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Original Paper

Epidemiology of Uromodulin-Associated Kidney Disease – Results from a Nation-Wide Survey

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Key Words
Clinical epidemiology · End-stage kidney disease · Genetic renal disease · Uromodulin

Abstract
Background/Aims: Uromodulin-associated kidney disease (UAKD) is caused by uromodulin mutations and leads to end-stage renal disease. Our objective was to examine the epidemiology of UAKD. ***Methods:*** Data from all UAKD families in Austria were collected. Patients included in the Austrian Dialysis and Transplantation Registry (OEDTR) with unclear diagnoses or genetic diseases were asked whether they had (1) a family history of kidney disease or (2) had suffered from gout. Patients with gout and autosomal dominant renal disease underwent mutational analysis. Kaplan-Meier and Cox analysis was employed to estimate time to renal failure. ***Results:*** Of the 6,210 patients in the OEDTR, 541 were approached with a questionnaire; 353 patients answered the questionnaire. Nineteen of them gave two affirmative answers. In 7 patients, an autosomal dominant renal disease was found; in 1 patient a UMOD mutation was identified. One family was diagnosed through increased awareness as a consequence of the study. At present, 14 UAKD patients from 5 families are living in Austria (1.67 cases per million), and 6 of them require renal replacement therapy (0.73 per 1,000 patients). Progression to renal failure was significantly associated with UMOD genotype. ***Conclusion:*** UAKD patients can be identified by a simple questionnaire. UMOD genotype may affect disease progression.

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Introduction

Uromodulin or Tamm-Horsfall protein is a 95-kDa glycoprotein consisting of 640 amino acids, which are encoded by the *UMOD* gene on chromosome 16p12.3. Uromodulin is synthesized by the cells of the thick ascending limb and early distal convoluted tubular cells in the kidney [1]. The highly glycosylated molecule is an avid binder, and after being secreted into the urine binds to several different constituents that include bacteria, crystals, and proteins.

Uromodulin mutations are found to be associated with three autosomal dominant conditions, namely familial juvenile hyperuricemic nephropathy (FJHN1; MIM 162000); medullary cystic kidney disease type 2 (MIM 603860), and glomerulocystic kidney disease (MIM 609886) [2–4]. The majority of *UMOD* mutations cluster in exons 4.5 and 8 [5] and cause replacement of cysteine residues, leading to misfolding of the uromodulin molecule, with the abnormal uromodulin becoming entrapped in the endoplasmatic reticulum of the cells of the thick ascending limb of the loop of Henle. Thus, these diseases, which on clinical presentation are hardly distinguishable from each other, may be referred to as uromodulin-associated kidney diseases (UAKDs) [4, 6–10], and large intracellular deposits can be seen in renal biopsies of affected patients [6].

Families with UAKD have been reported from the US, Austria, Spain, France, Portugal, the Czech Republic, the UK, Belgium, Germany, Switzerland, Latvia, Morocco, Japan, Turkey, and South Korea [2, 3, 5, 6, 8, 10–24]. However, we are unaware of any nationwide epidemiologic study of UAKD. Here, we present data on all Austrian families diagnosed with UAKD. We also demonstrate that with the use of the Austrian Dialysis and Transplant Registry (OEDTR) and a simple patient questionnaire it was possible to identify previously undiagnosed patients.

Patients and Methods

This epidemiological study has two components. First, data from all Austrian UAKD families that had been diagnosed independently from the structured study described below were collected. Second, in 2001, an epidemiologic study to identify other UAKD families was conducted by utilizing the OEDTR, which includes >99% of all patients receiving chronic renal replacement therapy (RRT) in Austria. The study population was comprised of all patients reported in the OEDTR and alive on January 26, 2001. At the time of the study, the disease was referred to as familial juvenile hyperuricemic nephropathy (FJHN), as its cause was still unknown. All patients enrolled in the OEDTR gave informed written consent to data analysis. In a first step, we identified renal disease codes used by the European Dialysis and Transplantation Association Registry and the OEDTR which might include cases of FJHN. We further included only those patients who started RRT between 20–50 years of age. The codes and the number of coded OEDTR patients are given in table 1 and shown in figure 1. In a next step, we sent a list of patients identified by this process to each nephrology center that participates in the OEDTR. In a questionnaire, each patient was asked the following two questions:

(1) Does anyone of your family members suffer from chronic kidney disease (CKD)?
(2) Did you have gout in the years before dialysis was initiated?

A de-identified list with the answers was returned to the study center at the Medical University of Innsbruck, Austria. Patients who gave an affirmative answer to both questions were asked to provide a focused and detailed medical history to the patient's nephrologists. In the presence of a family history compatible with autosomal dominant inheritance of re-

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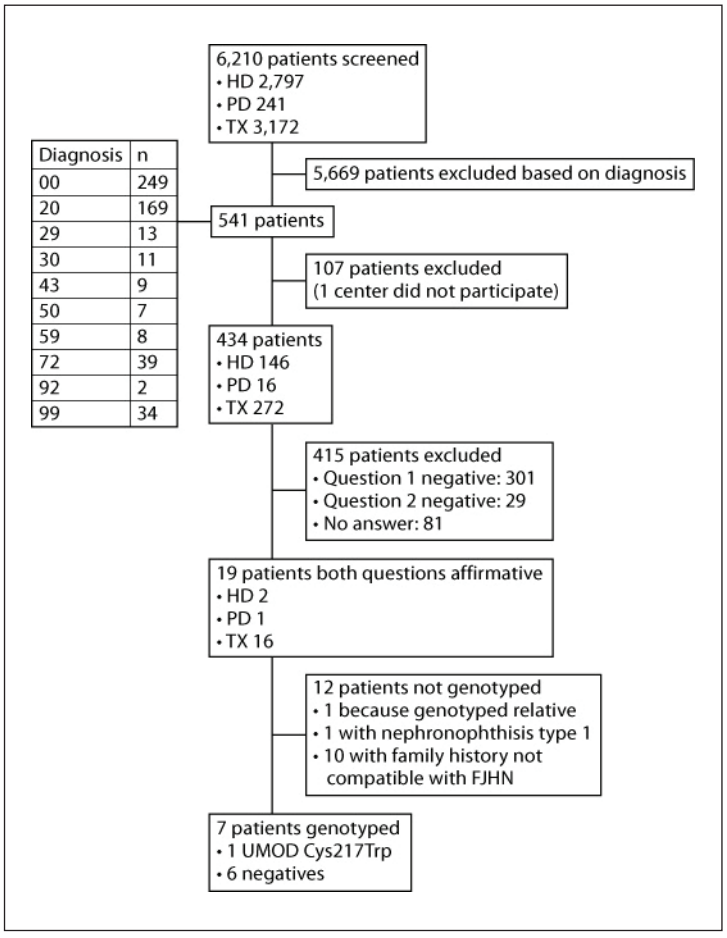

Diagnosis	n
00	249
20	169
29	13
30	11
43	9
50	7
59	8
72	39
92	2
99	34

Fig. 1. Study flow chart. Diagnosis codes are further detailed in table 1. HD = Hemodialysis; PD = peritoneal dialysis; TX = renal transplant.

nal disease and after exclusion of another clear diagnosis, patients were approached and after giving written informed consent in accordance with the Austrian law, underwent genetic testing for mutations in the uromodulin *(UMOD)* gene and the hepatocyte nuclear factor-1β *(HNF-1β)* gene. The methods for DNA sequence analysis have been described previously [10, 25].

End-stage renal disease (ESRD) was defined as either initiation of RRT or death because of renal failure without preceding RRT. Time to ESRD was assessed by Kaplan-Meier analysis and log-rank test, and Cox proportional hazard models stratified by UMOD genotype. IBM SPSS Version 19 was used for statistical analyses.

Results

Screening Study

A study flow chart is presented in figure 1. In January 2001, the OEDTR included 6,210 patients, 2,797 on hemodialysis, 241 on peritoneal dialysis, and 3,172 with functioning renal transplants. Of these 6,210 patients, 541 had one or more diagnoses potentially compatible with the presence of UAKD (table 1). Questionnaires were sent out to all 49 centers involved in the care of these patients and returned by 48 centers. The one non-participating center cared for 107 patients; since no additional information was available from these sub-

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Table 1. Renal diagnoses compatible with the presence of UAKD included in the center survey

Diagnosis	Code	Patients (n = 541)
Chronic renal failure, etiology uncertain	00	249
Pyelonephritis, cause not specified	20	169
Pyelonephritis due to other cause	29	13
Interstitial nephritis due to other cause	30	11
Medullary cystic disease	43	9
Familial nephropathy unspecified	50	7
Hereditary nephropathy – other specified type	59	8
Renal vascular disease due to hypertension	72	39
Gout	92	2
Other identified renal disorders	99	34

Renal diseases were classified according to the code used by the ERA-EDTA Registry.

jects, they were excluded from further analysis. Of the remaining 434 patients, a total of 334 patients (77%) answered either one or both questions with 'No', 81 patients (18.7%) did not provide any response at all, and 19 patients (4.3%) answered both questions affirmatively. Before proceeding to genotyping, patient responses to the questionnaire were reassessed by the attending nephrologists involved in the direct care of the patient. This reassessment revealed that 1 patient had unequivocally nephronophthisis type 1 and that the family histories in 10 patients were incompatible with autosomal dominant diseases. One patient was not genotyped because UMOD genotyping had been negative in a first-degree relative, who had been tested outside the study. Seven patients underwent sequencing of the *UMOD* gene and the *HNF-1β* gene. In 1 patient, a novel *UMOD* Cys217Trp mutation could be identified (fig. 2; family 4, patient 3:1). None of the 7 patients had a mutation in the *HNF-1β* gene.

The epidemiologic survey was presented and discussed extensively at national nephrology meetings and, thus, increased awareness for FJHN among Austrian nephrologists. This led to the diagnosis of another individual with CKD, gout, and a positive family history during the study. A novel Cys223Arg *UMOD* mutation was identified in that patient (fig. 2; family 5, patient 2:1).

Brief Description of UAKD Families

Independent of the screening study, 3 families were already diagnosed with UAKD. Thus, altogether, currently 5 families with UAKD comprising 14 patients live in Austria (table 2). Their pedigrees are shown in figure 2.

Family 1 (Cys77Tyr)

A description of the family and mutation analysis of the *UMOD* gene has been reported previously [13, 26, 27]. The index case (3:3) presented with gout and CKD stage III. Family history revealed that his maternal grandmother (1:1), his mother (2:2) and all of her sisters (2:1; 2:3; 2:4; 2:5) suffered from renal failure and gout. In addition, 3 of his cousins (3:1; 3:2; 3:4) have gout and CKD. One of his sons (4:1) is currently clinically unaffected but carries the *UMOD* mutation and has low fractional uric acid excretion.

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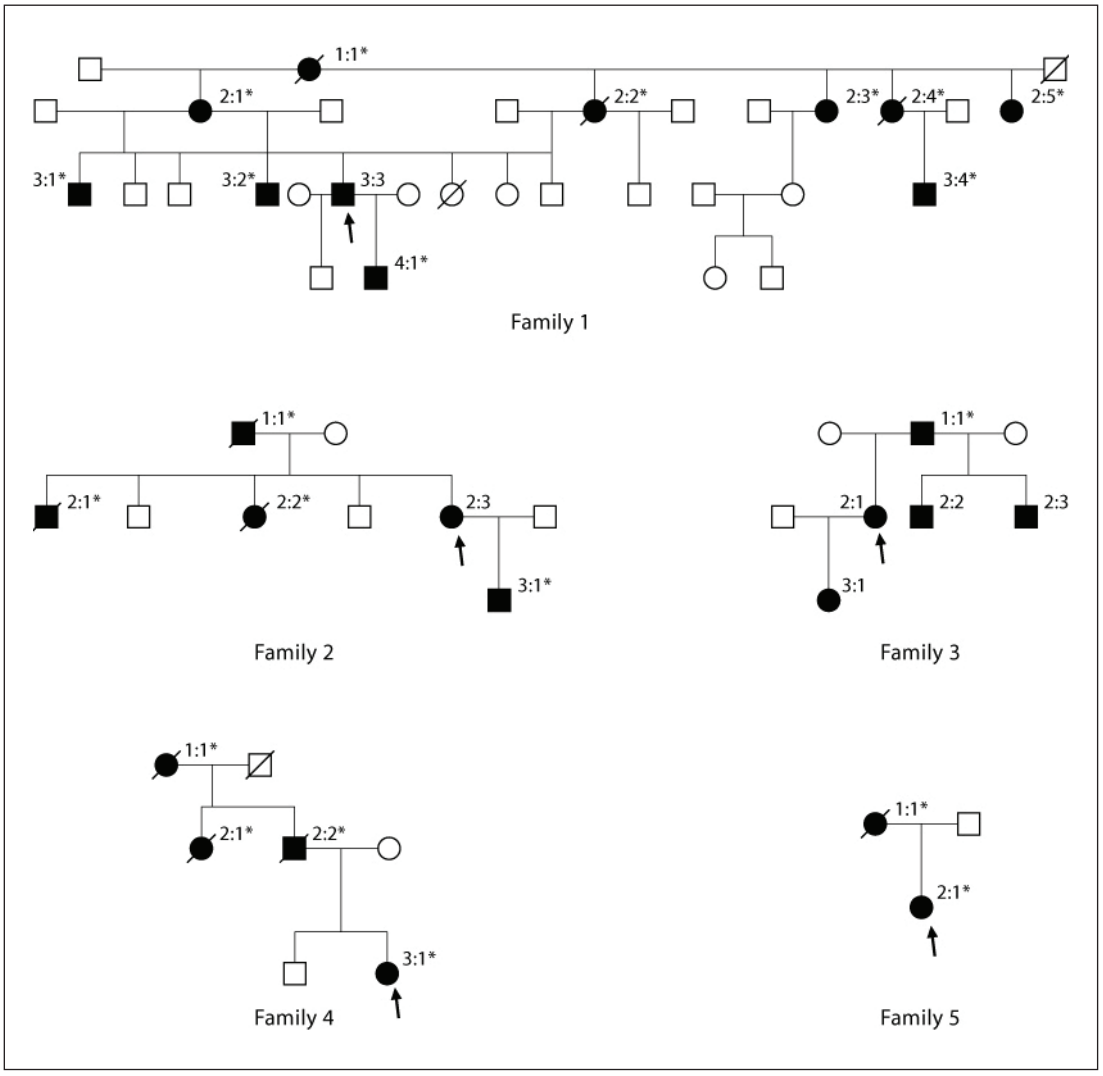

Fig. 2. Family trees. Squares indicate males, circles indicate females, arrows indicate index cases; filled squares/circles indicate subjects with FJHN1; asterisks indicate patients with ESRD; deceased patients are crossed out.

Family 2 (Cys126Arg)

This family has also been reported previously [13, 27, 28]. Only 2 individuals, mother (2:3) and son (3:1), who currently live in Austria, are included in this report. The mother's father (1:1) and 2 of her siblings (2:1; 2:2) had died from renal failure. Patient 2:3 is currently on hemodialysis and her son suffers from CKD stage III.

Family 3 (Asp196Tyr)

The family has been described previously [29]. The mother (2:1) suffers from CKD IV; in her daughter (3:1), a genetic diagnosis of UAKD was made immediately after birth. Three other affected family members live in Latvia. The father (1:1) is on hemodialysis, and her two half-brothers (2:2; 2:3) have CKD stages III and II, respectively.

Table 2. Austrian families with UAKD: mutations, in vitro effects, and ESRD

Family	Mutation	In vitro effects of mutation (ref.)	Alive				Died with ESRD	Total (dead or alive)
			total (Austria)	with ESRD (Austria)	without ESRD (Austria)	abroad		
1	Cys77Tyr	Reduced apical secretion [8]	8	4	4		3	11
2	Cys126Arg	ER retention, absence at plasma membrane, severely reduced maturation [7, 9]	2	1	1		3	5
3	Asp196Tyr	(Asp196Asn) ER retention, partial expression at plasma membrane, reduced maturation [9]	2	0	2	3		5
4	Cys217Trp	ND	1	1	0		3	4
5	Cys223Arg	ER retention, low expression at plasma membrane, severely reduced maturation [9]	1	0	1		1	2
Total			14	6	8	3	10	27

ER = Endoplasmatic reticulum; ND = not determined. For the Asp196Tyr mutation, which has not been tested in vitro, the results for the Asp196Asn mutation are shown. All five mutations are located within exon 4 of the UMOD gene.

Table 3. UAKD patients included in the OEDTR (n = 7)

Family	Patient	Gender	Age in 2011, years	Encoded diagnosis	Age at ESRD onset years
Family 1	2:1	female	67	10 – Glomerulonephritis, histologically not examined	45
	2:3	female	59	10 – Glomerulonephritis, histologically not examined	34
	2:5	female	55	42 – Polycystic kidneys; infantile (medullary sponge kidney)	35
	3:4	male	45	84 – Lupus erythematosus	29
Family 2	2:3	female	61	50 – Familial nephropathy, not specified (uromodulin storage disease)	59
Family 4	3:1	female	48	20 – Pyelonephritis, cause not specified	37
Family 5	1:1	female	died at the age of 60 from breast cancer	10 – Glomerulonephritis, histologically not examined	53

Family 4 (Cys217Trp)

The index case (3:1) was discovered during the nation-wide survey. The patient is a 48-year-old female who developed ESRD at age 37 years. She received a living donor allograft from her mother and currently lives with a functioning renal transplant. Her father (2:2), grandmother (1:1), and aunt (2:1) all died from renal failure.

Family 5 (Cys223Arg)

The index case (2:1) was identified through increased awareness of FJHN in the course of the epidemiologic study. The 51-year-old female patient suffers from recurrent gout and CKD stage III. Her mother (1:1) developed ESRD at age 53 years. She received a renal allograft 3 years later and died from breast cancer at age 60 years.

Table 4. Austrian UAKD patients not on RRT (n = 8)

Family	Patient	Age years	Gender	Creatinine mg/dl	eGFR, ml/min/1.73 m^2	Gout	Serum uric acid, mg/dl	FEUA %	Therapy
Family 1	3:1	35	male	1.1	75	yes	2.6	7.6	allopurinol, benzbromarone
	3:2	22	male	1.8	53	yes	7.8	3.8	allopurinol
	3:3	28	male	3.0	27	yes	7.7	3.6	allopurinol
	4:1	8	male	0.7	148	no	4.2	6.6	none
Family 2	3:1	39	male	1.9	41	no	8.7	2.8	allopurinol, benzbromarone
Family 3	2:1	25	female	2.0	34	yes	6.6	3.6	allopurinol
	3:1	2	female	0.33	161	no	5.6	4.6	allopurinol
Family 5	2:1	51	female	2.7	20	yes	3.6	4.0	allopurinol

eGFR = Estimated glomerular filtration rate; FEUA = fractional excretion of uric acid.

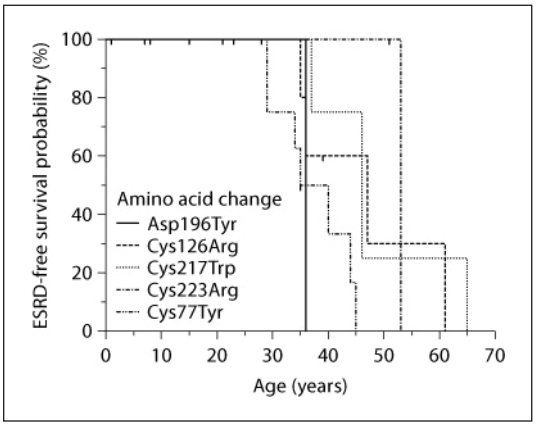

Fig. 3. Kaplan-Meier curves stratified by uromodulin amino acid change. Overall p = 0.039 (log-rank test).

Prevalence of UAKD in Austria

Table 3 shows a complete list of 7 patients (6 are alive, 1 is deceased due to breast cancer) which are included in the OEDTR. In table 4, clinical details as well as treatment of 8 patients not on RRT are summarized.

Taken together, at present, 14 living patients from 5 families with UAKD are known in Austria. Given a population of 8.4 million, the estimated prevalence of UAKD is therefore 1.67 cases per million population. Six out of these 14 patients currently require RRT. As the number of patients receiving RRT in Austria is at present 8,200, the estimated prevalence of UAKD is 0.73 per 1,000 RRT patients. Including patients who live in Latvia (3 patients from family 3; Asp196Tyr mutation) or suffered from ESRD and had died (10 patients), a total of 27 UAKD patients with 5 different UMOD mutations were documented (table 3). Renal cysts, another frequent finding in UAKD, were detected by ultrasound in 6 out of the 14 living Austrian patients.

UAKD and Progression to ESRD

Mean age at ESRD for all the UAKD patients combined was 43.8 (95% CI 38.8–48.8) years. To investigate whether there was any genotype-phenotype correlation between *UMOD* mutation and ESRD, Kaplan-Meier analysis (fig. 3) and Cox proportional hazard modeling

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Table 5. Results of the Cox proportional hazard model with Cys77Tyr as the reference group

Amino acid change	b	SE	p value	HR	95% CI of HR
Asp196Tyr	0.11	1.10	0.919	1.12	0.13–9.62
Cys126Arg	–1.53	0.79	0.052	0.27	0.05–1.00
Cys217Trp	–1.89	0.84	0.024	0.16	0.03–0.78
Cys223Arg	–2.58	1.20	0.031	0.08	0.01–0.78

Overall model fit, p = 0.054. b = Regression coefficient; SE = standard error; HR = hazard ratio.

(table 5) were carried out for patients with different *UMOD* mutations. These analyses showed that time to ESRD varied significantly between the UMOD genotypes (p = 0.039, log-rank test; fig. 3). Mean age at ESRD was 46 (95% CI 35.2–58) years with Cys126Arg, 48.5 (95% CI 36.9–60.1) years with Cys217Trp, 37.4 (95% CI 32.7–42) years with Cys77Tyr, 53 years (95% CI not applicable) with Cys223Arg, and 36 years (95% CI not applicable) with Asp196Tyr *UMOD* mutations. Patients with the Cys217Trp and Cys223Arg *UMOD* mutations had a significantly lower hazard ratio compared to patients with the Cys77Tyr *UMOD* mutation, whilst patients with the Asp196Tyr and Cys126Arg *UMOD* mutations did not have a significantly different hazard ratio compared to patients with the Cys77Tyr *UMOD* mutation (table 5). Results were materially identical after adjustment for gender and generation (data not shown).

Discussion

Our data shows that UAKD is a rare disease with a prevalence of 1.7 cases per million population and <1 case per 1,000 RRT patients. At the time of the epidemiologic survey, the disease was referred to as FJHN and its cause was still unknown. Our study includes only those families in whom FJHN is caused by an *UMOD* mutation (MIM 162000). FJHN is genetically heterogeneous, and in addition to uromodulin mutations found in 40% of families, it can be caused by mutations in the renin *(REN)* gene (associated with early onset anemia, FJHN2, MIM 179820) or by splice-site mutations in the *HNF-1β* gene (renal cysts and diabetes syndrome, MIM 189907), each found in 2.5% of families [30–32]. Recently, another locus linked to chromosome 2p22.1-p21 has been identified (FJHN3) [25]. Presently, UAKD comprises the allelic disorders FJHN1, medullary cystic kidney disease type 2, and glomerulocystic kidney disease, which are caused by mutations in the UMOD gene and share a largely overlapping phenotype.

Three of the 5 Austrian families described here were identified by clinical suspicion. Families 1 and 2 were diagnosed on clinical grounds before the genetic abnormalities involving *UMOD* mutations were known. Family 3 was also diagnosed on clinical grounds and a mutation in the *UMOD* gene was identified [29].

Families 4 and 5 were identified by this nationwide study in 2001 to identify further FJHN cases, proving that identification of such families is possible by an epidemiologic approach. This study was based on all RRT patients included in the OEDTR in 2001. Of note, >99% of all patients receiving chronic RRT in Austria are documented in the OEDTR [33]. We employed a three-pronged approach to ascertain potential patients with FJHN: (a) the presence of chronic RRT, (b) the presence of diagnoses deemed possible to comprise patients with FJHN, and (c) the presence of two characteristics of FJHN, namely a family history of renal disease and a history of gout. Both items can be determined by a simple questionnaire.

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For further work-up, the family history had to be compatible with autosomal dominant inheritance, and other clear diagnoses had to be excluded. The main drawback of the epidemiologic study appeared to be step b, the selection of patients who eventually were asked to answer the questionnaire, based on the list of diagnoses (table 1). We selected a group of diagnoses that might include FJHN cases and asked all patients who had started RRT between age 20 and 50 years. In retrospect, the selection of clinical diagnoses was not optimal. Members of family 1 did not show up in our survey, because their disease was coded as 'glomerulonephritis not histologically examined' and 'lupus erythematosus' (table 4). Second, the age range when these patients develop ESRD is probably wider than assumed at the time of our study. For example, in family 1, individual 3:4 developed ESRD at age 29 years (table 4); however, individual 2:1 in the same family with the same mutation is not yet on RRT at the age of 45 years (table 3). Later reports found earlier as well as later onset of ESRD in UAKD [6, 19]. Affected family members may develop ESRD between childhood and the seventh decade of life. Two of the patients described here required dialysis at age 59 years (family 2, subject 1:1) and 53 years (family 5, subject 1:1; table 3). These patients would also not have shown up in our survey. Therefore, it is possible that we missed other patients suffering from FJHN included in the registry and, thus, that the prevalence reported by us may be too conservative. Another factor causing underestimation of UAKD prevalence may be the fact that we did not receive the questionnaire from 188 of the 541 patients selected by renal diagnosis. In addition, 10% of UAKD patients seem to have no family history of kidney disease, and one third of them does not suffer from gout [5].

Our study also demonstrates that increased awareness of the disease may aid the diagnosis of UAKD, as exemplified by family 5. Furthermore, in the course of the study, 14 other families classified as or suspected of FJHN, but without UMOD mutations, have been identified, either by the epidemiological study itself or by increased awareness among nephrologists. These families enabled our identification of another genetic locus for FJHN linked to chromosome 2p22.1-p21 (FJHN3) [25].

We are not aware of a similar systematic study of the epidemiology of UAKD. Coming closest to such a study is the report of Vylet'al et al. [8] from the Czech Republic, who reported 3 families with 16 patients, 3 of them requiring RRT. The calculated prevalence would be 1.52 patients per million population and 0.58 per 1,000 RRT patients in the Czech Republic; these estimates are in the same range as those reported here for Austria (1.67 per million population, and 0.73 per 1,000 RRT patients). Bollee et al. [5] reported on 109 patients from France and Belgium. The calculated prevalence for both countries together would be 0.7 per million population. Simmonds et al. [34] reported on 158 patients from 31 FJHN kindreds in Britain. Genetic analysis showed UMOD mutations in 6 out of 25 tested families. The number of patients with an UMOD mutation, however, is not given in that report.

To put these numbers into perspective, it is interesting to compare them with the prevalence of Anderson-Fabry disease, which has also been studied systematically in Austrian RRT patients. In a study of 2,480 dialysis patients, 4 cases were identified by mutation analysis of the GAL gene (prevalence 1.6 per 1,000 RRT patients) [35]. Another report on 1,306 male renal transplant patients identified 5 cases (3.8 per 1,000 patients) [36].

Progression to ESRD is highly variable and seems to be affected by the UMOD genotype. The basis of the suspected genotype-phenotype relationship is unclear. Our in vivo clinical findings did not correlate with the relative in vitro effects of the mutations, which have been reported by our group and others [8–10]. For example, in vitro, uromodulin mutation of the Cys126 and Cys223 residues showed that the most severe maturation defects being retained in the endoplasmatic reticulum and absent or markedly reduced at the plasma membrane [10] (table 2), yet, were associated with the mildest clinical outcome in their association with the latest onset of ESRD (fig. 3; table 5). In contrast, the mutation of the uromodulin Asp196

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residue was associated with a milder maturation defect with some mutant uromodulin expressed at the plasma membrane in vitro [10] (table 2); yet, it was associated with the most severe clinical outcome in its association with the early onset of ESRD (fig. 3; table 5). Thus, the basis of the effect of the *UMOD* genotype on development of ESRD cannot be explained by in vitro findings but remains to be elucidated. The association between genotype and progression to ESRD we found is based on a small number of cases and needs confirmation by a study including a much larger group of patients.

In conclusion, this report provides for the first time UAKD prevalence estimates for the general population and for RRT patients and it suggest that UAKD is indeed a rare disease. A rather simple systematic approach and a questionnaire may allow identification of hitherto undiagnosed UAKD RRT patients. Our data indicate that UMOD genotype may affect progression of renal disease to ESRD.

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Disclosure Statement

The authors declare no conflict of interest.

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