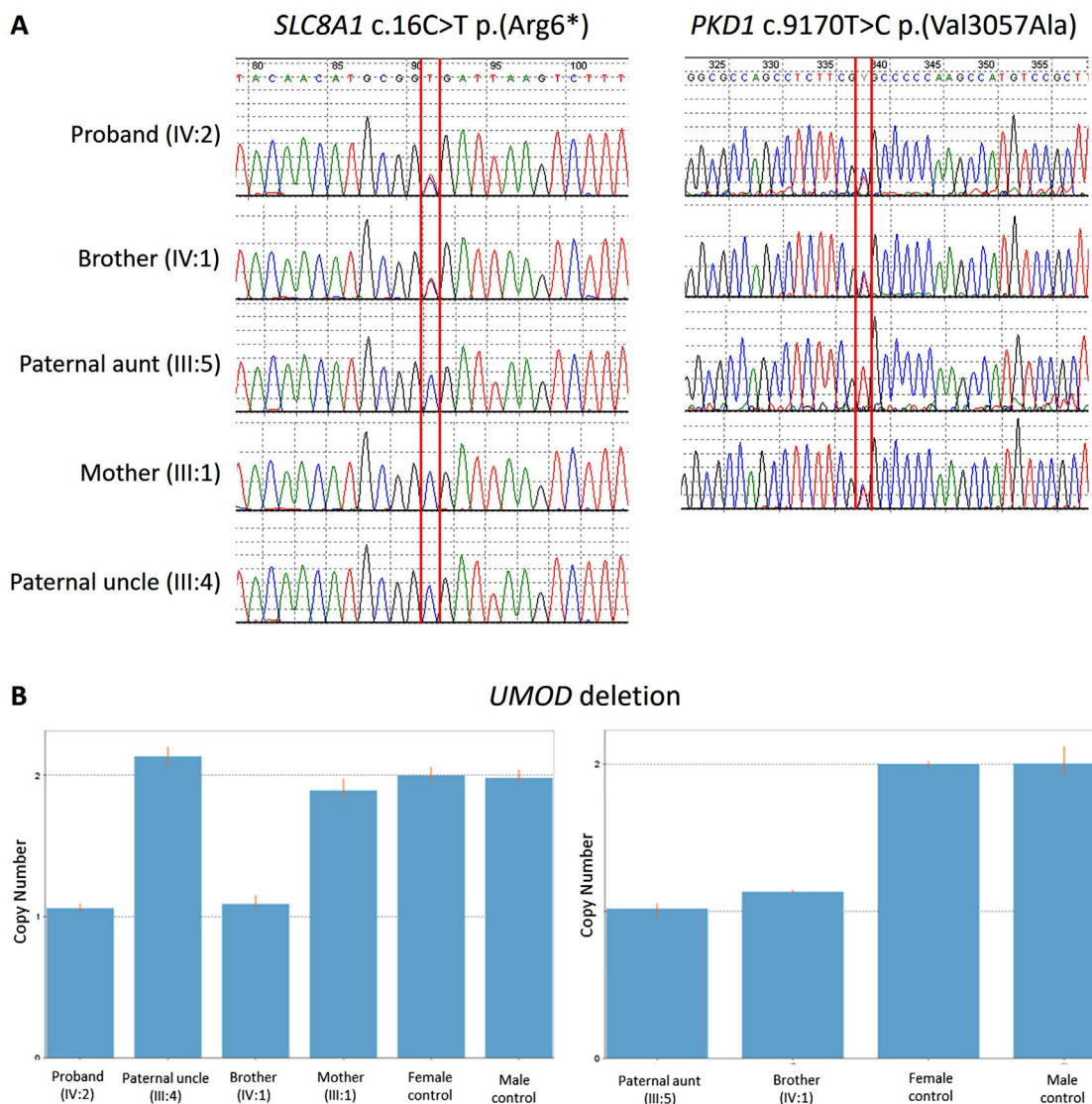
In families with ADTKD, the specific genetic diagnosis has important implications for the management, prognosis, genetic counseling, prevention of recurrence, and screening of individuals at risk.<sup>1</sup> In our family, coincidental genetic testing of two brothers clinically diagnosed with ADTKD, independently performed at different laboratories using distinct gene panels for kidney diseases, yielded three major results: (i) identification of a novel single-exon terminal deletion in *UMOD* that strictly cosegregated with kidney disease and gout, which constitutes strong clinical evidence of pathogenicity; (ii) detection of an ultra-rare *SLC8A1* nonsense allele that segregated with a more severe ADTKD phenotype, which, together with the predicted protein truncating effect, suggest pathogenicity<sup>9,12</sup>; (iii) detection of an ultra-rare *PKD1* missense

allele that did not segregate with polycystic kidneys, which is in agreement with the classification of neutral polymorphism attributed to the more common p.(Val3057Met) variant affecting the same codon.<sup>14</sup>

Uromodulin is a kidney-specific protein, mainly anchored in the apical membrane of the epithelial cells of the thick ascending limb of the loop of Henle, where it undergoes proteolytic cleavage to be released in urine.<sup>6,15</sup> Disease manifestations related to mutant *UMOD* are secondary to toxic gain of function, with endoplasmic reticulum accumulation and reduced urinary levels as the primary molecular defect.<sup>2,6,15–18</sup> So far, only two deletions in the *UMOD* gene, respectively involving 27 and 99 nucleotide pairs, and both affecting evolutionarily conserved residues in exon 4, have been associated with ADTKD/FJHN/MCKD.<sup>5,19</sup> Although the size of the *UMOD* deletion identified in our family is much larger than the two formerly described, it does not disrupt any of the structural domains or remove critical amino acid residues of uromodulin.<sup>6,15,20</sup> Since *UMOD* exon 11 encodes for the last amino acids of the C-terminal of the precursor protein, downstream from the anchoring site, as well as for the 3'-untranslated region (3'UTR), containing the polyadenylation signal sequence and the polyadenylation site, we postulate that its deletion might be pathogenic through loss of critical regulatory 3'UTR mRNA functions,<sup>21</sup> representing a novel pathogenic mechanism for ADTKD-*UMOD*.

The *SLC8A1* gene encodes the sodium/calcium exchanger 1 (NCX1), an ubiquitously expressed protein with a diversity of tissue-specific splice variants, belonging to the calcium/cation antiporter superfamily.<sup>8</sup> Altered expression and regulation of NCX1 proteins contribute to disturbed calcium homeostasis in cardiovascular disease (including hypertension, heart failure, arrhythmia and cerebral ischemia), diabetes, immune response, and tumor angiogenesis, as well as to impaired calcium reabsorption in the kidney.<sup>8</sup> In our family, heterozygosity for the *SLC8A1* p.(Arg6\*) allele was consistently associated with





**Fig. 2** – Sanger sequencing demonstrating (A, upper left) the presence of the variant *SLC8A1* c.16C>T p.(Arg6\*) in the affected brothers (IV:1 and IV:2) and its absence in the affected paternal aunt (III:5), the healthy uncle (III:4) and the mother (III:1); and (A, upper right) the presence of the variant *PKD1* c.9170T>C p.(Val3057Ala) in the two affected brothers (IV:1 and IV:2) and their healthy mother (III:1). (B) Quantitative polymerase chain reaction (qPCR) results confirmed the heterozygous *UMOD* deletion involving exon 11 in all affected family members (IV:1, IV:2, III:5) and its absence in the unaffected ones (III:4, III:1).

earlier clinical manifestations of ADTKD and progression to kidney failure (KF) requiring KRT. Since the natural history of ADTKD is more severe in males,<sup>22</sup> the fact that all three double heterozygous patients were males and the patient who inherited only the *UMOD* exon 11 deletion was a female needs consideration when interpreting those correlations. Unfortunately, on family screening, we could not identify any subject heterozygous only for the *SLC8A1* p.(Arg6\*) allele, or a double heterozygous female for both the *SLC8A1* p.(Arg6\*) allele and the *UMOD* exon 11 deletion, which would have helped establishing more robust genotype–phenotype correlations. However, the age difference at the initiation of KRT between the proband’s father and aunt was much larger than expected from gender-specific survival curves without KF for ADTKD-

*UMOD*,<sup>22</sup> an observation suggesting that the *SLC8A1* p.(Arg6\*) allele exerted a pathogenic role in this family, at least as a disease modifier.

*In conclusion:* genotyping analysis of a Portuguese family diagnosed with FJHN/ADTKD led to identifying a novel, large, terminal single-exon deletion in *UMOD*, cosegregating with an ultra-rare nonsense *SLC8A1* variant in most of the affected individuals, with the double heterozygous patients exhibiting a more severe clinical phenotype. These findings require further investigation to elucidate the molecular mechanism(s) underlying the pathogenicity of *UMOD* exon 11 deletion, which does not encode any of the critical structural domains or amino acid residues or uromodulin, as well as to clarify the role of the *SLC8A1* locus in ADTKD.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflict of interest

The authors have no conflict of interest to disclose.

## Acknowledgement

Results of this family study were presented as a poster (#5302) at the 60th Congress of the European Renal Association, that took place on June 15–18, 2023, in Milan (Italy), and published in the Abstract Book — Nephrol Dial Transplant. 2023;38 (Suppl. 2):i236–237.

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