GENEReviews

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UMOD-Related Kidney Disease

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Summary

Disease characteristics. The spectrum of *UMOD*-related kidney disease (uromodulin-associated kidney disease) includes familial juvenile hyperuricemic nephropathy (FJHN) and medullary cystic kidney disease type 2 (MCKD2). Clinical findings typically include reduced fractional excretion of uric acid resulting in hyperuricemia and gout (or precocious gout); interstitial kidney disease usually appearing between ages 15 and 40 years and leading to end-stage renal disease (ESRD) ten to 20 years later; and normal or small-sized kidneys. Medullary cysts (i.e., in the medulla or at the corticomedullary junction) are a late finding and may not be seen on imaging because of their small size. The age at ESRD varies both between and within families.

Diagnosis/testing. *UMOD*-related kidney disease is defined by: the presence of a mutation in *UMOD*, the gene encoding uromodulin; increased Tamm-Horsfall protein (THP) immunostaining on renal biopsy; and decreased uromodullin urinary excretion. *UMOD* is the only gene associated with *UMOD*-related kidney disease. Molecular genetic testing is clinically available.

Management. *Treatment of manifestations:* allopurinol or probenecid for treatment of gout; referral to a nephrologist (to monitor kidney function, evaluate for manifestations of chronic kidney disease, prepare for renal replacement therapy). Hemodialysis and peritoneal dialysis can replace renal function; kidney transplantation is curative. *Prevention of primary manifestations:* Treatment of hyperuricemia with allopurinol can prevent development of gout. *Surveillance:* measurement of serum concentration of creatinine and uric acid at least annually. *Agents/circumstances to avoid:* drugs known to be nephrotoxic; volume depletion and dehydration; high meat and seafood intake (may exacerbate hyperuricemia/gout). *Testing of relatives at risk:* If the *UMOD* mutation has been identified in an affected family member, offer molecular genetic testing to: (1) adolescent at-risk male relatives because of the benefit of allopurinol treatment for hyperuricemia/gout; (2) relatives at risk who are potential kidney donors.

Genetic counseling. *UMOD*-related kidney disease is inherited in an autosomal dominant manner. Most individuals diagnosed with *UMOD*-related kidney disease have an affected parent. Each child of an affected individual has a 50% chance of inheriting the mutation. Prenatal testing is available for pregnancies at risk in families in which the disease-causing

mutation has been identified. Requests for prenatal testing are not common for conditions such as *UMOD*-related kidney disease that do not affect intellect and have treatment available.

Diagnosis

Clinical Diagnosis

UMOD-related kidney disease (uromodulin associated kidney disease) is defined by the presence of a mutation in *UMOD*, the gene encoding uromodulin, the most abundant urinary protein [also known as the Tamm-Horsfall protein (THP)], resulting in increased THP immunostaining on renal biopsy and a decrease in uromodulin urinary excretion.

The phenotypic spectrum of *UMOD*-related kidney disease includes familial juvenile hyperuricemic nephropathy (FJHN) and medullary cystic kidney disease type 2 (MCKD2).

Clinical findings include the following:

- **Normal or small-sized kidneys.** Medullary cysts may or may not be present on renal ultrasound examination. Development of cysts (in the medulla or at the corticomedullary junction) is a late phenomenon and can escape detection by imaging because of the small size of the cysts [Swenson et al 1974]. Thin-section CT or magnetic resonance imaging (MRI) may improve the detection rate [Wise et al 1998].
- **Hyperuricemia and precocious gout or gout,** found in most (not all) affected individuals
- **Reduced fractional excretion of uric acid**
- **Bland urinary sediment.** Usually hematuria is not present and excretion of protein is less than 1 g/24 hours except when kidney failure is advanced.
- **Renal impairment,** usually appearing between age 15 and 40 years and leading to end-stage renal disease (ESRD) ten to 20 years later
- **Interstitial kidney disease and deposition of uromodulin/THP** in thick ascending limb tubular cells on renal biopsy

Testing

Uric acid

- **Hyperuricemia** (serum uric acid concentration >6 mg/dL) is present in the vast majority of individuals with *UMOD*-related kidney disease, even prior to the development of kidney failure. Usually, hyperuricemia in an individual with normal kidney function corresponds to a serum concentration of uric acid greater than one standard deviation of the normal value for age and sex (see Table 1).

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

Age	Serum Concentration (mg/dL)	
	Males	Females
<5 years	3.6±0.9	
5-10 years	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

- **Decreased fractional excretion of urinary uric acid** (usually <5%) is common in *UMOD*-related kidney disease [Moro, Ogg et al 1991]. The reduction of urate excretion is an early event since it can be detected in affected children with preserved renal function [McBride et al 1998; Moro, Ogg et al 1991]. The fractional excretion of urinary uric acid (FEur) can be calculated as: (urine uric acid concentration x serum creatinine concentration) / (serum uric acid concentration x urine creatinine concentration).

  Note: (1) The fractional excretion of urinary uric acid can be measured from a spot urine sample; however, a 24-hour urine collection is preferable. (2) Aspirin, diuretics, and nonsteroidal agents should be avoided during the collection. (3) Because the fractional excretion of uric acid rises above 5% as renal function worsens, this test is not sensitive in individuals with *UMOD*-related kidney disease who have renal insufficiency.

Kidney biopsy

- **Histology.** Histologic examination essentially shows chronic interstitial nephritis, with focal tubular atrophy and interstitial fibrosis, occasionally accompanied by lymphocytic infiltration. The main lesions include tubular basement membrane disintegration (thickening and attenuation) and medullary cyst formation in distal tubules and collecting ducts [Simmonds et al 1980, Richmond et al 1981, Gagnadoux et al 1989, Puig et al 1993, Dahan et al 2001]. However, biopsy interpretation may be misleading. Most pathologists focus on glomerular changes, which are secondary, frequently resulting in the (incorrect) diagnosis of focal glomerulosclerosis [Bleyer et al 2005].
- **THP immunostaining.** In the normal human kidney, THP is distributed primarily in the tubular cells lining the thick ascending limbs of the loops of Henle and early distal convoluted tubules with a staining pattern characteristic of apical membrane reactivity [Sikri 1981]. Significant modifications in the expression and immunostaining pattern for THP are detected in the kidneys of persons with a *UMOD* mutation, in particular an intense staining limited to a number of tubule profiles that sometimes are enlarged or even cystic. At higher magnification, the THP immunostaining is diffusely intracellular, with intratubular heterogeneity [Dahan et al 2003].
- **Low uromodulin excretion in the urine** is observed in individuals with *UMOD*-related kidney disease at a very young age prior to the decline in kidney function [Bleyer et al 2004]. Because decreased urinary uromodulin is associated with any type of chronic kidney disease, its measurement in a person with early chronic kidney

disease is nonspecific and non-diagnostic [Bleyer et al 2004]. Such testing is available on a research basis only.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *UMOD*, which encodes uromodulin (Tamm-Horsfall glycoprotein, or THP), the most abundant urinary protein [Hart et al 2002], is the only gene associated with *UMOD*-related kidney disease [Wolf, Karle et al 2003].

Clinical uses

- **Diagnostic testing**
  - For persons who have hereditary kidney disease of unknown cause in which the urinary sediment shows no hematuria or proteinuria (especially those with a strong family history of gout)
  - For persons who have interstitial kidney disease of unknown cause (especially young individuals with a history of precocious gout)
- **Confirmatory diagnostic testing of symptomatic relatives.** For persons in a family with known *UMOD*-related kidney disease who have hyperuricemia, gout, or renal insufficiency
- **Predictive testing.** For asymptomatic at-risk persons in a family with known *UMOD*-related kidney disease who are being considered for kidney donation to a relative
- **Prenatal diagnosis**

Clinical testing

- **Sequence analysis of select exons.** Sequencing of exons 4 and 5 of *UMOD* is clinically available. Over 90% of families with *UMOD*-related kidney disease have been found to have mutations in these exons.

  Note: One family has been reported to have a mutation in exon 6; however, clinically available testing currently does not evaluate exon 6.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in *UMOD*-Related Kidney Disease

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis of exons 4 and 5	*UMOD* sequence variants	>90%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by test method

Interpretation of test results. Identification of a mutation in exon 4 or exon 5 almost certainly confirms the diagnosis of *UMOD*-related kidney disease. The vast majority of mutations involve an amino acid substitution that results in either the addition or deletion of a cysteine residue. If there is concern whether a mutation is pathologic, other affected and unaffected family members can be tested to see if the mutation is segregating with the disease in the family.

If no mutation is found, *UMOD*-related kidney disease may still be present, caused by a mutation in exon 6 or another part of the *UMOD* gene that has not been sequenced during testing; alternatively, the individual may have some other hereditary renal disease.

For other issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

- Urinalysis to evaluate for presence or absence of hematuria or proteinuria. Significant hematuria or proteinuria in affected family members suggests that the diagnosis is NOT *UMOD*-related kidney disease.
- Renal ultrasound examination to evaluate for the presence or absence of cysts. Evidence of polycystic kidney disease suggests that the diagnosis is NOT *UMOD*-related kidney disease.
- If urinary sediment is "bland" (i.e., without hematuria or pyuria) and renal ultrasound examination does not reveal polycystic kidney disease, molecular genetic testing for *UMOD* is appropriate.
- If no *UMOD* mutation is found, referral to a research group interested in *UMOD*-related kidney disease could result in the following additional investigations:
  - Sequence analysis of the entire *UMOD* gene
  - Immunostaining of kidney biopsy material in an effort to identify uromodulin deposits in tubular cells
  - Measurement of urinary excretion of uromodulin in an individual with relatively preserved renal function
  - Linkage analysis for other similar hereditary renal diseases

Genetically Related (Allelic) Disorders

In one report a *UMOD* mutation is associated with glomerulocystic kidney disease (GCKD), characterized by dilatation of Bowman's space in most glomeruli [Rampoldi et al 2003]. Whether GCKD is truly part of the spectrum of *UMOD*-related kidney disease is yet to be determined.

Clinical Description

Natural History

Initial symptoms of *UMOD*-related kidney disease (uromodulin-associated kidney disease) are relatively mild. The impaired ability to maximally concentrate urine may give rise to polyuria. For this reason, enuresis is somewhat increased in childhood [Hart et al 2002], though it is not significantly higher than that seen in children without kidney disease. Enuresis resolves subsequently.

The usual presenting feature is hyperuricemia or gout. However, hyperuricemia is not a constant finding: women over age 16 years who have a *UMOD* mutation had a normal serum uric acid concentration [Bleyer & Hart 2003, Dahan et al 2003]. Furthermore, a history of gout is recorded in only 45% of individuals with a *UMOD* mutation, with onset of gout ranging from age eight to 38 years [Dahan et al 2003].

In those with a strong family history of *UMOD*-related kidney disease, diagnosis of gout is usually made by the affected individual or a parent. As renal function worsens, gout worsens

and the frequency of attacks increases. Without treatment, tophi (large subcutaneous depositions of uric acid) and crippling arthritis can develop.

Mild chronic renal insufficiency occurring in the late teens and early twenties is usually incidentally noted on laboratory testing for other reasons or when screening is performed in suspected individuals. The chronic tubulo-interstitial kidney disease of *UMOD*-related kidney disease usually leads to end-stage kidney disease (ESRD) in the fourth through seventh decade of life, although renal disease can progress to ESRD before age 30 years [Simmonds et al 1980, Richmond et al 1981, Cameron et al 1993, Puig et al 1993]. The age at ESRD varies both between families and among affected individuals in the same family. For example, three affected individuals in one family reached ESRD between age 46 and 50 years, whereas two others had autonomous renal function at age 56 and age 63 years [Puig et al 1993].

Early in the disease course hypertension is not a prominent finding.

No other systemic manifestations of disease are present.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known at the present time.

Penetrance

Penetrance appears to be complete, though some individuals — especially females — may not develop significant renal insufficiency until the sixth or seventh decade.

The penetrance of hyperuricemia has been estimated as 92% [Bleyer, Woodward et al 2003].

Anticipation

It is unknown if anticipation occurs. Gout may be more prevalent in younger generations because of the increase in worldwide consumption of meat.

Nomenclature

MCKD2 and FJHN are likely the same disease. Historically, pediatricians referred to the condition as FJHN and nephrologists treating adults referred to the condition as medullary cystic kidney disease.

The term medullary cystic kidney disease (MCKD) was initially used because post-mortem specimens showed microscopic or macroscopic medullary cysts [Bleyer & Hart 2006]. These cysts are usually not identifiable by radiologic imaging and, if present, are usually not seen until very late in the disease course.

Recent advances identifying a cause for the disease have resulted in names such as uromodulin-associated kidney disease and uromodulin storage disease. These names have not yet been commonly used [Scolari et al 2004].

Note: (1) The term "nephronophthisis/medullary cystic kidney disease (NPH/MCKD) complex" was used in the past to refer to both autosomal recessive and autosomal dominant forms of hereditary chronic tubulo-interstitial disease [Hildebrandt et al 1992]. Nephronophthisis is now used to refer specifically to autosomal recessive forms of kidney disease usually presenting in childhood. The majority of juvenile NPH is caused by deletion of the *NPHP1* gene on chromosome 2q13. A gene for infantile NPH is mapped to chromosome 9q22-q31 and a gene for adolescent NPH has been mapped to chromosome 3q22. A new locus, NPHP4, has been recently identified on chromosome 1p36. (2) Medullary sponge kidney

(MSK), associated with calcifications of the medulla of the kidney, hypercalciuria, hematuria, and tubular acidification defects [Gambaro et al 2006], is not in any way related to medullary cystic kidney disease.

Prevalence

UMOD-related kidney disease is rare, being responsible for fewer than 1% of cases of end-stage kidney disease. However, *UMOD*-related kidney disease has been chronically under-diagnosed and prevalence rates may be somewhat higher.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

In persons with kidney disease inherited in an autosomal dominant manner, one must first exclude autosomal dominant polycystic kidney disease (ADPKD), in which a large number of cysts are seen on renal ultrasound examination in affected individuals older than age 25 years.

Another condition to be considered is any form of hereditary glomerulonephritis. Affected individuals invariably have significant proteinuria (>3 g/24 hour urine) and/or hematuria. Although individuals with *UMOD*-related kidney disease may have minimal proteinuria, significant hematuria is not seen in *UMOD*-related kidney disease.

If the urinary sediment is bland and the individual does not have ADPKD, other forms of autosomal dominant tubulo-interstitial kidney disease must be considered. These conditions are characterized by chronic kidney disease that progresses at a rate similar to that seen in *UMOD*-related kidney disease; transplantation or dialysis is usually required from the fourth through seventh decade of life. Gout may also be seen in these conditions, but it is less common than in *UMOD*-related kidney disease.

Two other forms of autosomal dominant tubulo-interstitial kidney disease have been identified:

- Medullary cystic kidney disease type 1 (MCKD1), linked to chromosome 1q21 [Wolf et al 2006]
- Medullary cystic kidney disease type 3 (MCKD3), linked to chromosome 1q41

Gout may lead to the suspicion of chronic lead poisoning.

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 less than 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 usually exceeds that seen in *UMOD*-related kidney disease). Gradual deterioration of renal function to end-stage renal disease (ESRD) usually occurs in the third to fifth decade. Males with greater than 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.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *UMOD*-related kidney disease, the following evaluations are recommended:

- Determination of kidney function (measurement of serum creatinine concentration)
- Measurement of serum uric acid concentration

Treatment of Manifestations

Hyperuricemia/gout. Treatment with allopurinol or probenecid should be considered in individuals with gout. With allopurinol treatment, serum uric acid concentration returns to normal and gouty attacks can be entirely prevented. Lifelong therapy with allopurinol may be required.

Renal disease. Referral to a nephrologist is indicated to monitor kidney function, evaluate for manifestations of chronic kidney disease, and prepare for renal replacement therapy when renal insufficiency occurs.

Renal replacement therapy such as hemodialysis and peritoneal dialysis replaces renal function, but is associated with potential complications.

Kidney transplantation cures *UMOD*-related kidney disease. The transplanted kidney does not develop the disease.

It is possible that treatment with allopurinol or benzbromarone slows progression of medullary cystic kidney disease (most of which is likely *UMOD*-related kidney disease) [Fairbanks et al 2002, Bleyer & Hart 2003]; however, it is important to note that disease progression is very slow in younger individuals with *UMOD*-related kidney disease, and controlled trials have not been performed.

- Pirson et al (2000) reviewed the results of allopurinol administered to 20 individuals for at least four years. In 13 who were treated for seven to 23 years, deterioration of renal function continued; in the other seven, renal function remained stable or tended to improve. Of note, in the latter group, four persons had had the disease for less than 20 years when they started treatment; in three individuals, follow-up was for at least five years.
- A more recent study showed that 21 of 27 individuals from eight families maintained stable renal function during allopurinol treatment given for a mean of 14.5 years (mean age: 34 years) [Fairbanks et al 2002].
- In the majority of individuals studied by the authors, renal disease has progressed despite the use of allopurinol [Author, personal observation].

Prevention of Primary Manifestations

Treatment of hyperuricemia with allopurinol can prevent development of gout.

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

Volume depletion and dehydration may worsen hyperuricemia and lead to more frequent attacks of gout.

High meat and seafood intake could exacerbate gout.

Drugs known to be nephrotoxic (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) should be avoided.

Testing of Relatives at Risk

If the *UMOD* mutation has been identified in an affected family member, it is appropriate to offer molecular genetic testing:

- To adolescent at-risk male relatives because of their increased risk of gout, which can be prevented with allopurinol treatment;
- To relatives at risk who are interested in donating a kidney to an affected family member.

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

UMOD-related kidney disease (uromodulin associated kidney disease) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *UMOD*-related kidney disease have an affected parent.
- A proband with *UMOD*-related kidney disease may have the disorder as the result of a new gene mutation.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include *UMOD* genetic testing and measurement of serum uric acid and serum creatinine concentrations. 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 and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although most individuals diagnosed with *UMOD*-related kidney disease have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- Parental germline mosaicism has not been reported.

Offspring of a proband. Each child of an individual with *UMOD*-related kidney disease has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

See Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for *UMOD*-related kidney disease is available using the same techniques described in Molecular Genetic Testing. Such testing is helpful in predicting the future development of chronic kidney disease. When testing at-risk individuals for *UMOD*-related kidney disease, an affected family member should be tested first to confirm the molecular diagnosis in the family.

Testing for the disease-causing mutation in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Those seeking testing should be counseled about possible problems that they may encounter with regards to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up and evaluations.

Testing of at-risk individuals during childhood. Because of the increased risk of gout, which can be prevented with allopurinol treatment in adolescents who have a *UMOD* mutation, testing at-risk male family members during adolescence may be appropriate. In addition, individuals younger than age 18 years who are symptomatic usually benefit from having a specific diagnosis established.

See also the National Society of Genetic Counselors resolution on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents (pdf; Genetic Testing).

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100% and when all of the genes in which disease-causing mutations occur have not been identified. See 

for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: (1) Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements. (2) It is the policy of GeneReviews to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Requests for prenatal testing for conditions such as *UMOD*-related kidney disease that do not affect intellect and have treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather

than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Prenatal diagnosis has not been performed to date. Individuals who have from *UMOD*-related kidney disease will not be affected with kidney disease for 30 to 40 years. It is anticipated that rapid advances in transplantation, treatment, and renal replacement therapy will result in marked improvements in care for individuals with this disease.

Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of UMOD-Related Kidney Disease

Gene Symbol	Chromosomal Locus	Protein Name
UMOD	16p12.3	Uromodulin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for UMOD-Related Kidney Disease

162000	HYPERURICEMIC NEPHROPATHY, FAMILIAL JUVENILE; HNFJ
191845	UROMODULIN; UMOD
603860	MEDULLARY CYSTIC KIDNEY DISEASE 2; MCKD2
609886	GLOMERULOCYSTIC KIDNEY DISEASE WITH HYPERURICEMIA AND ISOSTHENURIA

Table C. Genomic Databases for UMOD-Related Kidney Disease

Gene Symbol	Entrez Gene	HGMD
UMOD	7369 (MIM No. 191845)	UMOD

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

UMOD-related kidney disease (uromodulin-associated kidney disease) is an endoplasmic reticulum storage disease resulting in chronic renal failure from deposition of abnormal uromodulin over time [Rampoldi et al 2003, Bleyer et al 2004].

Normal allelic variants: The gene comprises 11 exons.

Pathologic allelic variants: More than 40 mutations have been found in families with *UMOD*-related kidney disease [Hart et al 2002; Dahan et al 2003; Rampoldi et al 2003; Turner et al 2003; Wolf, Mucha et al 2003; Kudo et al 2004; Lens et al 2005; Puig et al 2006]. Mutations almost always are missense changes involving cysteine residue or highly conserved polar residue that are 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]. The localization of all mutations except one within exons 4 and 5 provides strong evidence of a hot spot region within the 5' coding region of the gene.

Normal gene product: Uromodulin is a large glycoprotein with a large number of cysteine residues [Serafini-Cessi et al 2003]. Uromodulin is produced only in the thick ascending limb of Henle's loop of the renal tubule; therefore, disease is limited to the kidney. Although 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, the kidney region in which the water permeability is remarkably low and salts are efficiently absorbed. Although it has been postulated that uromodulin is important in preventing urinary tract infections, individuals with abnormal uromodulin do not have an increased incidence of urinary tract infections or kidney stones.

Abnormal gene product: Almost all mutations causing *UMOD*-related kidney disease result in the addition or deletion of a cysteine residue to the uromodulin molecule, most likely resulting in defective uromodulin cross-linking. Histochemical studies have shown abnormal uromodulin deposition in the endoplasmic reticulum of cells of the thick ascending limb of Henle's loop. 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, an abnormal expression of the mutated uromodulin in the thick ascending limb of Henle's loop of the renal tubule could decrease NaCl reabsorption and subsequently induce a state of volume contraction known to promote the proximal reabsorption of urate.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Medline Plus
Medullary cystic kidney disease

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

Web: Information on MCKD

Dr. Bleyer pursues active clinical research in the area of MCKD. He is forming a registry of individuals with *UMOD* mutations. In addition, he is most interested in identifying families with the MCKD phenotype who have a mutational analysis that is negative. Please call with any questions about MCKD (336-716-4513).

Revision History

- 26 September 2007 (cd) Revision: prenatal diagnosis available

- 12 January 2007 (me) Review posted to live Web site
- 3 August 2006 (ajb) Original submission