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Autosomal Dominant Tubulointerstitial Kidney Disease – *MUC1*

Synonyms: ADTKD-*MUC1*, Medullary Cystic Kidney Disease Type 1 (MCKD1), *MUC1* Kidney Disease (MKD)

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Summary

Clinical characteristics

Autosomal dominant tubulointerstitial kidney disease – *MUC1* (ADTKD-*MUC1*) is characterized by slowly progressive tubulointerstitial disease that leads to end-stage renal disease (ESRD) and the need for dialysis or kidney transplantation. The rate of loss of kidney function for individuals is variable within and between families, with a median age of onset of end-stage renal disease (ESRD) of 46 years (range: ages 20-70 years). There are no other systemic manifestations.

Diagnosis/testing

The diagnosis of ADTKD-*MUC1* is established in a proband with suggestive clinical findings and molecular genetic testing that reveals a heterozygous pathogenic variant in *MUC1* that results in the creation of a specific frameshift protein (MUC1fs) responsible for the pathogenic changes in this disorder.

Management

Treatment of manifestations: Treatment follows standard guidelines for chronic kidney disease – based on the level of the serum creatinine and the estimated glomerular filtration rate (eGFR) – and its sequelae, which can include hypertension, anemia, and gout.

Affected individuals are encouraged to prepare for kidney transplantation, the definitive treatment of ADTKD-*MUC1*, by staying in optimal health (e.g., by exercising, avoiding obesity and tobacco usage, and maintaining

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strict control of hypertension, dyslipidemia, and other cardiovascular risk factors). Kidney transplantation is curative; the outcome is excellent.

Surveillance: Measurement of hemoglobin, serum concentrations of uric acid and creatinine and blood pressure annually prior to entering CKD Stage 3. Thereafter, follow up is determined by the treating nephrologist.

Agents/circumstances to avoid: Affected individuals should follow general recommendations for chronic kidney disease.

Pregnancy management: The use of ACE inhibitors should be avoided during pregnancy, as they can result in fetal damage and death. Women who are pregnant, planning a pregnancy, or not actively avoiding pregnancy should be transitioned to another antihypertensive medication. Allopurinol therapy should be stopped during pregnancy, if possible.

Evaluation of relatives at risk: For early diagnosis and treatment: It is appropriate to identify as early as possible apparently asymptomatic at-risk adult relatives who have the familial *MUC1* variant in order to monitor their serum creatinine levels and promptly initiate treatment and awareness of agents/circumstances to avoid. For kidney donation: Any relative who is a potential kidney donor should undergo molecular genetic testing to clarify the relative's genetic status so that only those who do not have the familial *MUC1* pathogenic variant are evaluated further.

Genetic counseling

ADTKD-*MUC1* is inherited in an autosomal dominant manner. Each child of an affected individual has a 50% chance of inheriting the *MUC1* pathogenic variant. Prenatal testing for *MUC1* pathogenic variants is not available in the US at this time.

Diagnosis

Autosomal dominant tubulointerstitial kidney disease – *MUC1* (ADTKD-*MUC1*) is caused by a heterozygous *MUC1* pathogenic variant which results in the creation of a specific frameshift protein (MUC1fs) responsible for slowly progressive chronic kidney disease, the sole manifestation of this disorder.

Consensus clinical diagnostic criteria for ADTKD-*MUC1* have been published [Eckardt et al 2015] (full text).

Suggestive Findings

ADTKD-*MUC1* **should be suspected** in individuals with the following clinical, laboratory and imaging findings, and family history.

Clinical Findings

Slowly progressive chronic tubulointerstitial kidney disease, evident as a slowly rising serum creatinine in the absence of hematuria and protein, is the sole clinical manifestation of this disorder; all other findings are secondary.

Laboratory Findings

The majority of affected individuals are asymptomatic when abnormal laboratory findings initially appear, usually in the late teens or early twenties.

- **Estimated glomerular filtration rate (eGFR),** calculated from the serum creatinine, is a measure of kidney function. Normal value is 90-140 mL/min/1.73m^2.

- The eGFR may decrease in childhood. The eGFR in ~50% of affected children is <90mL/min/1.73m^2 by age 15 years. Note: The eGFR is rarely <60 mL/min/1.73m^2 in affected children younger than age 18 years [Bleyer et al 2022].
- In contrast, in some individuals, the eGFR may not begin to decrease until adulthood; 14% of individuals ages 20 to 29 years (from an ADTKD-*MUC1* cohort of 311) had an eGFR >90 mL/min/1.73m^2, and 1% of individuals ages 30 to 49 years had an eGFR >90 mL/min/1.73m^2 [Authors, unpublished observations].

- **Urinary sediment** is bland (i.e., little blood or protein). Hematuria is generally not present; excretion of protein is <500 mg/24h except when chronic kidney disease (CKD) is advanced.

Imaging

Renal ultrasound examination is normal or shows small kidneys consistent with progressive CKD. As with CKD of other causes, occasional cysts may be seen.

Family History

Family history is consistent with **autosomal dominant inheritance** (i.e., the mother or father of the proband is also affected). Although individuals with no family history of the disorder are unlikely to have ADTKD-*MUC1*, *de novo* variants may occur; thus, the absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

NOTE: Kidney biopsy should **NOT** be performed because it is an invasive procedure with some risk, and histopathologic findings are too nonspecific to reliably identify ADTKD-*MUC1* (see Clinical Description). Molecular genetic testing, the gold standard for diagnosis, is safer and less expensive than kidney biopsy.

The diagnosis of ADTKD-*MUC1* **is established** in a proband with suggestive clinical findings and molecular genetic testing that reveals a heterozygous pathogenic (or likely pathogenic) variant in *MUC1* that results in the creation of a specific frameshift protein (MUC1fs) responsible for the pathogenic changes in this disorder [Kirby et al 2013] (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *MUC1* variant of uncertain significance does not establish or rule out the diagnosis.

Because of the complex molecular genetics of ADTKD-*MUC1,* the following stepwise approach to testing is recommended.

Step 1

Use of an inherited kidney disease multigene panel including *UMOD, REN*, and other genes of interest (see Differential Diagnosis):

- In 99% of individuals with ADTKD-*MUC1,* the causative *MUC1* variants occur within the variable-number tandem repeat (VNTR) domain, with 95% of these variants being a cytosine duplication within a sequence of seven cytosines. These variants **cannot be identified** using current clinically available multigene panels [Kirby et al 2013] or whole-exome or whole-genome sequencing (see Molecular Genetics, **Laboratory technical considerations**).
- Clinically available multigene panels that include *MUC1* will identify fewer than 1% of the causative variants (i.e., those that occur before the VNTR domain).

Step 2

If the multigene panel testing used in Step 1 does not identify a cause for the individual's clinical findings, consider use of a laboratory specifically performing *MUC1* targeted analysis. (See Molecular Genetics, **Laboratory technical considerations** for more information on this *MUC1* genetic analysis and its clinical availability.) Such targeted *MUC1* analysis will reliably identify the cytosine duplication that is responsible for approximately 95% of cases of ADTKD-*MUC1* but may miss other, rare pathogenic variants.

Step 3

If the specific *MUC1* genetic analysis recommended in Step 2 does not identify a cause for the individual's clinical findings, consider referral to an academic center with research expertise in identifying evidence of *MUC1* pathogenic variants that may not be identified by specific *MUC1* genetic analysis [Živná et al 2018]. (See Author Notes.)

Table 1. Molecular Genetic Testing Used in ADTKD-*MUC1*

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MUC1	Targeted analysis for pathogenic variants [3]	All variants identified to date [4]

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. Pathogenic variants are not identifiable by routine sequence analysis (Sanger sequencing or next generation sequencing) [Kirby et al 2013]. See Molecular Genetics, **Laboratory technical considerations** for information on methods used and clinical test availability.
4. Evidence suggests that some families with ADTKD-*MUC1* could have a *MUC1* alteration not detected by current clinically available test methods [Živná et al 2018].

Clinical Characteristics

Clinical Description

Autosomal dominant tubulointerstitial kidney disease – *MUC1* (ADTKD-*MUC1*) is characterized by slowly progressive tubulointerstitial disease that leads to end-stage renal disease (ESRD) and the need for dialysis or kidney transplantation.

The rate of loss of kidney function for individuals is variable within and between families, with a median age of onset of ESRD of 46 years [Olinger et al 2020]; however, the age range of ESRD is extremely variable, with rare individuals developing ESRD before age 20 years and some affected individuals not having ESRD past age 70 years.

Onset. ADTKD-*MUC1* rarely manifests in childhood. Abnormal serum creatinine concentration or reduced estimated glomerular filtration rate (eGFR) may initially appear in the late teens or early twenties (see Suggestive Findings).

Progression. With time, kidney function slowly worsens and serum creatinine concentration slowly rises from the normal range to the high normal range, and then to above normal.

As kidney function worsens, manifestations of chronic kidney disease (CKD) develop, including high blood pressure, gout, and anemia.

Gout in ADTKD-*MUC1* is not a primary manifestation of the disease and is solely related to progressive CKD and the loss of ability to excrete uric acid. In one study, hyperuricemia was found in approximately 50% of

individuals with ADTKD-*MUC1* with CKD and in 81% of individuals with ESRD [Stavrou et al 2002]. Gout was reported in five of 75 affected individuals.

Kidney function progressively worsens until dialysis or kidney transplantation is required.

Post transplantation. Because ADTKD-*MUC1* does not recur in the transplanted kidney, affected individuals are excellent transplant candidates [Cormican et al 2020].

Other. Kidney biopsy reveals focal tubular atrophy, secondary glomerular scarring, and interstitial fibrosis. Biopsy findings are nonspecific.

Genotype-Phenotype Correlations

There are no known genotype-phenotype correlations.

Penetrance

Penetrance is complete.

Nomenclature

ADTKD-*MUC1* was historically referred to as medullary cystic kidney disease type 1 (MCKD1). MCKD1 is a misnomer in that cysts in the renal medulla are not a common clinical characteristic, and the presence of medullary cysts is not a good predictor of the presence of ADTKD-*MUC1*.

According to the 2015 nomenclature [Eckardt et al 2015], the term "autosomal dominant tubulointerstitial kidney disease" (ADTKD) refers to disorders characterized by the following [Bleyer et al 2010]:

- Autosomal dominant inheritance
- Slowly progressive chronic tubulointerstitial kidney disease resulting in end-stage renal disease (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

Prevalence

ADTKD-*MUC1* is estimated to affect one to four individuals per million population [Devuyst et al 2019]; however, this is likely an underestimate, as diagnosis is difficult due to unremarkable clinical findings and the inability to include *MUC1* molecular genetic testing in multigene panels. It is estimated that 1% of individuals with ESRD harbor heterozygous *UMOD* pathogenic variants; the prevalence of ADTKD-*UMOD* and of ADTKD-*MUC1* is believed to be similar [Devuyst et al 2019].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *MUC1*.

Differential Diagnosis

See Figure 1 for the recommended testing strategy for the diagnosis of inherited kidney disease.

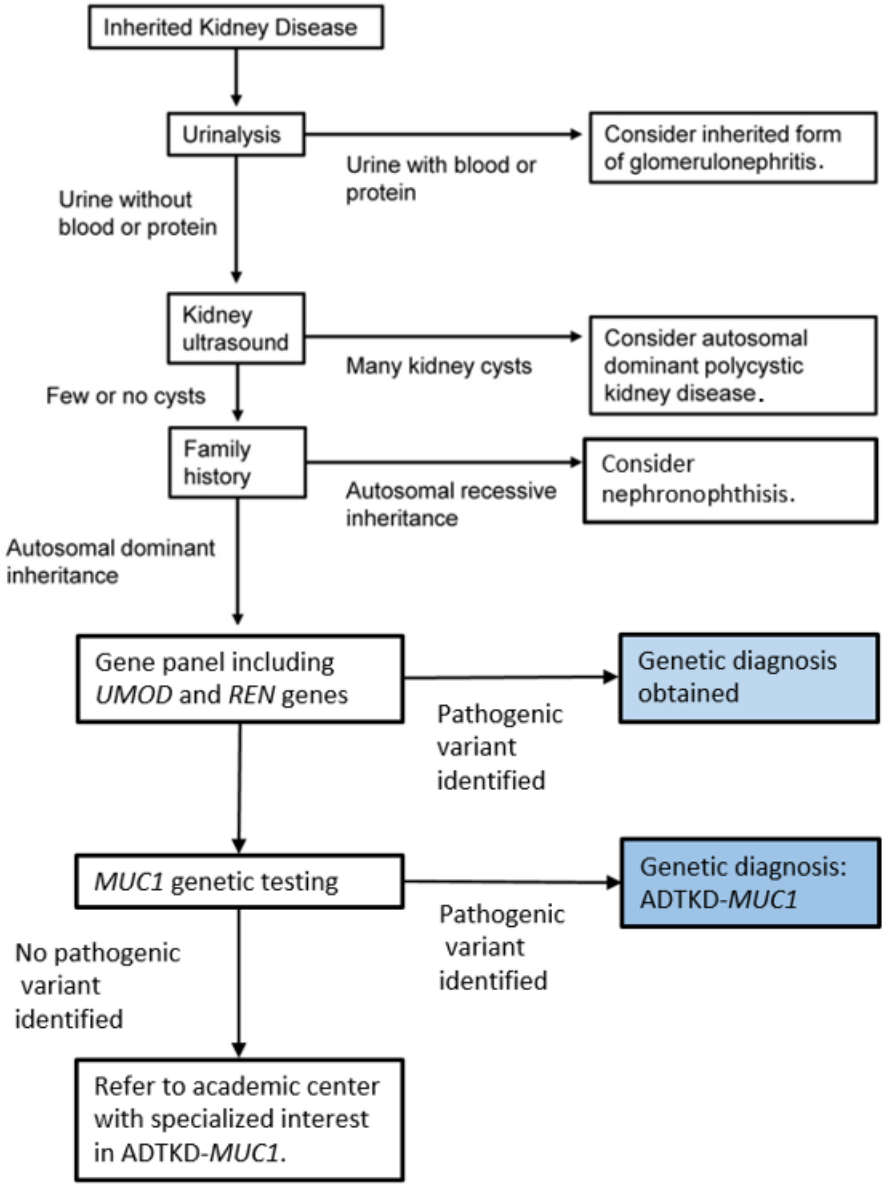

Figure 1. Testing strategy for inherited kidney disease – 2021 update

Urinalysis

If blood and protein are present, consider evaluation for inherited glomerulonephritis. If the urine sediment is bland (trace or no blood and protein <500 mg/24 h), obtain a family history to determine the likely inheritance pattern. If autosomal recessive (i.e., only sibs are affected), consider autosomal recessive polycystic kidney disease or the group of disorders termed "nephronophthisis" (see Table 2).

Renal Imaging

Renal imaging should always be performed. Ultrasound examination is typically performed first. If numerous cortical and medullary cysts and enlarged kidneys are present, consider autosomal dominant polycystic kidney disease (ADPKD).

If the number of cysts is fewer than required for a diagnosis of ADPKD, the family history suggests autosomal dominant inheritance, the urine is bland, the kidneys are normal or reduced in size with or without medullary

cysts, and renal histology (if performed) has shown interstitial fibrosis, consider screening for pathogenic variants in *UMOD*, *REN*, or *MUC1*.

The most common condition in the differential will be autosomal dominant tubulointerstitial kidney disease – *UMOD* (ADTKD-*UMOD*) [Bleyer et al 2010]. Gout occurs in approximately 50% of individuals with ADTKD-*UMOD* and develops before the onset of chronic kidney disease [Kidd et al 2020]. However, many individuals and families with ADTKD-*UMOD* may not have gout, and their presentation is identical to that of ADTKD-*MUC1* [Bleyer et al 2010].

If family members have a history of anemia in childhood and mildly elevated serum potassium concentrations, consider autosomal dominant tubulointerstitial kidney disease – *REN* [Živná et al 2009].

Table 2. Monogenic Kidney Diseases in the Differential Diagnosis of ADTKD-*MUC1*

Gene(s)	Disorder	MOI	Renal Phenotype	Distinguishing Features of this Disorder vs ADTKD-*MUC1*
Most likely disorders to consider				
UMOD	ADTKD-*UMOD*	AD	Proteinuria is rare; slowly progressive CKD	Gout often occurs during adolescence in ADTK-*UMOD*. Otherwise, it presents very much like ADTKD-*MUC1*.
REN	ADTKD-*REN*	AD	Slowly progressive CKD w/anemia, metabolic acidosis, hyperkalemia, & mild hypotension, often presenting in childhood. Gout may occur in late teens & adolescence.	ADTKD-*REN* presents more often in childhood than ADTKD-*MUC1* & is assoc w/hyperkalemia, metabolic acidosis, & anemia.
Other disorders to consider				
CEP290 *INVS* *IQCB1* *NPHP1* *NPHP3* *NPHP4* *TMEM67* (19 genes [1])	Isolated nephronophthisis (NPH)	AR	Tubulointerstitial kidney disease; often seen in childhood & can be assoc w/anemia & mild hypotension	• Absence of affected family members in multiple generations • ESRD usually occurs earlier (affected persons usually require dialysis in teens & early 20s).
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 > than 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.
DNAJB11 [4]	Atypical ADPKD-ADTKD	AD	Slowly progressive chronic kidney disease, multiple renal cysts.	Numerous kidney cysts are common.

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Renal Phenotype	Distinguishing Features of this Disorder vs ADTKD-*MUC1*
HNF1B	ADTKD-*HNF1B*	AD		Variable presence of other manifestations accompany renal disease, incl MODY, hyperuricemia, hypomagnesemia & gout, CKD, CAKUT, & unexplained liver function test abnormalities.
mtDNA	m.547A>T [5]	Mat	Chronic tubulointerstitial kidney disease	
PAX2	*PAX2*-related disorder	AD	Glomerular proteinuria & hematuria	Glomerular renal disease w/hematuria, proteinuria, & ocular coloboma
SEC61A1	ADTKD-*SEC61A1*	AD	Slowly progressive CKD	• Leukopenia (w/abscess formation), intrauterine & postnatal growth restriction • Renal disease often presents in childhood.

AD = autosomal dominant; AR = autosomal recessive; CAKUT = congenital anomalies of the kidneys and urinary tract; CKD = chronic kidney disease; ESRD = end-stage renal disease; Mat = maternal; MODY = maturity-onset diabetes of the young; MOI = mode of inheritance; mt(DNA) = mitochondrial; XL = X-linked

1. Listed genes represent the most common genetic causes of isolated nephronophthisis (NPH). 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 caused by pathogenic variants in *MUC1* (ADTKD-*MUC1*) have been published [Eckardt et al 2015] (full text). At present, there are no specific therapies for ADTKD-*MUC1*, and affected individuals should receive symptomatic care appropriate for their stage of chronic kidney disease.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ADTKD-*MUC1*, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with ADTKD-*MUC1*

System/Concern	Evaluation
Hypertension risk	Measurement of blood pressure
Anemia	Hemoglobin level
Acidosis	Serum bicarbonate (part of basic metabolic panel)
Hyperkalemia	Serum potassium (part of basic metabolic panel)
Kidney function	Serum creatinine (part of basic metabolic panel)
Gout risk	Serum urate concentration

Table 3. continued from previous page.

System/Concern	Evaluation
Kidney structure	Renal ultrasound exam
Kidney function	Nephrology referral
Genetic counseling	By genetics professionals [1] to inform affected persons re nature, MOI, & implications of ADTKD-*MUC1* 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.

Treatment follows standard guidelines for chronic kidney disease – based on the level of the serum creatinine and estimated glomerular filtration rate (eGFR) – and its sequelae, which can include hypertension, anemia, and gout.

Affected individuals are encouraged to prepare for kidney transplantation, the definitive treatment of ADTKD-*MUC1*, by staying in optimal health (e.g., by exercising, avoiding obesity and tobacco usage, and maintaining strict control of hypertension, dyslipidemia, and other cardiovascular risk factors).

Affected individuals should be referred for evaluation for kidney transplantation when their eGFR declines to <19 mL/min/1.73m^2. (See Evaluation of Relatives at Risk for kidney donation.)

Kidney transplantation is curative; the outcome is excellent [Cormican et al 2020].

Surveillance

Monitor the following annually, starting at the time of diagnosis and continuing until chronic kidney disease (CKD) Stage 3:

- Hemoglobin concentration
- Serum concentrations of uric acid and creatinine
- Blood pressure

After CKD Stage 3, follow up is determined by the treating nephrologist.

Agents/Circumstances to Avoid

Affected individuals should follow general recommendations for chronic kidney disease.

Evaluation of Relatives at Risk

For early diagnosis and treatment. It is appropriate to identify as early as possible apparently asymptomatic at-risk adult relatives who have the familial *MUC1* variant in order to monitor their serum creatinine levels and promptly initiate treatment and awareness of Agents/Circumstances to Avoid. (Note: Normal kidney function in and of itself does not exclude ADTKD-*MUC1* in at-risk family members.) See Related Genetic Counseling Issues for discussion of testing of children.

For kidney donation. Any relative who is a potential kidney donor should undergo molecular genetic testing to clarify the relative's genetic status so that only those who do not have the familial *MUC1* pathogenic variant are evaluated further.

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

Pregnancy Management

Pregnancies in women with ADTKD tend to have better outcomes for themselves and their children compared to women with other kidney diseases who have similar levels of kidney function: about 20% of women develop hypertension during pregnancy, about 10% deliver before 38 weeks' gestation, and the rate of cæsarean section is not increased. Fetal outcomes are in general excellent [Authors, unpublished data].

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. Ideally, women should avoid taking either an ACE inhibitor or allopurinol during pregnancy.

- **ACE inhibitors.** The use of ACE inhibitors during pregnancy can result in fetal damage and death. Women who are pregnant, planning a pregnancy, or not actively avoiding pregnancy 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).

The acute treatment of gout may require the use of other medications, such as prednisone or colchicine.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Of note, basic science and animal studies have identified a potential therapy for the small molecule BRD4780, which was found to clear MUC1 frameshift protein deposits in cells in culture, organoids, and a mouse model of ADTKD-*MUC1*. This compound is anticipated to enter clinical trials within the next two to five years [Dvela-Levitt et al 2019].

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 – *MUC1* (ADTKD-*MUC1*) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

Most individuals diagnosed with ADTKD-*MUC1* have an affected parent.

- A proband with ADTKD-*MUC1* may have the disorder as the result of a *de novo* pathogenic variant. Because only a few simplex cases (i.e., a single occurrence in a family) have been identified, the proportion of ADTKD-*MUC1* caused by a *de novo* pathogenic variant is unknown.
- 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 and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - 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.
- The family history of an individual with ADTKD-*MUC1* may appear to be negative because of early death of the parent before the onset of symptoms, a milder phenotypic presentation, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the *MUC1* pathogenic variant identified in the proband.

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 *MUC1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Although the penetrance of ADTKD-*MUC1* is complete, the rate of progression of kidney disease varies among heterozygous sibs.
- If the proband has a known *MUC1* 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 *MUC1* pathogenic variant but are clinically asymptomatic, sibs are still presumed to be at increased risk for ADTKD-*MUC1* 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-*MUC1* has a 50% chance of inheriting the *MUC1* 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 *MUC1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

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

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the *MUC1* 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.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- In general, predictive testing of minors for adult-onset disorders is considered inappropriate unless such testing has a compelling medical benefit. Concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For parents desiring closer surveillance of their children, blood pressure can be monitored and serum creatinine can be tested on an annual basis.
  - It is important for parents to realize that normal serum creatinine levels in childhood do not rule out ADTKD-*MUC1* and the child may develop worsening kidney function with age.
  - For children in whom the serum creatinine is elevated, genetic testing can be considered to rule out other possible causes of kidney disease.
- Genetic testing may be considered in children when affected family members have an earlier age of onset of kidney disease and end-stage renal disease.
- Bleyer et al [2019] describe high levels of personal satisfaction reported by seven individuals who underwent predictive ADTKD-*MUC1* testing as children.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of ADTKD-*MUC1*, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- Women with ADTKD-*MUC1* who are considering pregnancy should be advised that, if appropriate, pregnancy should not be deferred but considered at younger ages when kidney function is better (as the decline in eGFR occurs during child-bearing years) and there is less chance of complications.
- 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

Prenatal testing for the *MUC1* pathogenic variant is not available in the US at this time.

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. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

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

- **MUC1-Related Kidney Disease Registry**

  Dr. Anthony Bleyer has established a registry of individuals with MUC1 pathogenic variants. Clinical genetic testing is available at no cost. Patient educational materials (including pamphlets and webinars) are available upon request. Please contact Dr. Bleyer 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 -- MUC1: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
MUC1	1q22	Mucin-1	MUC1	MUC1

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 -- MUC1 (View All in OMIM)

158340	MUCIN 1, CELL SURFACE ASSOCIATED; MUC1
174000	TUBULOINTERSTITIAL KIDNEY DISEASE, AUTOSOMAL DOMINANT, 2; ADTKD2

Molecular Pathogenesis

Mucin-1, encoded by *MUC1*, a membrane-anchored mucoprotein found in breast, respiratory tract, sebaceous gland, salivary gland, and kidney tubules, is important in signal transduction. Mucin-1 provides (among other functions) a protective barrier that prevents pathogens from accessing the cell surface.

MUC1 pathogenic variants causing ADTKD-*MUC1* always result in the creation of the same frameshift protein (MUC1fs) (see ***MUC1*-specific laboratory technical considerations**). This protein accumulates within the endoplasmic reticulum Golgi intermediate compartment (ERGIC) [Dvela-Levitt et al 2019]. In individuals with ADTKD-*MUC1*, MUC1fs is found in all cell types normally expressing *MUC1* (including breast, gastric mucosa, and lung); however, clinical manifestations of disease only occur in the kidney, where its deposition leads to accelerated apoptosis [Staubach et al 2018], tubular cell death, nephron dropout, and progressive chronic kidney disease.

Mechanism of disease causation. Gain of function. All affected individuals harbor pathogenic variants creating the same MUC1fs protein; no person with this disorder has had truncating variants or other variants that would result in loss of function [Olinger et al 2020].

MUC1-specific laboratory technical considerations

- *MUC1* contains within the coding region a domain of multiple variable-number tandem repeats (VNTRs), called the "VNTR domain."
- Each VNTR is an oligonucleotide comprising 60 nucleotides (also referred to as a "60-mer"). Each 60-nucleotide repeat includes a sequence of seven cytosines (also called "a 7-cytosine tract").
- The normal number of 60-mer VNTRs comprising a VNTR domain ranges from 20 to 125.

In most *MUC1* disease-causing variants an additional nucleotide inserted within a seven-cytosine sequence causes a frameshift that encodes an abnormal MUC1 protein called a "frameshift protein," known as MUC1fs. The most commonly inserted nucleotide is cytosine; less commonly, it is a different nucleotide (e.g., adenosine).

The additional nucleotide can either be within the VNTR [Kirby et al 2013] or immediately before the VNTR [Yamamoto et al 2017]; however, in approximately 95% of cases, MUC1fs results from insertion of a cytosine in the seven-cytosine sequence within the VNTR [Authors, personal observations based on 196 families with ADTKD-*MUC1*]. See Figure 2.

Clinical testing issues. Due to the high guanosine-cytosine content and the repetitive nature of the 60-mer VNTR sequences, variants within a VNTR cannot be identified by commonly used sequencing methods (e.g., exome sequencing, Sanger sequencing).

The CLIA-certified Broad Institute of Harvard and MIT laboratory performs targeted analysis for the common *MUC1* frameshift variant (i.e., insertion of a cytosine within the 7-cytosine sequence) and the less common frameshift variant (insertion of an adenine in a 7-cytosine sequence). (See Author Notes regarding testing available at no cost to families with autosomal dominant tubulointerstitial kidney disease.)

Other published test methods for detecting variants not identified by standard genetic sequencing techniques include the following:

- Long-read single-molecule real-time (SMRT) sequencing can identify the insertion of a cytosine within the seven-cytosine sequence as well as many (but not all) other disease-causing *MUC1* variants. This method also determines the length and structure of the *MUC1* VNTR and the exact position of the variant within the VNTR [Wenzel et al 2018, Knaup et al 2018, Wang et al 2020].
- Illumina-based sequencing of *MUC1* VNTR amplicons can identify the cytosine insertion as well as many (but not all) other disease-causing variants [Živná et al 2018].

Table 4. Notable *MUC1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002456.5 NP_002447.4	c.253C>T	p.Gln85Ter	Presence of an adenine in the 7-cytosine sequence w/in a VNTR results in encoding of MUC1fs protein.[1] Exact position of this VNTR w/in the VNTR domain is unknown & may vary between families [Živná et al 2018].
NC_000001.10	g.(155160963_155162030)insC [2]	Frameshift resulting in early termination	Insertion of a cytosine w/in 7-cytosine sequence in a VNTR is most common variant encoding MUC1fs protein. Exact position of this VNTR in VNTR domain is unknown & may vary between families [Kirby et al 2013].
	g. 155161911_155161912delAG	Frameshift resulting in early termination	Occurs before VNTR domain but nonetheless encodes MUC1fs protein [Yamamoto et al 2017]
	g.(155160963_155162030)insG [2]	Frameshift resulting in early termination	Variant (not detected by clinically available *MUC1* genetic testing) encodes MUC1fs protein [Živná a et al 2018].

Table 4. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	g.(155160963_155162030)delinsAT [2]	Frameshift resulting in early termination	Variant (not detected by clinically available *MUC1* genetic testing) encodes the MUC1fs protein [Živná et al 2018].
	g.(155160963_155162030)dupGCCGGCCCCGGGTCC [2]	Frameshift resulting in early termination	Variant (not detected by clinically available *MUC1* genetic testing) encodes MUC1fs protein [Živná et al 2018].

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.
VNTR = variable-number tandem repeat
1. Figure 2 illustrates a hypothetic example.
2. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

Dr Stanislav Kmoch (skmoch@lf1.cuni.cz) and Dr Anthony Bleyer (ableyer@wakehealth.edu) are actively involved in clinical research regarding individuals with ADTKD-*MUC1* and other forms of inherited kidney disease and would be happy to communicate with individuals who have any questions regarding diagnosis or other considerations.

MUC1 molecular genetic testing is available at several commercial laboratories in Europe. Clinical *MUC1* genetic testing is available free of charge through the Broad Institute of Harvard and MIT. Contact Dr Bleyer (ableyer@wakehealth.edu) to inquire about testing or to review *MUC1* variants of uncertain significance.

Dr Bleyer is also 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.

Revision History

- 21 October 2021 (bp) Comprehensive update posted live
- 30 June 2016 (ha) Comprehensive update posted live
- 15 August 2013 (me) Review posted live
- 30 April 2013 (ab) Original submission

Figure 2. Illustration of the mechanism by which the MUC1fs protein is encoded within a 60-mer block of repeated sequence that forms a *MUC1* variable-number tandem repeat (VNTR). In this figure of a hypothetic coding sequence of ten 60-mer blocks of repeated sequence, the seven-cytosine sequence of the first 60-mer repeat has an additional cytosine (red arrow) that causes a shift in the reading frame (i.e., it is a *MUC1* frameshift variant). If, for example, the insertion of this cytosine were to occur in the 30th VNTR of a 100-VNTR domain, the first 30 VTNRs would encode the protein properly, whereas the next 70 VTNRs would encode a truncated (abnormal) MUC1fs protein (as the last VNTR will have a stop codon).

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