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Autosomal Dominant Tubulointerstitial Kidney Disease – *UMOD*

Synonyms: ADTKD-*UMOD*, Uromodulin Kidney Disease

Anthony J Bleyer, MD, MS,[1] Kendrah Kidd, MS,[2] Martina Živná, PhD,[3] and Stanislav Kmoch, PhD[4]

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Summary

Clinical characteristics

Autosomal dominant tubulointerstitial kidney disease – *UMOD* (ADTKD-*UMOD*) is characterized by normal urinalysis and slowly progressive chronic kidney disease (CKD), usually first noted in the teen years and progressing to end-stage renal disease (ESRD) between the third and seventh decades. Hyperuricemia is often present from an early age, and gout (resulting from reduced kidney excretion of uric acid) occurs in the teenage years in about 8% of affected individuals and develops in 55% of affected individuals over time.

Diagnosis/testing

The diagnosis of ADTKD-*UMOD* is established in a proband with suggestive findings and a heterozygous pathogenic variant in *UMOD* identified by molecular genetic testing.

Management

Treatment of manifestations: With allopurinol treatment, serum uric acid concentration returns to normal and gout attacks can be entirely prevented. Lifelong therapy with allopurinol is required for future gout prevention. Referral to a nephrologist to monitor kidney function; evaluate for manifestations of CKD, and prepare for renal replacement therapy when ESRD occurs. Renal replacement therapies such as hemodialysis and peritoneal dialysis replace kidney function but are associated with potential complications; kidney transplantation is curative.

Author Affiliations: 1 Section on Nephrology Wake Forest University School of Medicine Winston-Salem, North Carolina; Email: ableyer@wakehealth.edu. 2 Section on Nephrology Wake Forest University School of Medicine Winston-Salem, North Carolina; Email: kkidd@wakehealth.edu. 3 Research Unit of Rare Diseases Department of Paediatrics and Inherited Metabolic Disorders First Faculty of Medicine Charles University Prague, Czech Republic; Email: mzivna@lf1.cuni.cz. 4 Research Unit of Rare Diseases Department of Paediatrics and Inherited Metabolic Disorders First Faculty of Medicine Charles University Prague, Czech Republic; Email: skmoch@lf1.cuni.cz.

Surveillance: Measurement of serum creatinine concentration at least annually in affected individuals, and more frequently in those with severe disease; measurement of serum uric acid concentration at least annually.

Agents/circumstances to avoid: Drugs known to be nephrotoxic; volume depletion and dehydration. Nonsteroidal anti-inflammatory drugs are generally discouraged but could be used for short-term administration for treatment of gout or similar painful conditions in early CKD (prior to Stage 3 CKD). Chronic daily use should be avoided.

Evaluation of relatives at risk: Asymptomatic at-risk relatives younger than age 18 years from a family with ADTKD-*UMOD* with an early age of onset of gout may benefit from testing for the familial *UMOD* pathogenic variant so that those with the variant can initiate treatment that would prevent gout.

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk adult relatives in order to identify those with the familial *UMOD* pathogenic variant (and thus, at risk for CKD) who would be benefit from routine surveillance and awareness of agents/circumstances to avoid.

Any relative who is a potential kidney donor should be tested for the familial *UMOD* pathogenic variant so that only those without the variant are evaluated further for kidney donation.

Pregnancy management: The use of angiotensin-converting enzyme inhibitors even in early pregnancy can result in fetal damage and death. Use of allopurinol during pregnancy should be avoided.

Genetic counseling

ADTKD-*UMOD* is inherited in an autosomal dominant manner. Each child of an affected individual has a 50% chance of inheriting the *UMOD* pathogenic variant. Once the *UMOD* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at risk and preimplantation genetic testing are possible.

Diagnosis

Consensus clinical diagnostic criteria for autosomal dominant tubulointerstitial kidney disease – *UMOD* (ADTKD-*UMOD*) have been published [Eckardt et al 2015] (full text).

Suggestive Findings

ADTKD-*UMOD* **should be suspected** in individuals with the following findings and family history.

Autosomal dominant inheritance is a key finding in this disease with few distinctive clinical features. One should consider this diagnosis when both the patient and a parent have kidney disease, even if the parent's kidney disease is suspected of having another cause.

Slowly progressive chronic kidney disease (CKD) is often present from childhood, as manifested with an estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73m^2 [Kidd et al 2020].

Bland urinary sediment without blood or protein is present in almost all individuals. Urinary protein is <250 mg/24 hours except when CKD is advanced (e.g., eGFR <40 mL/min/1.73m^2).

Hyperuricemia results from decreased renal excretion of uric acid and is found in almost all affected individuals. The fractional excretion of urate is <5% in most individuals with this disorder, but such a value can also be seen in healthy individuals [Stibůrková & Bleyer 2012]. In children with the disorder, serum creatinine levels may be normal but elevated serum urate levels are usually present.

Usually, hyperuricemia in an individual with normal kidney function corresponds to a serum concentration of uric acid >1 SD of the normal value for age and sex. It is important to use age-related norms for serum urate [Wilcox 1996] (see Table 1).

Table 1. Serum Uric Acid Concentration in Individuals with Normal Renal Function

Age	Serum Concentration (mg/dL)	
	Males	Females
<5 years	3.6±0.9	3.6±0.9
5-10 years	4.1±1.0	4.1±1.0
12 years	4.4±1.1	4.5±0.9
15 years	5.6±1.1	4.5±0.9
>18 years	6.2±0.8	4.0±0.7

Mikkelsen et al [1965], Harkness & Nicol [1969], Wilcox [1996]

Gout due to hyperuricemia occurs in 55% of affected individuals [Kidd et al 2020]; 8% of affected children develop gout before age 18 years [Bleyer et al 2021].

Establishing the Diagnosis

NOTE: Kidney biopsy should **NOT** be performed because it is an invasive procedure with some risk, and pathologic findings are too nonspecific to reliably identify the causative disorder (see Clinical Description). Molecular genetic testing, the gold standard for diagnosis, is safer and less expensive than kidney biopsy.

The diagnosis of ADTKD-*UMOD* **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *UMOD* identified by molecular genetic testing (see Table 2).

Note: Identification of a heterozygous *UMOD* variant of uncertain significance does not by itself establish or rule out the diagnosis of this disorder. The authors of this chapter have offered to review with clinicians *UMOD* variants of uncertain significance; see Molecular Pathogenesis, ***UMOD*-specific laboratory technical considerations**, and Chapter Notes.

Molecular genetic testing approaches can include **gene-targeted testing** (multigene panel) (Option 1) or **comprehensive genomic testing** (exome sequencing, genome sequencing) (Option 2).

Option 1

A kidney disease multigene panel that includes *UMOD* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

Note: Single-gene testing of *MUC1* is required to diagnose ADTKD-*MUC1*, a condition in the differential diagnosis of ADTKD-*UMOD*, as the techniques used in multigene panels and in genome sequencing will not detect variants in *MUC1* [Kirby et al 2013].

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in ADTKD-*UMOD*

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
UMOD	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported to date [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No exon or whole-gene deletions or duplications have been reported as a cause of ADTKD-*UMOD*. This type of pathogenic variant would be an unlikely cause of this condition; thus, the clinical utility of such testing is unknown.

Clinical Characteristics

Clinical Description

Autosomal dominant tubulointerstitial kidney disease – *UMOD* (ADTKD-*UMOD*) is characterized by a normal urinalysis and slowly progressive chronic kidney disease (CKD), usually first noted in the teen years and progressing to end-stage renal disease (ESRD) between the third and seventh decades [Kidd et al 2020]. Hyperuricemia is often present from an early age, and gout (resulting from reduced kidney excretion of uric acid) occurs in the teenage years in about 8% of affected individuals and develops in 55% of affected individuals over time [Hart et al 2002, Bleyer et al 2021].

Slowly Progressive Chronic Tubulointerstitial Kidney Disease

Most commonly, the presenting sign is elevated serum creatinine in an individual with a family history of kidney disease. A mild elevation in serum creatinine may occur in childhood and is usually incidentally noted on laboratory testing for other reasons or when screening children of an affected parent.

Kidney disease usually progresses to ESRD between the third and seventh decades of life [Kidd et al 2020], rarely occurring in children [Wolf et al 2007]. The age at which ESRD occurs varies both between and within families [Kidd et al 2020, Olinger et al 2020]. A family may have a member who reaches ESRD at age 30 years, while another family member does not reach ESRD until age 70 years.

Hyperuricemia and Gout

Hyperuricemia occurs in the majority of individuals with this disorder, though there are exceptions [Kidd et al 2020]. Unlike other kidney disorders, hyperuricemia (due to decreased urinary excretion of uric acid) occurs prior to any decline in kidney function or elevation in serum creatinine [Moro et al 1991].

Fifty-five percent of individuals with ADTKD-*UMOD* will develop gout, with a median age of onset of 28 years [Kidd et al 2020]. While not all affected individuals have gout, almost all families with ADTKD-*UMOD* have family members who have gout. In individuals with a strong family history of ADTKD-*UMOD*, gout is usually diagnosed by family members who are familiar with its manifestations.

Onset of gout is acute with severe tenderness and redness of the affected joint –characteristically the big toe, other areas of the feet, the ankles, and/or the knees. As kidney function worsens, gout worsens, and the frequency of attacks increases. Gout may occur in children and may be precipitated by a sporting event. As gout is uncommon in childhood, this condition may elude diagnosis. Without treatment, tophi (large subcutaneous depositions of uric acid) and crippling arthritis can develop.

Kidney Biopsy

Note: The following information is provided in the event that some affected individuals (or their relatives) may have undergone kidney biopsy prior to consideration of ADTKD-*UMOD* as a diagnostic possibility.

Histologic examination reveals chronic interstitial fibrosis, with focal tubular atrophy and interstitial fibrosis, occasionally accompanied by lymphocytic infiltration. Accumulation of mutated uromodulin may be detected by PAS staining as polymorphic unstructured materials [Onoe et al 2021].

Genotype-Phenotype Correlations

The pathogenic variant p.Val93_Gly97del/insAASC is associated with less frequent gout and possibly a later age of onset of ESRD [Smith et al 2011] (see Table 5).

Penetrance

Penetrance appears to be complete, but age related. Some individuals (especially females) may not develop ESRD until the sixth or seventh decade.

Nomenclature

According to the 2015 nomenclature [Eckardt et al 2015], the term "autosomal dominant tubulointerstitial kidney disease" (ADTKD) refers to disorders characterized by the following:

- Autosomal dominant inheritance
- Slowly progressive chronic tubulointerstitial kidney disease resulting in ESRD in the third through seventh decade of life
- Urinalysis revealing a bland urinary sediment (i.e., little blood or protein)
- Renal ultrasound examination that is normal early in the disease course [Bleyer et al 2010]

Terms previously used to refer to ADTKD-*UMOD* that are no longer in use:

- Familial juvenile hyperuricemic nephropathy 1
- Medullary cystic kidney disease 2 (MCKD2)
- *UMOD*-associated kidney disease

Prevalence

ADTKD-*UMOD* accounts for approximately 0.2% of individuals with ESRD [Cormican et al 2019, Groopman et al 2019]. The prevalence is expected to be similar in all populations. Approximately 2,000 individuals have been identified with this disorder; however, these numbers are expected to increase significantly due to better recognition and genetic testing for this condition [Bleyer et al 2020].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline heterozygous pathogenic variants in *UMOD*.

Differential Diagnosis

Figure 1 provides a diagnostic algorithm for inherited kidney disease.

Hereditary glomerulonephritis. Affected individuals usually have proteinuria and/or hematuria. If blood or protein is present in the urine, consider hereditary forms of glomerulonephritis or hematuria (e.g., Alport syndrome). Rarely, individuals with ADTKD-*UMOD* have had proteinuria; however, this is uncharacteristic.

Autosomal dominant polycystic kidney disease. If the urinary sediment is bland (i.e., with little blood or protein) in persons with kidney disease inherited in an autosomal dominant manner, one must exclude autosomal dominant polycystic kidney disease (ADPKD), in which a large number of cysts are seen on kidney ultrasound examination in affected individuals older than age 25 years.

Other forms of ADTKD. If the individual does not have ADPKD and the urinary sediment is bland, consider the following forms of autosomal dominant tubulointerstitial kidney disease:

- ADTKD-*MUC1* is associated with pathogenic variants in *MUC1*. Affected individuals have slowly progressive CKD and minimal proteinuria. An important differentiating factor is that in ADTKD-*MUC1* gout usually only occurs in the setting of Stage 3 or later CKD. Affected individuals do not have anemia or other manifestations in childhood.
- ADTKD-*REN* is associated with pathogenic variants in *REN* [Zivná et al 2009]. Like ADTKD-*UMOD*, this condition is associated with early-onset gout and slowly progressive CKD. Persons with a *REN* pathogenic variant also manifest hypoproliferative anemia in childhood.

Fabry disease, an X-linked disorder, results from deficient activity of the enzyme α-galactosidase (α-Gal) A and progressive lysosomal deposition of globotriaosylceramide (GL-3) in cells throughout the body. The classic form, occurring in males with <1% α-Gal A activity, usually has its onset in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesias), the appearance of vascular cutaneous lesions (angiokeratomas), hypohidrosis, characteristic corneal and lenticular opacities, and proteinuria (which exceeds that seen in ADTKD-*UMOD*). Gradual deterioration of kidney function leads to ESRD, usually occurring in the third to fifth decade. Males with >1% α-Gal A activity have a cardiac or renal variant phenotype. Rarely, heterozygous carrier females may have symptoms as severe as those observed in males with the classic phenotype.

Table 3. Monogenic Kidney Diseases in the Differential Diagnosis of ADTKD-*UMOD*

Gene(s)	DiffDx Disorder	MOI	Renal Phenotype	Distinguishing Features of DiffDx Disorder
CEP290 *INVS* *IQCB1* *NPHP1* *NPHP3* *NPHP4* *TMEM67* (19 genes [1])	Isolated nephronophthisis	AR	TKD, often seen in childhood; may be assoc w/anemia & mild hypotension	Absence of affected family members in multiple generations. Anemia usually correlates w/level of kidney function (i.e., may not be present in childhood). Severity of kidney failure is usually much greater (usually requiring dialysis in the teens & early 20s). Hyperkalemia & acidemia are not as pronounced.
COL4A3 *COL4A4* *COL4A5*	Alport syndrome (& other types of hereditary glomerulonephritis)	XL AR AD	Microscopic hematuria (microhematuria); proteinuria; progression to ESRD	Frequent cochlear & ocular manifestations; hematuria; males affected much more severely than females
DNAJB11 *GANAB* *PKD1* *PKD2*	Autosomal dominant polycystic kidney disease (ADPKD)	AD	Bland urinary sediment [2]; large # of cysts in persons age >25 yrs	Numerous cysts seen on kidney ultrasound
GLA	Fabry disease, classic form	XL	Proteinuria (usually exceeding that seen in ADTKD-*UMOD*). Gradual deterioration of renal function to ESRD occurs in ~3rd-5th decade. [3]	Classic form (males w/<1% α-Gal A activity) usually has onset in childhood or adolescence w/periodic crises of severe pain in extremities (acroparesthesias), appearance of vascular cutaneous lesions (angiokeratomas), hypohidrosis, & characteristic corneal & lenticular opacities.
MUC1	ADTKD-*MUC1*	AD	Minimal proteinuria; slowly progressive CKD	Only clinical finding is CKD & its sequelae. [4]
DNAJB11 [4]	Atypical ADPKD-ADTKD	AD	Slowly progressive CKD, multiple renal cysts	Numerous kidney cysts are common.
HNF1B	ADTKD-*HNF1B*	AD	Variable other manifestations incl MODY, hyperuricemia & gout, CKD, CAKUT, & unexplained liver function abnormalities	Incomplete penetrance for characteristic renal involvement & absence of the other variable manifestations
mtDNA	m.547A>T [5]	Mat	Chronic TKD	Absence of childhood anemia, hyperkalemia, & acidemia
PAX2	*PAX2*-related disorder	AD	Glomerular proteinuria, hematuria, CKD, & ocular coloboma	Absence of hematuria, proteinuria, & coloboma

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Renal Phenotype	Distinguishing Features of DiffDx Disorder
SEC61A1	ADTKD-*SEC61A1*	AD	Slowly progressive CKD, leukopenia, abscess formation, IUGR & postnatal growth restriction	Absence of leukopenia, abnormal growth

α-Gal = α-galactosidase; AD = autosomal dominant; AR = autosomal recessive; CAKUT = congenital anomalies of the kidneys and urinary tract; CKD = chronic kidney disease; ESRD = end-stage renal disease; IUGR = intrauterine growth restriction; Mat = maternal; MODY = maturity-onset diabetes of the young; MOI = mode of inheritance; TKD = tubulointerstitial kidney disease; XL = X-linked

1. Listed genes represent the most common genetic causes of isolated nephronophthisis. Other genes known to be associated with nephronophthisis are *ANKS6, CEP164, CEP83, DCDC2, GLIS2, IFT172, NEK8, RPGRIP1L, SDCCAG8, TTC21B, WDR19*, and *ZNF423*.

2. Bland refers to urinary sediment with little blood or protein.

3. Males with >1% α-Gal A activity have a cardiac or renal variant phenotype. Rarely, heterozygous carrier females may have symptoms as severe as those observed in males with the classic phenotype.

4. Devuyst et al [2019]

5. Connor et al [2017]

Management

Consensus management guidelines for autosomal dominant tubulointerstitial kidney disease, *UMOD* (ADTKD-*UMOD*) have been published [Eckardt et al 2015] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ADTKD-*UMOD*, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

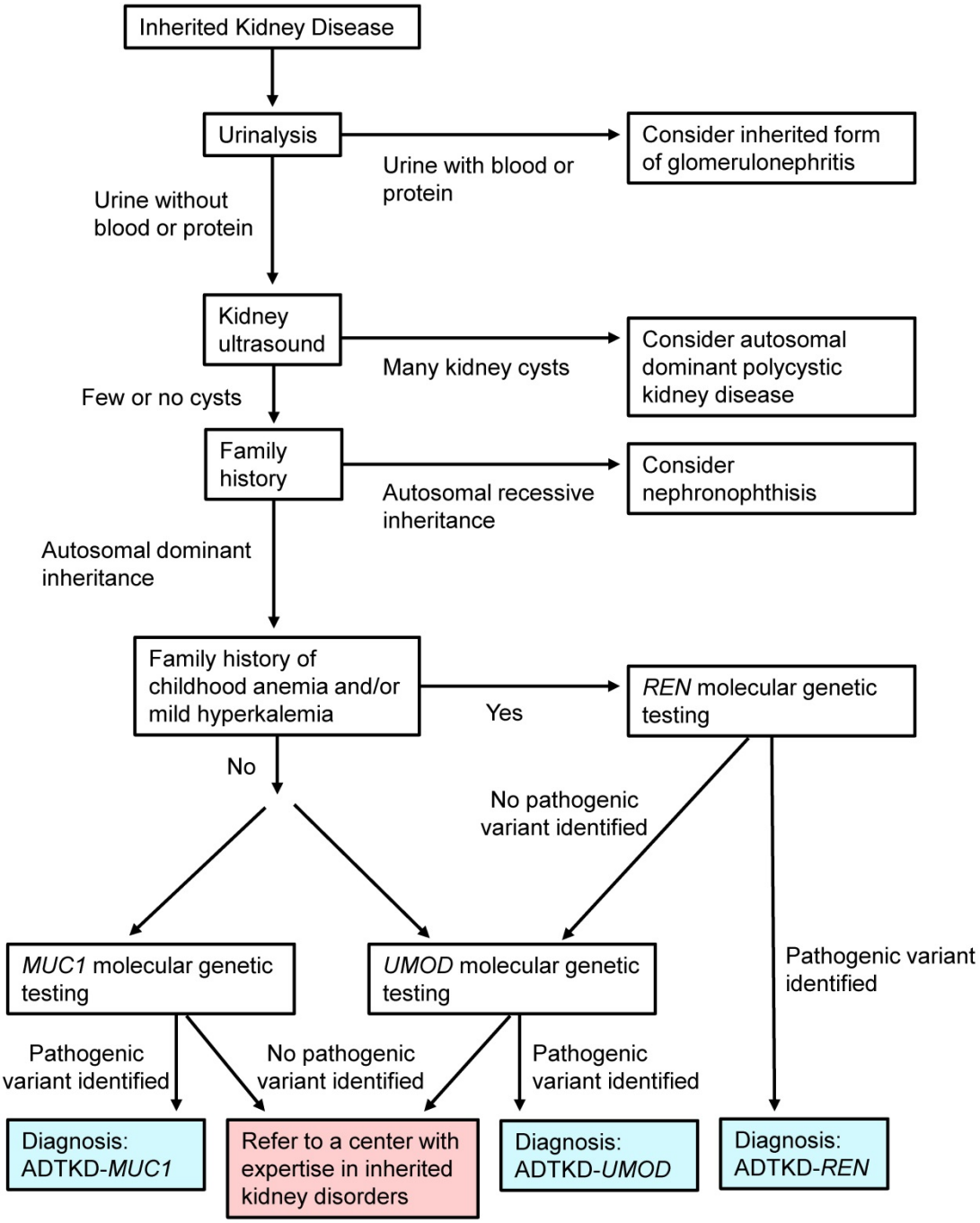

Figure 1. Testing strategy for inherited kidney disease – 2015 update

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with ADTKD-*UMOD*

System/Concern	Evaluation
Hypertension risk	Measurement of blood pressure
Anemia	Hemoglobin level
Kidney function	Serum creatinine (part of basic metabolic panel)
Gout risk	Serum urate concentration
Kidney structure	Renal ultrasound exam
Nephrology referral	
Genetic counseling	By genetics professionals [1] to inform affected persons re nature, MOI, &implications of ADTKD-*UMOD* in order to facilitate medical & personal decision making

MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Care by a nephrologist is recommended.

Hyperuricemia/Gout

Prevention of gout attacks with allopurinol should be considered in individuals with gout. With allopurinol treatment, serum uric acid concentration returns to normal and gout attacks can be entirely prevented. Lifelong therapy with allopurinol is required for future gout prevention.

In individuals with allergies or intolerance to allopurinol, febuxostat may be considered; however, no data on the use of this medication in ADTKD-*UMOD* are available at present.

Acute gout typically responds well to prednisone, short-term nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine. One should avoid NSAIDs in the setting of CKD Stage 3 or greater.

Kidney Disease

Referral to a nephrologist is indicated to monitor kidney function, evaluate for manifestations of CKD, and prepare for renal replacement therapy when end-stage renal disease (ESRD) occurs.

Renal replacement therapies such as hemodialysis and peritoneal dialysis replace kidney function but are associated with potential complications.

Individuals with ADTKD-*UMOD* are excellent transplant candidates. Progression of CKD is usually slow, allowing time to find a living donor. Besides gout, there are no other associated systemic manifestations of ADTKD-*UMOD*, resulting in most individuals having low comorbidities prior to transplant. Kidney transplantation cures ADTKD-*UMOD*, as the transplanted kidney does not develop the disease.

There is insufficient evidence that allopurinol slows the progression of kidney disease. Some authors have suggested that it may slow progression, but these studies were small, not randomized, and with short-term follow-up. In addition, genetic diagnoses were not available at the time of these studies [Pirson et al 2000, Fairbanks et al 2002].

Surveillance

Appropriate surveillance includes the following:

- Measurement of serum creatinine concentration at least annually in affected individuals, and more frequently in those with severe disease
- Measurement of serum uric acid concentration at least annually

Agents/Circumstances to Avoid

Avoid use of the following:

- Nonsteroidal anti-inflammatory drugs. NSAIDs are generally discouraged except for short-term treatment of gout or similar painful conditions in early CKD (prior to Stage 3 CKD). Chronic daily use should be avoided.
- Drugs known to be nephrotoxic
- The low sodium diet, which is typically prescribed in the treatment of CKD
- Volume depletion, dehydration, and physical exertion under extreme conditions (e.g., in hot weather), as these may worsen hyperuricemia, leading to more frequent attacks of gout

Evaluation of Relatives at Risk

For early diagnosis and treatment

- **Asymptomatic at-risk relatives younger than age 18 years.** Many experts believe that testing of asymptomatic children for genetic disorders for which there are no specific treatments is inadvisable and violates the child's autonomy. However, genetic testing of a child from a family with ADTKD-*UMOD* may be considered for the purpose of early diagnosis to initiate treatment that would prevent gout (a secondary manifestation of ADTKD-*UMOD*). For example, a child may belong to a family with an early age of onset of ESRD and the occurrence of gout in the teenage years. If the child is an athlete or dancer, testing could be considered in order to provide preventive therapy for gout and thus avoid the inopportune occurrence of gout prior to an important sporting event or performance. In contrast, testing of asymptomatic individuals younger than age 18 years should likely be avoided in families with a late age of onset of ESRD and no history of gout in childhood.

  If performed, testing should only be done after a full discussion with the child and after obtaining the child's assent and the parents'/guardians' consent.

- **Asymptomatic at-risk adult relatives.** It is appropriate to clarify the genetic status of apparently asymptomatic * at-risk adult relatives (by molecular genetic testing for the familial *UMOD* pathogenic variant) in order to identify those individuals who would benefit from surveillance and awareness of agents/circumstances to avoid.

  * Chronic kidney disease, one of the primary manifestations of this disorder, is often asymptomatic.

For kidney donation. Any relative who is a potential kidney donor should undergo molecular genetic testing to clarify his/her genetic status so that only those who do not have the *UMOD* pathogenic variant are evaluated further.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy in women with ADTKD-*UMOD* is associated with fetal outcomes comparable to the general population. There is an increased risk of hospitalization for high blood pressure [Author, personal observation]. Acceleration of loss of kidney function can be seen in some kidney diseases during pregnancy; data specifically for ADTKD-*UMOD* are not available.

Women of childbearing age who are taking medications such as an angiotensin-converting enzyme (ACE) inhibitor or allopurinol should discuss their medication regimen with their physician prior to conception.

ACE inhibitors. The use of ACE inhibitors even in early pregnancy can result in fetal damage and death. Women who are taking ACE inhibitors prior to pregnancy or at the time of conception should be transitioned to another antihypertensive medication.

Allopurinol. Published data on the fetal risk associated with use of allopurinol during pregnancy is limited. While a number of pregnancies in which allopurinol was used resulted in the birth of healthy infants, the rare occurrence of a pattern of malformations similar to what is observed in women who use mycophenolate mofetil during pregnancy was reported in two infants born to women who took allopurinol throughout pregnancy [Kozenko et al 2011, Hoeltzenbein et al 2013].

This finding is concerning because the mechanism of action of allopurinol (inhibiting purine degradation) is similar to the mechanism of action of mycophenolate mofetil (inhibition of *de novo* purine biosynthesis).

Prednisone. Use of prednisone during pregnancy has been associated with fetal growth restriction. Use in the first trimester of pregnancy is associated with a slightly increased risk of orofacial clefting [Carmichael et al 2007].

Colchicine. Chronic use of colchicine that includes the immediate preconception and conception period has been associated with an increased risk of fetal chromosome abnormalities [Berkenstadt et al 2005]. However, the risk of adverse fetal outcome for short courses of colchicine during pregnancy outside of the periconeptional period is low.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

By definition, autosomal dominant tubulointerstitial kidney disease – *UMOD* (ADTKD-*UMOD*) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with ADTKD-*UMOD* have an affected parent.
- A proband with ADTKD-*UMOD* may have the disorder as the result of a *de novo UMOD* pathogenic variant.

- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism (although no instances of germline mosaicism have been reported, it remains a possibility). Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- An apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the *UMOD* pathogenic variant identified in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome, a milder phenotypic presentation, early death of the parent before the onset of symptoms, and/or late onset of the disease in the affected parent.

Sibs of a proband. The risk to the sibs of a proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *UMOD* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The rate of chronic kidney disease progression and age of onset of end-stage renal disease (ESRD) can vary significantly between heterozygous sibs and does not correlate well with the age of ESRD in the affected parent.
- If the proband has a known *UMOD* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *UMOD* pathogenic variant but are clinically asymptomatic, sibs are still presumed to be at increased risk for ADTKD-*UMOD* because of the possibility of later onset in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with ADTKD-*UMOD* has a 50% chance of inheriting the *UMOD* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *UMOD* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing for at-risk asymptomatic family members requires prior identification of the *UMOD* pathogenic variant in the family. Such testing is helpful in predicting the future development of chronic kidney disease and should be performed if the family member is considering becoming a kidney donor.

Testing of at-risk asymptomatic individuals younger than age 18 years. Because of the increased risk for gout, which can be prevented with allopurinol treatment in adolescents who have a *UMOD* pathogenic variant, testing of at-risk family members during adolescence may be appropriate in families in which gout occurs at a younger

age. In contrast, testing of asymptomatic individuals younger than age 18 years should likely be avoided in families with a late age of onset of ESRD and no history of gout in childhood.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *UMOD* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Medline Plus**

  Autosomal dominant tubulointerstitial kidney disease

- **UMOD-Related Kidney Disease Registry**

  Dr. Anthony Bleyer has established a registry of individuals with UMOD pathogenic variants. Patient educational materials (including webinars) are available upon request; genetic testing can be offered as part of a research protocol. Please contact Dr. Bleyer (ableyer@wakehealth.edu) if interested in participation.

  Email: ableyer@wakehealth.edu

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Autosomal Dominant Tubulointerstitial Kidney Disease -- UMOD: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
UMOD	16p12.3	Uromodulin	UMOD database UMOD Mutation Registry	UMOD	UMOD

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Autosomal Dominant Tubulointerstitial Kidney Disease -- UMOD (View All in OMIM)

162000	TUBULOINTERSTITIAL KIDNEY DISEASE, AUTOSOMAL DOMINANT, 1; ADTKD1

Table B. continued from previous page.

191845	UROMODULIN; UMOD

Molecular Pathogenesis

Autosomal dominant tubulointerstitial kidney disease – *UMOD* (ADTKD-*UMOD*) is an endoplasmic reticulum storage disease resulting in chronic kidney disease from deposition of abnormal uromodulin over time [Rampoldi et al 2003, Bleyer et al 2004, Williams et al 2009]. Uromodulin is produced only in the thick ascending limb of Henle's loop of the renal tubule; therefore, disease is limited to the kidney. While uromodulin is the most common protein found in normal human urine, its function is uncertain. Uromodulin is likely responsible for maintaining the integrity of the thick ascending limb of Henle's loop, in which the water permeability is remarkably low and salts are efficiently absorbed.

UMOD pathogenic variants are mostly missense variants [Kidd et al 2020]. The majority involve the addition or deletion of a cysteine residue or highly conserved polar residue that is likely to alter either disulfide bond formation, thereby disrupting the correct protein folding [Whiteman & Handford 2003] or hydrophobicity distribution responsible for protein spatial flexibility [Xu et al 1997].

Mechanism of disease causation. In heterozygotes, urinary excretion of uromodulin is much less than half the expected amount, likely resulting from a dominant-negative effect (e.g., interference with synthesis of the normal uromodulin by abnormal uromodulin). Accordingly, the abnormal expression of the mutated uromodulin in the thick ascending limb of Henle's loop of the renal tubule decreases NaCl reabsorption and subsequently induces a state of volume contraction known to promote the proximal reabsorption of urate [Renigunta et al 2011].

***UMOD*-specific laboratory technical considerations.** *UMOD* comprises 11 exons. Exon 1 is noncoding. Note: Exon numbering may vary in the literature; this *GeneReview* uses that of Williams et al [2009].

Pathogenic variants in *UMOD* have been identified in exons 3, 4, 5, and 7 [Williams et al 2009]. Most variants are in exons 3 and 4.

For interpretation of variants of uncertain significance:

- An updated list of more than 200 clinically significant *UMOD* variants maintained by the authors is available here.
- Variants that affect cysteine residues are highly likely to be pathogenic.
- Other testing can include in vitro testing [Kidd et al 2020] and/or immunohistochemical examination of kidney biopsy tissue, if obtained.

Table 5. Notable *UMOD* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [1]	
			# of families	Median age of ESRD
NM_003361.4 NP_003352.2	c.115G>A	p.Ala39Thr	(Later onset of ESRD)	
			4	66 yrs [2]
	c.263G>A	p.Gly88Asp	Common pathogenic variant (Later onset of ESRD)	
			8	65.5 yrs [2]
	c.274T>G	p.Cys92Gly	(Early onset of ESRD)	
			2	31.5 yrs [2]

Table 5. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [1]	
			# of families	Median age of ESRD
	c.278_289delTCTGCCCCGAAGinsCCGCCTCCT	p.Val93_Gly97delinsAlaAlaSerCys	Common pathogenic variant; assoc w/ less frequent gout (Later onset of ESRD) [3]	
			11	48 yrs [2]
	c.317G>T	p.Cys106Phe	Common pathogenic variant (Later onset of ESRD)	
			10	55 yrs [2]
	c.529_555del27	p.His177-Arg185del	Common pathogenic variant	
			25	46 yrs [2]
	c.533G>C	p.Arg178Pro	Common pathogenic variant (Later onset of ESRD)	
			9	53 yrs [2]
	c.744C>G	p.Cys248Trp	(Later onset of ESRD)	
			3	71 yrs [2]

ESRD = end-stage renal disease

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Comments shown in ( )s are possible associations that require further evidence.

2. Kidd et al [2020]

3. Smith et al [2011]

Chapter Notes

Author Notes

Dr Bleyer pursues clinical and genetic research of autosomal dominant tubulointerstitial kidney disease (ADTKD).

Regarding ADTKD-*UMOD*:

- He and his colleagues (who have diagnosed more than 200 families with ADTKD-*UMOD*) are committed to using their laboratory and genetic expertise in the interpretation of *UMOD* variants of uncertain significance.
- He is developing a registry of individuals with benign and pathogenic *UMOD* variants.

In addition:

- He is most interested in hearing about families with ADTKD in whom no causative variant has been identified on molecular genetic testing of the genes known to cause ADTKD.
- Single-gene testing for *MUC1* pathogenic variants can be provided free of charge.

Please contact Dr Bleyer (ableyer@wakehealth.edu) with any questions about ADTKD.

Related website: www.wakehealth.edu

Author History

Anthony J Bleyer, MD, MS (2007-present)
Karn Gupta, MD; Wake Forest University School of Medicine (2007-2011)
P Suzanne Hart, PhD; National Human Genome Research Institute (2011-2021)
Kendrah Kidd, MS (2021-present)
Stanislav Kmoch, PhD (2016-present)
Martina Živná, PhD (2021-present)

Revision History

- 23 December 2021 (sw) Revision: nomenclature corrections (Table 5)
- 8 April 2021 (bp) Comprehensive update posted live
- 30 June 2016 (ha) Comprehensive update posted live
- 12 September 2013 (me) Comprehensive update posted live
- 15 March 2011 (me) Comprehensive update posted live
- 26 September 2007 (cd) Revision: prenatal diagnosis available
- 12 January 2007 (me) Review posted live
- 3 August 2006 (ajb) Original submission

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