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Homozygosity for uromodulin disorders: FJHN and MCKD-type 2

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Homozygosity for uromodulin disorders: FJHN and MCKD-type 2.

Background. Autosomal-dominant medullary cystic kidney disease type 2 (MCKD2) and familial juvenile hyperuricemic nephropathy (FJHN) are heritable renal diseases with autosomal-dominant transmission and shared features, including polyuria, progressive renal failure, and abnormal urate handling, which leads to hyperuricemia and gout. Mutations of the *UMOD* gene, disrupting the tertiary structure of uromodulin, cause MCKD2 and FJHN.

Methods. Haplotype analysis of a large Spanish family with MCKD was carried out to determinate genetic linkage to MCKD2 locus. Mutation detection was performed by direct sequencing of the *UMOD* gene. The level of Tamm-Horsfall protein in the urine was measured by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western blot analysis.

Results. Linkage to MCKD2 locus was demonstrated (LOD score: 4.13), and a known pathogenic uromodulin mutation was found in exon 4, corresponding to Cys255Tyr, disrupting the light chain binding domain of the protein. In this consanguineous family there were three patients homozygous for the C255Y mutation, and multiple heterozygous cases, allowing the MCKD phenotypes associated with one or two mutant alleles to be compared. The homozygous individuals survived to adulthood, although presenting an earlier onset of hyperuricemia and faster progression to end-stage renal disease than heterozygous individuals. Western analysis revealed lower levels of urine THP in one heterozygous patient compared with a normal control patient, both with normal renal function.

Conclusion. The study shows that individuals with two UMOD mutations are viable, but they do have more severe disease on average than heterozygotes. This family sheds light on the possible disease mechanism in this disorder.

Autosomal-dominant medullary cystic kidney disease (MCKD) and familial juvenile hyperuricemic nephropathy (FJHN) are renal diseases with an autosomal-dominant pattern of inheritance and shared features, including polyuria, progressive renal failure, and abnormal urate handling, which leads to hyperuricemia and gout. Both diseases are associated with corticomedullary cysts, interstitial fibrosis secondary to infiltration by inflammatory cells, and marked thickening of tubular basement membranes [1].

This group of disorders has been shown to be genetically heterogeneous, with linkage established to three distinct loci up to the present. The MCKD1 gene (MIM 174000) has been localized to chromosome 1q21 [2]. Another locus, MCKD2 (MIM 603860), was shown to map to chromosome 16p11-p13 [3]. Although MCKD2 and FJHN (MIM 162000) were initially thought to be associated with mutations in different genes, subsequent studies showed that both diseases were allelic [4], and that mutations of the *UMOD* gene, disrupting the tertiary structure of uromodulin, cause MCKD2 and FJHN [5–11]. A mutation in the hepatocyte nuclear factor-1B gene was recently described in a family presenting FJHN and diabetes [12].

Uromodulin, originally identified over 50 years ago and referred as Tamm-Horsfall protein (THP) [13], is the most abundant protein in human urine (50 to 100 mg per day), consists of 640 amino acids, several glycosilation sites, and 48 cysteine residues, allowing for the potential formation of 24 intramolecular disulphide bonds [14]. Uromodulin plays an important role in renal salt and water transport [15], urate metabolism, modulation of immune responses [14], renal stone formation [16], and urothelial cytoprotection [17].

Although homozygosity for a dominant disease is rare in humans, probably because of consanguinity, is often uncommon and lacks viability (i.e., intrauterine demise), some molecularly confirmed cases for non-renal diseases have been reported. In some of them, homozygotes are more severely affected than heterozygotes, such as in achondroplasia, aniridia, Waardenburg, Charcot-Marie-Tooth, Marfan's, synpolydactyly, dentatorubralpallidoluysian atrophy, and Machado-Joseph diseases. On the other hand, in Huntington's, Creutzfeldt-Jakob, familial amiloidotic polyneuropathy, and multiple endocrine neoplasia (MEN1) diseases, homozygotes and

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heterozygotes are similarly affected. Gain of function or dominant negative effects are examples of the above mentioned, while the loss of function is a mechanism where homozygosity is associated with more severe phenotypes [18].

Here, we report for first time a clinically and molecularly proven situation of homozygosity in a dominant cystic kidney disease. We show homozygosity for C255Y uromodulin mutation is not a lethal condition; three affected individuals were able to live until an adult age. The comparison of different phenotypes between heterozygotes and homozygotes can provide some clues about the molecular mechanisms involved in development, cystogenesis, progressive renal damage, and renal uric acid transport.

METHODS

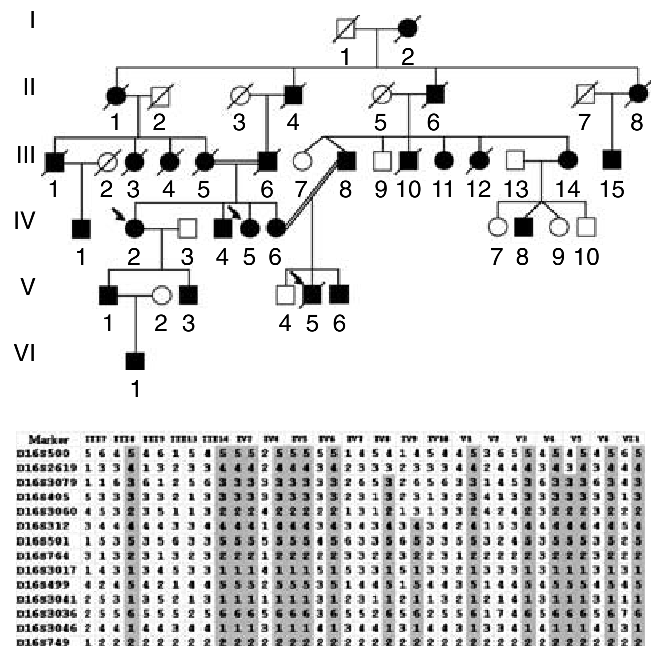
Patients and diagnosis of MCKD2

The patients included in this study are members of a large family originating from the northern part of Spain (Fig. 1). The diagnosis of MCKD in this family was established on the basis of the coexistence of (*1*) autosomal-dominant chronic renal failure; (*2*) similar appearances of chronic interstitial nephritis, with marked thickening of tubular membranes, for all three subjects for whom kidney tissue was available, (*3*) a history of hyperuricemia or gout preceding renal failure; and (*4*) ultrasound showing small or normal size kidneys, with or without occasional cysts in the medulla. The clinical characteristics of the 11 affected subjects are presented in Table 1. All the participants were informed of the goal of the study, and consent was obtained.

Haplotype analysis and linkage

Peripherical blood was collected in tubes with a vacuum system (BD Vacutainer, Plymouth, UK) containing EDTA. DNA was isolated using Puregene kit (Gentra, Minneapolis, MN, USA). Fourteen microsatellite markers were used (D16S500, D16S2619, D16S3017, D16S312, D16S499, D16S3036, D16S3041, D16S501, D16S405, D16S3079, D16S3060, D16S749, D16S764, D16S3046), which covered a region of approximately 7 cM along chromosome 16p. Primers and sequence for these markers are available in the Genome Database.

Amplifications were carried with a PCR Express Hybaid (Ashford, UK) thermocycler using the following conditions: 50 to 100 ng of genomic DNA, PCR Supermix [200 μmol/L dNTPs, 50 mmol/L KCl, 10 mmol/L Tris-HCl, pH 9.3, 1.5 mmol/L $MgCl_2$, and 1 U/L of Taq polymerase (Invitrogen, Carlsbad, CA, USA)], and 0.25 μmol/L of each primer (5′ end labeled with Cy5) for a final volume of 25 μL. An ALF Express II fluorescent sequencer was used for separation and detection of fragments from microsatellite markers. To estimate values of LOD score, Superlink software (Durham, NC, USA) was used [19].



Marker	III7		III8		III9		III13		III14		IV2		IV4		IV5		IV6		IV7		IV8		IV9		IV10		V1		V2		V3		V4		V5		V6		VI1	
D16S500	5	6	4	5	4	6	1	5	4	5	5	5	2	5	5	5	5	5	1	4	5	4	1	4	5	4	4	5	3	6	5	5	4	5	4	5	4	5	6	5
D16S2619	1	3	3	4	1	3	2	3	3	4	4	4	2	4	4	4	3	4	2	3	3	3	2	3	3	3	4	4	2	4	4	4	3	4	3	4	3	4	4	4
D16S3079	1	1	6	3	6	1	2	5	6	3	3	3	3	3	3	3	3	3	2	6	5	3	2	6	5	6	3	3	1	4	5	3	6	3	3	3	6	3	4	3
D16S405	5	3	3	3	3	3	2	1	3	3	3	3	3	3	3	3	3	3	2	3	1	3	2	3	1	3	2	3	4	1	3	3	3	3	3	3	3	3	1	3
D16S3060	4	5	3	2	3	5	1	1	3	2	2	2	4	2	2	2	2	2	1	3	1	2	1	3	1	3	3	2	4	2	4	2	3	2	2	2	3	2	2	2
D16S312	3	4	4	4	4	4	3	3	4	4	4	4	1	4	4	4	3	4	3	4	3	4	3	4	3	4	2	4	1	5	3	4	4	4	4	4	4	4	5	4
D16S501	1	5	3	5	3	5	6	3	3	5	5	5	5	5	5	5	4	5	6	3	3	5	6	5	3	3	5	5	3	2	4	5	3	5	5	5	3	5	2	5
D16S764	3	1	3	2	3	1	3	2	3	2	2	2	1	2	2	2	2	2	3	3	2	2	3	2	2	3	1	2	2	2	2	2	3	2	2	2	3	2	2	2
D16S3017	1	4	3	1	3	4	5	3	3	1	1	1	4	1	1	1	5	1	5	3	3	1	5	1	3	3	2	1	3	3	3	1	3	1	1	1	3	1	3	1
D16S499	4	2	4	5	4	2	1	4	4	5	5	5	2	5	5	5	3	5	1	4	4	5	1	5	4	4	3	5	1	4	4	5	4	5	5	5	4	5	4	5
D16S3041	2	5	3	1	3	5	2	1	3	1	1	1	1	1	1	1	3	1	2	3	1	1	2	1	1	3	2	1	2	1	4	1	3	1	1	1	3	1	1	1
D16S3036	2	5	5	6	5	5	5	2	5	6	6	6	5	6	6	6	3	6	5	5	2	6	5	6	2	5	5	6	1	7	4	6	5	6	6	6	5	6	7	6
D16S3046	2	4	4	1	4	4	3	4	4	1	1	1	3	1	1	1	4	1	3	4	4	1	3	1	4	4	3	1	3	3	4	1	4	1	1	1	4	1	3	1
D16S749	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Fig. 1. Pedigree of the family with medullary cystic kidney disease type 2 (MCKD2). Haplotypes for polymorphic markers are shown. The disease-associated haplotype is shadowed. Arrows, homozygous individuals.

Three classes of liability were considered in accordance with penetrance of distinct age groups—50% for those under 30 years, 90% for those aged between 30 and 50 years, and 99% for those older than 50 years.

Mutation detection

In order to detect mutations in the *UMOD* gene, direct sequencing of the polymerase chain reaction (PCR) products, amplified from a set of primers flanking exons of the *UMOD* gene, was performed [5]. All members of the last three generations of the family were collected for the mutation screening, except individuals IV:12 and IV:14, which were not available. PCR amplifications were optimized to a final volume of 30 μL containing 0.2 mmol/L dNTPs, 1 U/L of Taq polymerase, 2.5 mmol/L $MgCl_2$, 50 mmol/L KCl, 10 mmol/L Tris-HCl (pH 8.3), 50 to 100 ng of genomic DNA, and 20 pmol of each primer after the thermocycler program: 96°C for 5 minutes, followed by 95°C for 30 seconds, 56°C for 30 seconds, and 72°C for 1 minute (35 cycles). Direct sequence reactions of the PCR fragments were carried out using the Big Dye Terminator version 1.0 sequence kit (Applied Biosystems, Foster City, CA, USA) in accordance with manufacturer's recommendations. An ABI Prisma 3100 Avant (Applied Biosystems) fluorescent sequencer was used to determine sequence profiles.

SDS-PAGE and Western blotting

Fresh urine samples were separated in sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) (6% acrylamide). Western blotting was

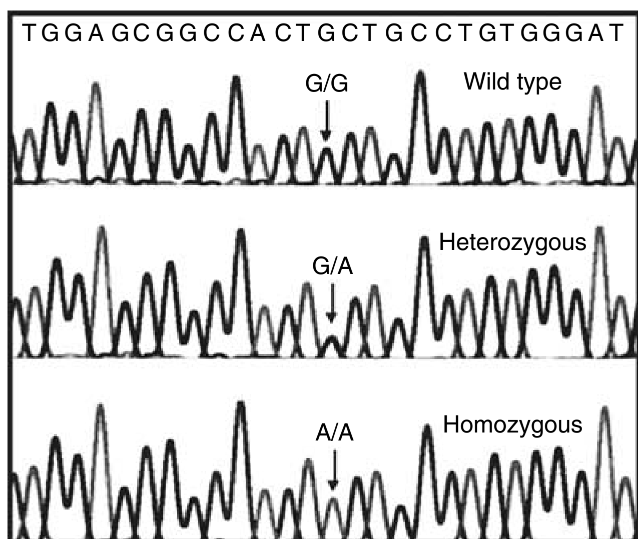


Fig. 2. ***UMOD*** **gene: exon 4 sequence showing heterozygosity and homozygosity for 764G >A.**

performed by standard procedures after electrophoretic separation of total proteins, and transferred to a polyvinylidine difluoride (PVDF) membrane (Amersham Pharmacia Biotech, Little Chalfont, UK), which was successively incubated for 1 hour in TBS-T (50 mmol/L Tris-HCl, 200 mmol/L NaCL, and 0.2% Tween 20). The membrane was blocked and incubated for 2 hours at room temperature with polyclonal antibody against Tamm-Horsfall protein (Biomedical Technologies, Stoughton, MA, USA), washed, and incubated again for 1 hour at room temperature with appropriate rabbit peroxidase-labeled antibody (Dako, Glostrup, Denmark). It was washed and visualized using an enhanced ECL chemiluminescence (Amersham Pharmacia Biotech). Specificity of the blotting was determined by detection of the purified human uromodulin (Biomedical Technologies, Stoughton, MA, USA).

RESULTS

Haplotypes and matings

Computational analysis of 14 STR polymorphic markers was carried out. The LOD score reached was 4.13 (Theta = 0.00), which provides clear-cut evidence of linkage to MCKD2 locus. Two recombinations occurred on the intervals between D16S500-D16S749 and D16S500-D16S2619 markers on the disease-linked haplotype of members IV:8 and IV:9, respectively, but they were not sufficient to impede the transmission of the disease (Fig. 1). Based on the order of the markers defined by the NCBI human genome map and adopted in the present study, the *UMOD* gene is found flanked by the makers D16S3036 and D16S3041, although the gene did not participate in the recombinations. Another small recombination in the member V:5 was found, but without relevance for linkage analysis.

Mutation analysis of the *UMOD* gene

Sequence analysis of the 12 exons of the *UMOD* gene from patients of this family revealed the existence of a mutation recently described [6]. That nonconservative missense mutation was produced in exon 4 by a substitution from G to A in the genomic DNA position 1772G > A equivalent to 764G > A in cDNA (Fig. 2). Cysteine located in the position 255 of the protein sequence was changed to tyrosine.

We have identified the mutation C255Y in 14 of 20 members of the family (Table 1). Individuals IV:2, IV:5, and V:5 are offspring of consanguineous partners, and were homozygous for the 764G >A mutation. Two individuals, age 26 (V:4) and 40 (IV:9) years old, respectively, were heterozygous for the 764G >A change, but are presently asymptomatic. Because they are carriers of the disease-linked haplotype and the mutation, we have to consider the possibility that they will develop the affected phenotype.

Genotype-phenotype relationship in heterozygous patients

Complete phenotypic and molecular data were available for 11/20 individuals presumed to be heterozygous for UMOD mutations (Table 1). Nine of them (82%) suffered from hyperuricemia. The average age of onset for hyperuricemia (not including homozygotes) was 28 years for males (range 12 to 50), and 46 for the only affected female (IV:6). Two males developed gout at 23 and 29 years at age. No female member of this family suffered from gout.

At an average age of 38 years, heterozygous males developed an increase in the serum creatinine levels (range 30 to 51). This clinical manifestation progressed to end-stage renal disease (ESRD) in 8 patients (5 males and 3 females). An average age of onset for ESRD for males was 58 years (range 45 to older than 71), and 66 years for females (range 61 to older than 74).

Genotype-phenotype relationship in homozygous patients

The main clinical and molecular characteristics are described in Figures 1 and 2 and Table 1. As is shown in Figure 1, the first homozygous patient (IV:2), now 57 years old, is the daughter of a consanguineous mating (III:5 × III:6). Hyperuricemia, onset of renal insufficiency, and progression to ESRD was diagnosed 32, 28, and 6 years earlier, respectively, than in the case of heterozygous women. High blood pressure was found when the patient was 20 years old.

The second homozygous patient (IV:5), now 43 years old, is also a daughter of the same consanguineous mating (III:5 × III:6). Hyperuricemia and onset of renal insufficiency were diagnosed 30 and 28 years earlier, respectively, than the most precocious heterozygous women. In

Table 1. Genotype-phenotype relationship in heterozygous and homozygous affected individuals

Patient	Gender	Genotype C255Y	Current age *years*	Onset of hyperuricemia	Highest serum uric acid *mg/dL*	First attack of gout	Onset of renal insufficiency	Current serum creatinine *mg/dL*	ESRD age	Renal cysts	Other clinical manifestations
Homozygotes											
IV:2	F	Y/Y	57	14	8.1	No	25	ESRD	55	35	Arterial hypertension at 20 years
IV:5	F	Y/Y	43	16	9.1	No	25	2.4	No	36	Pectus excavatum
V:5	M	Y/Y	Dead	8	8.8	14	10	Dead	22	22	Salt-wasting at 19 years
Heterozygotes											
III:3	F	ND	Dead	ND	ND	ND	ND	ND	65	ND	
III:4	F	ND	Dead	ND	ND	ND	ND	ND	61	ND	
III:5	F	ND	Dead	ND	ND	ND	ND	ND	Not at 67 y.	ND	
III:6	M	ND	Dead	ND	ND	ND	ND	ND	Not at 71 y.	ND	Pectus excavatum
III:8	M	C/Y	70	ND	ND	ND	ND	ESRD	50	ND	Prostate cancer
III:10	M	ND	Dead	ND	ND	ND	ND	ND	58	ND	
III:11	F	ND	74	ND	ND	ND	ND	3.0	No	ND	
III:12	F	ND	Dead	ND	ND	ND	ND	ND	66	ND	
III:14	F	C/Y	66	ND	ND	ND	ND	ESRD	60	ND	
III:15	M	ND	68	ND	ND	ND	ND	ND	56	ND	
IV:1	M	ND	63	ND	ND	ND	ND	ND	45	ND	
IV:4	M	C/Y	55	50	8.5	No	51	1.4	No	No	Arterial hypertension at 50 years
IV:6	F	C/Y	53	46	8.4	No	No	1.1	No	No	
IV:8	M	C/Y	40	30	7.6	No	30	1.7	No	No	
IV:9	F	C/Y	40	No	5.4	No	No	0.9	No	No	
V:1	M	C/Y	39	23	10	23	32	1.6	No	No	
V:3	M	C/Y	29	29	8.5	29	No	1.1	No	No	
V:4	M	C/Y	32	No	6.5	No	No	1.2	No	No	
V:6	M	C/Y	26	22	7.2	No	No	1.0	No	No	
VI:1	M	C/Y	15	12	7.4	No	No	0.7	No	No	

Abbreviations are: ND, Not determined; ESRD, end-stage renal disease.

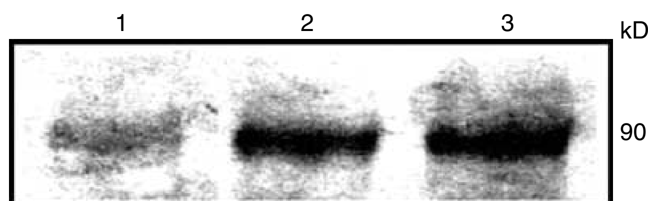


Fig. 3. Detection of urinary excretion of uromodulin by Western blot. Heterozygote for C255Y mutation with normal renal function is shown in band 1. Control individual with normal renal function is shown in band 2. Purified uromodulin is shown in band 3.

comparison, their sister (IV:6), heterozygous for the mutation C255Y, now 53 years old, presented hyperuricemia at 46 years. Furthermore, she has no cysts in the kidneys, and her serum creatinine is normal (1.0 mg/dL; Table 1). Their affected parents, both heterozygous (III:5 and III:6; first cousins), still had not progressed to ESRD by the time they died at ages 67 and 71 years, respectively.

The third homozygous patient (V:5) was a son of another consanguineous mating (III:8 × IV:6). Hyperuricemia, onset of renal insufficiency, and progression to ESRD was diagnosed 4, 14, and 35 years, respectively, earlier than the most precocious heterozygous male. The patient's first attack of gout was already at age 14 years. He was diagnosed as having a salt-losing nephropathy at 19 years of age. When he was 22 years old, he received a kidney transplant, and died one month after because of acute respiratory distress syndrome. The necropsy showed pulmonary calciphylaxia. In comparison, his brothers (V:4 and V:6), heterozygous for C255Y mutation, now 26 and 32 years old, respectively, have normal renal function, no cysts, and only V:6 was diagnosed as having hyperuricemia when he was 22 years old. In comparison to his parents (III:8 and IV:6; first cousins), he progressed to ESRD 38 years earlier than his father, and his mother, now 53 years old, still has a normal renal function.

Uromodulin excretion in MCDK2 patients

Western analysis revealed lower levels of urine THP in one heterozygous patient compared with a normal control patient, both with normal renal function (Fig. 3). One homozygous patient displayed undetectable urine THP level, but the fact that he was in renal failure makes this observation inconclusive. In fact, another evaluated patient, a heterozygote with renal failure, also showed undetectable urine THP level. The patients in renal failure, therefore, were not included in Figure 3.

DISCUSSION

In this family with a uromodulin disorder (autosomal-dominant medullary cystic kidney disease-type 2, so

called familial juvenile hyperuricemic nephropathy), linkage to MCKD2 locus was demonstrated and a known pathogenic uromodulin mutation was found [6]. Three affected people had two copies of the disease-linked haplotype, which was produced by two consanguineous marriages. Sequencing analysis showed that all three had two copies of the mutated MCKD2 allele.

Mutations of the *UMOD* gene, disrupting the tertiary structure of uromodulin and resulting in abnormal accumulation within tubular cells and reduced urinary excretion, are responsible for the clinical manifestations of renal disease and hyperuricemia found in MCKD2 and FJHN [5–11]. Uromodulin is polymeric in its native form, composed of monomeric subunits of 85 kD, with 30% of the molecular weight from carbohydrates and the remaining 70% from the polypeptide chain [20]. Electron microscopy showed that it is composed of thin, intertwining fibers with a helical structure. The filaments consist of two protofilaments wound around each other, forming a right-handed helix [21]. It contains an amino terminus signal peptide, 3 calcium-binding epidermal growth factor-like domains with a calcium-coordinating segment [14], a zona pellucida domain [21], a binding domain for light chains of immunoglobulins [22] specifically to the third complementary-dependent region of both kappa and lambda light chains [23], and a glycosilphosphatidylinositol (GPI) membrane anchor site [24]. Uromodulin is expressed in the thick ascending limb of the loop of Henle and the most proximal part of the distal convoluted tubule [15].

Our data suggest that C255Y homozygosity is associated with more severe phenotypes in terms of earlier onset age of hyperuricemia, starting age of renal impairment, and progression to ESRD. A more pronounced decrease of uromodulin functions is accompanied by a missing immunomodulatory function, with increased chemoattraction for cytokines [14], a lack of its gel properties in the tubular lumen. A decreased protection against infections or toxins would be the mechanism mediating an earlier and accelerated damage to renal parenchyma [17].

The fact that homozygotes did not have higher serum uric acid levels than heterozygotes suggests that uromodulin does not act physiologically like a urate transporter, in the post-secretory reabsorption in the thick ascending limb of the loop of Henle and the most proximal part of the distal convoluted tubule [25], although uromodulin is precisely and exclusively expressed in that portion of the nephron [15]. Furthermore, its secondary structure does not contain any membrane-spanning domain as is the case in URAT1, a urate-anion exchanger in the proximal tubule, and other members of the organic anion transporter family [26]. Hyperuricemia and reduced urate excretional fraction existing in MCKD2 and FJHN could result from extracellular volume contraction because of the loss of uromodulin's role in renal salt and water transport, as it has been proposed [4, 15].

The C255Y uromodulin mutation disrupts the light chain binding domain: AHWSGHC (Y)CL [22], a single binding site for the third complementary determining region of both kappa and lambda immunoglobulin light chains [23]. The two cystein residues seem to be critical for the binding of light chains physiologically filtered from the blood by the kidney.

We showed that homozygosity for C255Y uromodulin mutation is not a lethal condition, human embryos are viable, and three affected individuals were able to live until an adult age. This situation is completely different than other cystic kidney diseases, such as autosomal-dominant polycystic kidney disease type 1 and type 2, where, until now, no case of homozygosity has been reported, although it was intensively looked for. Viability of C255Y homozygotes has likely implications about the nature of the function of the protein, uromodulin having redundant properties or a nonessential function during development.

The fact that individuals with two UMOD mutations have more severe disease on average than heterozygotes suggests that the C255Y allele is hypomorphic, homozygotes having a gene dosage even lower, as has been described for other diseases like PAX3 and PAX6 gene mutations in Waardenburg syndrome and aniridia. Hypomorphic mutations would cause a decrease in the amount of protein formed, or a decrease in the ability of the protein to function. Differences in the levels of THP in urine of homozygotes and heterozygotes could contribute to the elucidation of such a mechanism.

Western analysis revealed lower levels of urine THP in one heterozygous patient compared with a normal control patient, both with normal renal function (Fig. 3). These data reproduce Dahan et al's observations [10]. One homozygous patient displayed undetectable urine THP levels, but the fact that he was in renal failure makes this observation inconclusive. In fact, another evaluated patient, a heterozygote with renal failure, also showed undetectable urine THP levels (data not shown). Together, the data provided above are permissive for the "hypomorphic allele" hypothesis, but are certainly not conclusive.

Other studies have suggested that the disease is caused by intracellular accumulation of the mutant protein [10, 11]. We have also performed immunohistochemistry analyses in kidney sections of heterozygous patients, finding a similar pattern of protein accumulation in epithelial cells of thick ascending limb of Henle (data not shown). No kidney specimens from homozygotes were available.

These data also suggest that the role of uromodulin in human kidney development is different from other products involved in the pathogenesis of cystic diseases, like polycystin 1 or polycystin 2. In comparison with PKD1 [27] or PKD2 [28], the two-hit hypothesis (germline

mutation plus somatic inactivation) must not be invoked in the case of MCKD2. The three homozygous patients had two mutated MCKD2 alleles in each renal tubular cell since their conception, and even so they did form just a small number of cysts, and only when they were in an advanced situation of renal failure. Maybe the presence of cysts in this entity is not a primary event but only a secondary phenomenon, although receiving a denomination of cystic disease. On the other hand, cysts are relatively common in many kidney diseases leading to a decrease of the renal function [29].

In this work, we have described a family with several individuals who carry a homozygous missense change in uromodulin. These individuals survived to adulthood, but they also may present a more severe renal phenotype. They had an earlier onset of hyperuricemia and progressed to ESRD at an earlier age than family members who were heterozygous for the same mutation. Genotype-phenotype relationship in homozygosity can provide some clues and generate new hypotheses about the molecular mechanisms involved in the alteration of renal acid uric transport and the structural renal abnormalities resulting in cystogenesis and progressive renal failure in MCKD2 and FJHN.

APPENDIX

Electronic database information

Accession numbers and URLs for data in this article are as follows:

NCBI human genome map: www.ncbi.nlm.nih.gov/mapview/map_search.cgi

Online Mendelian Inheritance in Man (OMIM): www.ncbi.nlm.nih.gov/Omim

Genome Database (GDB): www.gdb.org

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