Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—A KDIGO consensus report

Kai-Uwe Eckardt[1], Seth L. Alper[2], Corinne Antignac[3,4], Anthony J. Bleyer[5], Dominique Chauveau[6], Karin Dahan[7], Constantinos Deltas[8], Andrew Hosking[9], Stanislav Kmoch[10], Luca Rampoldi[11], Michael Wiesener[1], Matthias T. Wolf[12] and Olivier Devuyst[13]

[1]Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; [2]Divisions of Nephrology and Molecular and Vascular Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA; [3]INSERM U1163, Laboratory of Hereditary Kidney Diseases, Paris, France; [4]Paris Descartes University, Imagine Institute, Paris, France; [5]Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [6]Département de Néphrologie et Transplantation d'organes, CHU Rangueil, Toulouse, France; [7]Centre de Génétique Humaine, Institut de Pathologie et de Génétique, Gosselies, Belgium; [8]Department of Biological Sciences, Molecular Medicine Research Center and Laboratory of Molecular and Medical Genetics, University of Cyprus, Nicosia, Cyprus; [9]UKD Foundation, New York, New York, USA; [10]Institute for Inherited Metabolic Disorders, Charles University in Prague, Prague, Czech Republic; [11]Molecular Genetics of Renal Disorders Unit, Division of Genetics and Cell Biology, Dulbecco Telethon Institute c/o IRCCS San Raffaele Scientific Institute, Milan, Italy; [12]Division of Pediatric Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas, USA and [13]Institute of Physiology, University of Zurich, Zurich, Switzerland

Rare autosomal dominant tubulointerstitial kidney disease is caused by mutations in the genes encoding uromodulin (*UMOD*), hepatocyte nuclear factor-1β (*HNF1B*), renin (*REN*), and mucin-1 (*MUC1*). Multiple names have been proposed for these disorders, including 'Medullary Cystic Kidney Disease (MCKD) type 2', 'Familial Juvenile Hyperuricemic Nephropathy (FJHN)', or 'Uromodulin-Associated Kidney Disease (UAKD)' for UMOD-related diseases and 'MCKD type 1' for the disease caused by *MUC1* mutations. The multiplicity of these terms, and the fact that cysts are not pathognomonic, creates confusion. Kidney Disease: Improving Global Outcomes (KDIGO) proposes adoption of a new terminology for this group of diseases using the term 'Autosomal Dominant Tubulointerstitial Kidney Disease' (ADTKD) appended by a gene-based subclassification, and suggests diagnostic criteria. Implementation of these recommendations is anticipated to facilitate recognition and characterization of these monogenic diseases. A better understanding of these rare disorders may be relevant for the tubulointerstitial fibrosis component in many forms of chronic kidney disease.

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Correspondence: *Kai-Uwe Eckardt, Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Ulmenweg 18, Erlangen, 91054, Germany. E-mail: kai-uwe.eckardt@uk-erlangen.de or Olivier Devuyst, Institute of Physiology, University of Zurich, Winterthurer Strasse 190, 8057 Zurich, Switzerland. E-mail: olivier.devuyst@uzh.ch*

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Chronic kidney disease (CKD) reflects a severe and growing health burden.[1] Diabetes, arterial hypertension/atherosclerosis, and immune-mediated glomerular diseases are considered the main causes of CKD. However, the etiology of kidney diseases is often not firmly established and, in many patients, remains unknown.[2] Despite increasing knowledge about inherited kidney disorders,[3] a monogenic disorder is currently identified in fewer than 10% of CKD patients. However, unexplained familial clustering among dialysis patients suggests that genetic causes of CKD may be underrecognized.[1,3,4]

Autosomal dominant polycystic kidney disease (ADPKD) has received significant attention over recent decades, resulting in an increased understanding of the pathogenesis and the establishment of diagnostic criteria, as well as leading to a growing number of interventional trials.[5] A less commonly encountered group of nonglomerular autosomal dominant kidney diseases, characterized by progressive tubulointerstitial fibrosis and progression to end-stage renal disease, has also been described over many years.[6–15] Four genes with disease-causing mutations have been identified thus far: uromodulin (*UMOD*),[16–20] renin (*REN*),[21] hepatocyte nuclear factor 1β (*HNF1B*)[22], and, most recently, mucin-1 (*MUC1*).[23] Of note, all these genes are expressed in tubular cells of the intermediate and/or distal nephron, and,

in the case of *UMOD*, exclusively in the thick ascending limb (TAL) of Henle's loop. The clinical manifestations of diseases caused by mutations in *UMOD*, *MUC1*, and *REN* appear to be confined to the kidney, whereas *HNF1B* mutations result in variable extrarenal manifestations.[24,25] Nevertheless, a minority of *HNF1B*-related disease patients presents solely with progressive kidney interstitial fibrosis and thus also needs to be considered in this context.

Many terms have been used over the years to describe the corresponding subentities of inherited tubulointerstitial kidney diseases, the most frequent being Medullary Cystic Kidney Diseases (MCKD). We now know that MCKD type 1 is due to *MUC1* mutations and MCKD type 2 is caused by *UMOD* mutations. However, investigators have repeatedly pointed out that neither tubular microcysts nor larger cysts detected by clinical imaging are pathognomonic for these diseases. Moreover, the medulla appears not to be a specific location for the occasionally observed cysts.[26–28] Thus, these terms are misleading. Additional terms that have been used to describe these conditions include the following: Familial Juvenile Hyperuricemic Nephropathy, Hereditary Interstitial Kidney Diseases, Tubulointerstitial Nephritis, and, as recently proposed, Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD).[29–32] It is highly likely that the use of such variable (and in some ways misleading) nomenclature and the lack of uniform diagnostic criteria have hampered both detection of these diseases and their systematic study.

Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) recently hosted a consensus conference to develop a proposal for a uniform terminology and a rational clinical approach to these types of inherited diseases. The topic was considered timely for three main reasons: (1) With the recent identification of *MUC1*, identification of the four genes that cause most, *albeit* not all, of the cases resulting in the clinical syndrome has apparently been achieved; (2) there is growing interest to delineate the clinical features and diagnostic criteria for these disorders; (3) emerging opportunities for genetic testing will create novel diagnostic options for routine clinical practice, but will require expertise in indications, interpretation, and technical aspects. This KDIGO consensus report summarizes the recommendations developed at this conference. (The conference took place in Boston on 10–11 September 2014. All participants are listed as authors, contributed to meeting preparations, and agreed on the content of this report. K-UE and OD co-chaired the meeting.)

TERMINOLOGY

We recommend that the term ADTKD be used to describe these diseases. The term ADTKD offers several advantages: (1) It reflects the genetic cause and inheritance pattern; (2) it summarizes phenotypic conformity of a family of diseases caused by mutations in different genes; (3) it allows definition of cases as 'suspected' on clinical grounds (before or in the absence of histologic or genetic testing); (4) it differentiates from other autosomal dominant diseases of tubular origin (e.g., ADPKD and distal renal tubular acidosis); (5) it avoids misnomers that have arisen in the past (e.g., MCKD); and (6) it is simple and easy to use.

It is recognized that, in a strict sense, the clinical representation of ADTKD as defined here reflects a 'syndrome' rather than one disease. However, for practical reasons and in accordance with established usage, we believe that the term 'disease' is justified. It is also for practical reasons that we recommend using the singular rather than plural, despite the multiple disease types distinguishable on a genetic basis. In this respect, the term ADTKD shares some similarities with ADPKD, which also describes a disease with similar clinical manifestation and morphology caused by mutations in more than one gene. Although the analogy between ADTKD and ADPKD may help implementation of the new term, it could potentially cause errors owing to similarity of the acronyms. However, as the phenotypes of ADPKD and ADTKD present major clinical differences, we believe that risk is low.

We further suggest that a subclassification of ADTKD be based on the underlying genetic defect and that the affected gene, if identified, be included in the disease term (Table 1). The alternative possibility to use numbered subcategories (type 1, type 2, and so on) might have some advantages.

Table 1 | New gene-based classification and terminology of different types of ADTKD

Causal Gene	Proposed terminology	Previously used terminology
UMOD	ADTKD–*UMOD*	UKD (Uromodulin Kidney Disease)[a] UAKD (Uromodulin-Associated Kidney Disease) FJHN (Familial Juvenile Hyperuricemic Nephropathy) MCKD2 (Medullary Cystic Kidney Disease type 2)
MUC1	ADTKD–*MUC1*	MKD (Mucin-1 Kidney Disease)[a] MCKD1 (Medullary Cystic Kidney Disease type 1)
REN	ADTKD–*REN*	FJHN2 (Familial Juvenile Hyperuricemic Nephropathy type 2)
HNF1B	ADTKD–*HNF1B*	MODY5 (Maturity-Onset Diabetes mellitus of the Young type 5) RCAD (Renal Cyst and Diabetes Syndrome)
Not known; i.e., not otherwise specified (either not tested or genetic test without definitive result)	ADTKD—*NOS*	

Abbreviations: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease; HNF1B, hepatocyte nuclear factor 1β; MUC1, mucin-1; NOS, not otherwise specified; REN, renin; UMOD, uromodulin.
[a]These terms may be easier to use in communicating with patients.

However, as long as the disease classification criterion is based solely on the underlying gene defect, such a numerical nomenclature would create a 'translation step' (and thus a possible source of error) without providing additional information. Should new evidence become available about disease prevalence, additional causative genes, genotype/phenotype correlations, or important phenotypic differences among patients within or beyond the current gene-based categories, the proposed nomenclature may require re-evaluation.

A limitation of the term ADTKD and its proposed subclassifications is that their use in communication with patients may not be easy. To address this practical concern, more colloquial terms, such as Uromodulin Kidney Disease or Mucin-1 Kidney Disease, could be used in parallel with the proposed formal term ADTKD. However, we strongly recommend that the use of the misleading term 'MCKD' be henceforth discontinued.

CLINICAL CHARACTERISTICS

The central unifying characteristic of ADTKD is that most clinical and laboratory findings (Table 2), as well as histological findings (Table 3), are largely nonspecific. Apart from the findings that are almost uniform, some features appear to be relatively specific for individual genetic subcategories (Table 4).

Typically, there is a positive family history in ADTKD, with a number of family members involved, but the disease may not be diagnosed in all affected individuals—e.g., owing to death before disease manifestation or variable rates of disease progression. In addition, *de novo* mutations may occur (particularly for *HNF1B*). Penetrance of the different types of ADTKD appears close to 100% if patients live long enough. However, disease severity and age of disease onset may vary among affected individuals within and between families. Thus, individuals with *UMOD* mutations were reported to reach end-stage renal disease between the ages of 25 and 70 years or older, and those with a history of gout experienced its onset between the ages of 3 and 51 years.[27,33] Patients harboring mutations in *HNF1B* may present their first renal manifestations during the antenatal period or in childhood.[24] In a series of 35 individuals, end-stage renal disease was reached in a minority of subjects between the ages of 7 and 48 years.[24]

Table 2 | Usual clinical findings in patients with ADTKD

- Autosomal dominant inheritance
- Progressive loss of kidney function
- Bland urinary sediment
- Absent-to-mild albuminuria/proteinuria
- No severe hypertension during early stages
- No drug exposure potentially causing tubulointerstitial nephritis
- Normal or small-sized kidneys on ultrasound
- Nocturia or enuresis in children (owing to loss of renal concentration ability)

Abbreviation: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease.

Table 3 | Usual findings on renal histology in patients with ADTKD

- Interstitial fibrosis
- Tubular atrophy
- Thickening and lamellation of tubular basement membranes
- Possibly tubular dilatation (microcysts)
- Negative immunofluorescence for complement and immunoglobulins

Abbreviation: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease.

Occasionally, nephronophthisis may present in young adults with characteristics suggestive of ADTKD, but autosomal recessive inheritance distinguishes it from ADTKD[3] (although pseudo-dominant cases of nephronophthisis have been described[34]).

The rate of decline of estimated glomerular filtration rate is highly variable in ADTKD-*UMOD*,[27] ADTKD-*MUC1*,[26] and ADTKD-*HNF1B*.[24] The age of onset of kidney failure requiring renal replacement therapy (RRT) varies widely among and within families, and usually lies between ages 20 and 80 years, with most individuals requiring RRT between ages 30 and 50 years. The urinary sediment is typically normal, but occasionally microhematuria can occur.[24,26,27] Proteinuria is typically mild or absent.[24,26,27] Only rarely has glomerular involvement been found (e.g., secondary focal segmental glomerulosclerosis or glomerulocystic disease).[18,35] The initially normal kidney size declines with advancing disease. Although renal cysts of varying number and size can occur, their frequency is no higher than in other 'non-cystic' kidney diseases.[24,26–28] These cysts are generally found in advanced rather than in early stages of CKD, and thus they are certainly not causing the decline in glomerular filtration rate.

Patients typically have no history of arterial hypertension preceding the onset of impaired kidney function. With progressive disease, blood pressure may increase, but usually only modestly.

Renal histology shows interstitial fibrosis with tubular atrophy and normal glomeruli. Thickening and lamellation of tubular basement membranes is a frequent finding.[8,14,24,26–28,36] Tubular dilatation can occur and tubular microcysts have been reported. Immunofluorescence for complement and immunoglobulins is negative. Electron microscopy usually provides little or no additional diagnostic discrimination, although it may reveal accumulation of mutant uromodulin in the endoplasmic reticulum of TAL cells.[36]

The prevalence of the different types of ADTKD has not been established, but ADTKD-*UMOD* and ADTKD-*MUC1* are probably more frequently encountered than is ADTKD caused by mutations in *HNF1B* or *REN*.

Among factors differentiating the different forms, ADTKD-*UMOD* is typically characterized by inappropriately decreased fractional urate excretion, causing hyperuricemia and often gout (Table 4).[27] Gout will often be present in multiple although not necessarily all affected family members, and this can be key to the diagnosis. Hyperuricemia can begin in childhood[37] before the development of significant

Table 4 | Possible but not obligatory findings according to the underlying genetic defect (patient or family)

	UMOD	*MUC1*	*REN*	*HNF1B*
Clinical/imaging	Early gout (for age), occasional renal cysts (usually not medullary)[26–28]	No characteristic findings, occasional renal cysts (usually not medullary)[26–28]	Mild hypotension, increased risk for AKI, anemia during childhood	MODY5, few bilateral renal cysts, genital abnormalities, pancreatic atrophy
Presentation during childhood	Rare (occasionally with gout)	None	Frequent	Frequent (prenatal ultrasound findings)
Laboratory	Hyperuricemia, low fractional excretion of urate (<5%), low urinary excretion of uromodulin	None yet described	Hyperuricemia and hyperkalemia, low urinary excretion of uromodulin	Hypomagnesemia, hypokalemia, liver function test abnormalities
Histology	Intracellular uromodulin deposits in TAL profiles	Intracellular accumulation of MUC1-fs in distal tubules[a]	Reduced renin staining in cells of the juxtaglomerular apparatus	

Abbreviations: AKI, acute kidney injury; HNF1B, hepatocyte nuclear factor 1β; MODY5, maturity onset diabetes mellitus of the young type 5; MUC1, mucin-1; MUC1-fs, mucin-1 frameshift protein; REN, renin; TAL, thick ascending limb of Henle's loop; UMOD, uromodulin.
[a]This test is currently available only in selected research laboratories.

renal insufficiency. If gout develops, its age of onset can vary significantly, occurring as early as in the teenage years, especially in male individuals. However, neither hyperuricemia nor gout are pathognomonic, and values of fractional urate excretion, as well as serum urate levels, overlap with CKD of other etiologies.[27]

Patients with *REN* mutations develop anemia during childhood unrelated to the level of estimated glomerular filtration rate. The anemia resolves during puberty[21] but may recur in the setting of progressive loss of kidney function. The reasons for this transient childhood anemia are not fully understood. Little is known about a role for renin in the regulation of erythropoiesis, but recent experimental evidence suggests that renin-producing cells themselves have erythropoietin biosynthetic capacity.[38] The increase in hemoglobin levels during adolescence has been attributed to an increase of testosterone secretion.[21] Dysfunction of the renin–angiotensin system places affected individuals at risk for volume depletion and acute kidney injury, with important implications for clinical management (see below). However, renin and aldosterone levels are not of diagnostic value.

HNF1B mutations can cause multiple extrarenal manifestations, and only a minority of cases will present solely with tubulointerstitial disease.[24,25,39] Accordingly, not all cases of *HNF1B*-related disease should be summarized under the term ADTKD. Although a clear distinction is difficult, it appears reasonable to confine the term ADTKD to those *HNF1B*-related cases in which tubulointerstitial fibrosis is the leading manifestation.

Descriptions of the phenotype of patients with *MUC1* mutations (or a disease segregation with the respective locus) have so far not revealed any extrarenal manifestations or clinical abnormalities beyond tubulointerstitial fibrosis.[26]

GENE DEFECTS AND PATHOPHYSIOLOGY

UMOD (OMIM 16p12.3 and 191845) encodes uromodulin, also called Tamm–Horsfall Protein, which is produced in the epithelial cells lining the TAL of Henle's loop.[32] Although uromodulin is the most abundant protein in normal urine, its function remains incompletely understood.[32] The disease mechanism in ADTKD-*UMOD* probably includes accumulation of mutant uromodulin in the endoplasmic reticulum of TAL cells, with secondary decreased cellular release and urinary excretion of wild-type protein.[16,18,40,41] In addition, the defective biogenesis and intracellular transport of uromodulin inhibits trafficking of the Na^+-K^+-$2Cl^-$ cotransporter NKCC2 to the luminal surface of TAL epithelial cells.[40,42] The resulting defect in urinary concentration and consequent mild volume depletion can secondarily increase proximal reabsorption of uric acid as a possible cause of hyperuricemia.[32,40,43]

MUC1 (OMIM 1q22 and 158340) encodes mucin-1, a highly glycosylated transmembrane protein with high expression throughout the distal nephron.[44,45] Mucins are thought to provide a protective function by maintenance of a luminal epithelial mucobarrier. In ADTKD-*MUC1*, a frameshift mutation in the *MUC1* gene creates an abnormal sequence, encoding a new peptide (MUC1-fs) that accumulates inside the MUC1-expressing renal tubular epithelial cells. How this novel gene product causes tubulointerstitial fibrosis, and why patients do not exhibit disorders in the lung where mucin-1 is also highly expressed, remains unknown.

HNF1B (OMIM 17q12 and 189907) encodes hepatocyte nuclear factor 1β (HNF1β), a transcription factor that regulates multiple genes expressed in the kidney, pancreas, and liver.[46,47] This expression pattern explains the frequently syndromic presentation of affected individuals. Of note, HNF1β regulates the *UMOD* gene, as well as several genes involved in polycystic kidney disease.[48] How *HNF1B* mutations cause tubulointersitial fibrosis has not been clarified.

REN (OMIM 1q32.1 and 179820) encodes preprorenin, which is subsequently proteolytically processed to prorenin and renin. Prorenin modulates various signaling pathways in the kidney through its interaction with the prorenin receptor.[49] Renin is a protease, which cleaves angiotensinogen

into angiotensin 1 and controls angiotensin formation. Disease-causing mutations may result in apoptosis of renin-producing cells in the vas afferens of the glomeruli owing to intracellular accumulation of abnormal renin.[21] Renin is also expressed in tubular cells of the distal nephron, overlapping with the tubular expression patterns of other ADTKD genes.[21,50] However, the mechanisms by which *REN* mutations cause tubulointerstitial fibrosis remain unclear. Additional disease characteristics can be attributed to hypoactivation of the renin–angiotensin–aldosterone system.[21]

CRITERIA FOR SUSPECTED AND ESTABLISHED DIAGNOSIS

Proposed criteria for a suspected or established diagnosis of ADTKD are listed in Table 5. The presence of a family history compatible with autosomal dominant inheritance (i.e., at least one affected individual in at least two generations) in conjunction with nonspecific clinical and histological manifestations (if histology is available) and the absence of evidence for kidney disease of other etiology should raise strong suspicion for ADTKD. The likelihood of the diagnosis increases with the number of affected family members identified in different generations.

ADTKD should also be considered in single cases without a positive family history, if they present with the characteristic findings. Such cases could be due to *de novo* mutations[27] or a missed diagnosis of CKD in other affected individuals within the family. However, we believe that in the absence of a positive family history alternative diagnoses should be considered. Such single cases should not be considered as 'suspected ADTKD' without pathologic evidence (kidney biopsy) to avoid overdiagnosis.

An established diagnosis of ADTKD should ideally be based on demonstration of the underlying genetic defect. However, although genetic testing for *UMOD*, *REN*, and *HNF1B* mutations is well established, *MUC1* genetic testing remains challenging.[23,28] The difficulty lies in the detection of the insertion of a single cytosine within a 60bp repeat unit of a variable tandem repeat sequence (VNTR) in the open reading frame of *MUC1*. The VNTR comprises 25-125 repeat units over a region of 1.5 to 7.5 kb, $>80\%$ GC-rich and the insertion is positioned in a family-specific manner, i.e., it occurs in a different unit of the repeat in each family.[23] For the diagnosis of ADTKD-*MUC1*, the most appropriate roles for genetic testing and for other possible tests, such as identification in the urine of the polypeptide product of the mutant allele, remain to be established. Given that genetic testing for MUC1 is not yet clinically available (except to large families by linkage analysis to 1q22) and that other yet unidentified genes may also cause ADTKD, it appears reasonable that the diagnosis can also be based on a positive family history with compatible clinical findings and a kidney biopsy in at least one affected individual. Once the disease diagnosis is established, biopsies from additional family members are usually not required if their presentation is compatible with the autosomal dominant inheritance pattern and the clinical presentation of the disease.

GENETIC TESTING

As with other diseases, genetic testing requires that the patient be fully informed about costs, interpretation, and implications. Although no specific therapies are yet available for the different types of ADTKD, genetic testing is currently the only way to definitively prove ADTKD and its respective subtypes, and exclude the disease in affected family members. Owing to the lack of disease-specific therapeutic options, testing of minors is not generally recommended, but decisions need to be individualized. Possible reasons for genetic testing are listed in Table 6. Importantly, failure to identify a mutation does not exclude the diagnosis of ADTKD, as not all pathogenic genes have yet been identified. Conversely, genetic findings, in the presence or absence of clinical manifestations, need to be supported by functional studies to establish the causative role of genetic variants.

If genetic testing reveals a mutation that is likely to cause the disease, patients need to be counseled with respect to the risk of disease inheritance. It is important that other family members be informed as to the risk of having the disease, and this responsibility will usually fall to the patient receiving the counseling. For potential kidney donors in affected families with a known causative mutation, genetic testing should be mandatory.

The methodological approach to identify ADTKD-causing mutations depends on availability and is likely to change in the near future. Clinical findings typical for a specific gene defect (Table 1) may guide a rational stepwise approach. Multiplex panels for next-generation sequencing could be advantageous.[3] Although genetic testing for *UMOD*, *REN*, and *HNF1B* mutations is well established, *MUC1* genetic

Table 5 | Diagnostic criteria for ADTKD

A. Criteria for suspecting a diagnosis of ADTKD
- Family history compatible with autosomal dominant inheritance of CKD fulfilling the clinical characteristics (Table 2).
- In absence of a positive family history of CKD fulfilling the clinical characteristics (Table 2), demonstration of compatible histology on kidney biopsy (Table 3) or extrarenal manifestations compatible with *HNF1B* mutations or history of early-onset hyperuricemia and/or gout.

B. Criteria for establishing the diagnosis of ADTKD
- Family history compatible with autosomal dominant inheritance of CKD fulfilling the clinical characteristics (Table 2) and compatible histology in at least one affected family member. (Note: it is not possible to make a definitive diagnosis by renal biopsy alone)
  or
- Demonstration of a mutation in one of the four genes in an affected individual or at least one family member.

Abbreviations: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease; CKD, chronic kidney disease; HNF1B, hepatocyte nuclear factor 1β.

testing remains challenging[23,28] and not yet clinically available (see above). Referral to specialized centers should be considered in these cases. Further details on genetic testing are provided in Table 7.

FOLLOW-UP AND TREATMENT

It appears reasonable that potentially affected family members be well controlled for other risk factors that are known to aggravate or cause CKD (e.g., arterial hypertension, diabetes, obesity, smoking) and that they undergo annual testing of their kidney function. Decisions to test kidney function and other laboratory values in asymptomatic minors at risk for ADTKD depends on the gene causing the disease and on individual family preferences. Treatment options for minors at risk for *UMOD*- or *MUC1*-related diseases are few, and the need for treatment is infrequent. In contrast, children with *HNF1B*- and *REN*-related disease are likely to benefit from early management, and therefore children at risk should be referred to a pediatric nephrologist.

Affected individuals should in general be treated according to established CKD guidelines.[51] Specific recommendations are not based on high-level evidence, as there are no randomized controlled trials. There are no data in ADTKD patients concerning possible benefits of treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on CKD progression. If these agents are used, those with hyperuricemia should be treated with losartan, as it is the only agent that lowers serum urate levels owing to increased urinary urate excretion.[52–54]

Patients with *UMOD*-associated disease who develop gout will likely have further episodes.[27,33] Allopurinol provides a good therapy for gout in this condition and may prevent further attacks.[27] Patients should therefore be started on allopurinol or febuxostat (when allopurinol cannot be tolerated)[55] after the first attack of gout has resolved. Whether allopurinol slows the progression of kidney disease is unclear. Initiation of allopurinol can exacerbate gout, but the drug should not be discontinued. Rarely, patients can develop severe allergic reactions to allopurinol. If a rash develops, allopurinol should be stopped immediately. Allopurinol should also be stopped before pregnancy, as it has been associated with cleft palate and other facial anomalies. A strict low purine diet is not known to be of benefit in hyperuricemic patients with *UMOD* mutations.

Diuretics should be used with caution in all patients with ADTKD, as they may aggravate hyperuricemia and volume depletion.[56] Liberal water intake is recommended to compensate for possible urinary concentration defects. A low-salt diet frequently prescribed in CKD is not recommended for ADTKD-*UMOD* and ADTKD-*REN* patients; it may aggravate hyperuricemia in the former and volume depletion in the latter. Nonsteroidal anti-inflammatory drugs should be avoided in all patients with ADTKD; in particular patients with *REN* mutations are highly susceptible to acute worsening of kidney function in response to these agents.

In ADTKD-*REN* patients, erythropoiesis-stimulating agents and fludrocortisone can be used for the treatment of anemia and symptomatic hypotension, respectively.[21,57] However, possible beneficial effects of fludrocortisone on symptoms and disease progression need to be balanced against the possible risk of aggravating interstitial fibrosis. Fludrocortisone should not be used in those with declining kidney function, hypertension, hyperkalemia, or edema.

Table 6 | Possible reasons for genetic testing of ADTKD

- Adults with CKD suspected to have ADTKD who wish to confirm the diagnosis
- Members of affected families with normal kidney function who wish to donate a kidney
- Healthy adult individuals at risk who are interested in establishing a genetic diagnosis
- Adults interested in undergoing preimplantation genetic diagnosis to avoid their child's inheritance of a disease-causing mutant allele
- Children suspected of having a *REN* mutation

Abbreviations: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease; CKD, chronic kidney disease; REN, renin.

Table 7 | Genetic testing for genes causing ADTKD

Gene (protein product)	OMIM #	Chromosome	Exons	Genetic testing method
UMOD (Uromodulin)	191845	16p12.3	11	Direct sequencing of coding regions (mutations in exons 3 and 4 account for 93% of reported mutations)
MUC1 (Mucin-1)	158340	1q22	8	Targeted mutation analysis[23,28] (Single cytosine insertion at a position (common in all families) within any single, family-specific repeat of the multiple 60 bp repeats (ranging in family-specific number from 25 to 125) that comprise the coding VNTR of *MUC1*) Genetic linkage analysis is an option in informative families
REN (Renin)	179820	1q32.1	10	Direct sequencing of coding regions (mutations in exon 1 account for 100% of reported mutations[a]); see Zivna *et al.*,[21] Bleyer *et al.*,[57] and Beck *et al.*[61]
HNF1B (Hepatocyte nuclear factor 1-β)	189907	17q12	9	Direct sequencing (for point mutations), multiplex ligation-dependent probe amplification, quantitative PCR (for deletions/duplications)

Abbreviations: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease; HNF1B, hepatocyte nuclear factor 1β; OMIM, Online Mendelian Inheritance in Man; VNTR, variable number tandem repeat.
[a]Only four *REN* mutations have been reported to date.

Table 8 | Research recommendations

- Better understanding of the physiological role of the genes involved and the pathomechanisms causing kidney disease and progression
- Identification of possible commonalities with epidemic interstitial nephropathy
- Diagnostic tests for *MUC1* (genetic and/or non-genetic)
- Large registries of affected families
- Better understanding of the genetic epidemiology
- Further phenotypic characterization, including tubular function and concentrating ability
- Better understanding of the clinical manifestations in childhood
- Establishment of genotype/phenotype correlations
- Identification of additional causal genes and disease modifier genes that may be responsible for the phenotypic heterogeneity
- Identification of biomarkers for disease progression that might help in designing therapies
- New and improved cell and animal models to identify and test therapeutic strategies
- Investigation of the potential benefit of nephroprotective therapies for ADTKD patients
- Improved understanding of the role of involved genes in multifactorial CKD

Abbreviations: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease; CKD, chronic kidney disease; MUC1, mucin-1.

Kidney transplantation is the treatment of choice for kidney failure caused by ADTKD, as the disease does not recur in the graft.[58] In *HNF1B* patients with diabetes mellitus, combined kidney/pancreas transplantation should be considered.

PERSPECTIVES

We expect that adoption of the proposed ADTKD terminology will lead to increased awareness and detection of these diseases. We further hope that a uniform terminology will enhance observational and mechanistic research in this field, thereby on the longterm improving diagnosis and prognosis of affected individuals and families. A list of research recommendations is provided in Table 8. Although ADTKD is at present considered a very rare disease, it is tempting to speculate that its uncharacteristic presentation, together with a confusing terminology, has resulted in significant underdiagnosis.

A better understanding of rare monogenic diseases often has implications for more prevalent diseases in which similar mechanisms frequently have a role.[1,3] As tubulointerstitial fibrosis is a hallmark of CKD and is highly correlated with disease progression, the potential gains from a better understanding of monogenic tubulointerstitial fibrosis may have implications far beyond the small number of individuals affected by the Mendelian disorders. In agreement with this possibility, several DNA variants in the *UMOD* locus have been reproducibly associated with kidney function and risk for CKD and hypertension in several cohorts worldwide.[59,60]

DISCLOSURE

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