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Autosomal Dominant Tubulo-Interstitial Kidney Disease

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Abstract

There are three major forms of autosomal dominant tubulo-interstitial kidney disease (ADTKD): ADTKD due to *UMOD* mutations, *MUC1* mutations, and mutations in the *REN* gene encoding renin. Lack of knowledge about these conditions contributes to frequent non-diagnosis, but with even limited knowledge, nephrologists can easily obtain a diagnosis and improve patient care. There are three cardinal features of these disorders: 1) the conditions are inherited in an autosomal dominant manner and should be considered whenever both a parent and child suffer from kidney disease; the presence of even more affected family members provides further support. 2) These conditions are associated with a bland urinary sediment, ruling out glomerular disorders. 3) There is a variable rate of decline in kidney function. The mean age of ESRD is approximately 45, but the range is from 17 to >75. ADTKD-*UMOD* is often but not always associated with gout in the teenage years. ADKTKD-*REN* is associated with signs of hyporeninemia: mild hypotension, mild hyperkalemia, anemia in childhood, and hyperuricemia and gout in the teenage years. The only clinical manifestation of ADTKD-*MUC1* is slowly progressive chronic kidney disease. Diagnosis should be made by genetic testing, and kidney biopsy should be avoided.

Keywords

Autosomal dominant; tubulo-interstititial; renin; uromodulin; mucin-1; inherited

Autosomal dominant tubulo-interstitial kidney disease (ADTKD) refers to disorders with the following characteristics: (1) autosomal dominant inheritance, (2) bland urinary sediment with no or trace proteinuria, and (3) slowly progressive chronic kidney disease (CKD) with a variable age of onset of end-stage renal disease, ranging from ages 17 to >75 (see Table 1). There are three major subgroups of ADTKD. ADTKD-*UMOD* - is caused by mutations in the *UMOD* gene encoding uromodulin (Tamm Horsfall glycoprotein) and associated with a high prevalence of adolescent gout; ADTKD-*MUC1* is caused by mutations in the *MUC1*

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gene encoding mucin-1. ADTKD-*REN* is caused by mutations in the *REN* gene that encodes renin and is associated with signs of relative hyporeninemia.

Case example

A 21 year old white man is referred for evaluation of an elevated serum creatinine level of 1.4 mg/dl (124 mmol/L), which was found as part of routine laboratory studies for a life insurance physical. The patient is otherwise healthy, on no medications, and has no known risk factors for kidney disease. The patient's father required kidney transplantation at age 45, and the patient's paternal uncle has chronic kidney disease at the age of 55. The paternal grandfather died at 70 of kidney failure prior to the advent of dialysis. Physical examination is unremarkable, and the patient's urinalysis surprisingly reveals no protein or blood. A renal ultrasound is normal. A kidney biopsy is performed and is nondiagnostic, revealing tubulo-interstitial scarring without an inflammatory infiltrate. A diagnosis of hereditary nephrosclerosis is made. Several months later, the patient attends a family reunion and finds out that several of his family members have been diagnosed with ADTKD-*MUC1*. He undergoes *MUC1* genetic testing and is found to have a mutation in the *MUC1* gene.

General principles in diagnosis

The key diagnostic feature of ADTKD is the presence of at least an affected parent and child with chronic kidney disease. From a clinical standpoint, the lifetime chance for a white individual of developing end-stage kidney disease (ESRD) is about 3.6%.[1] The chance that two individuals from the same family will have different kidney diseases and develop ESRD is about 1 in 1,000, while the chance that the child of an affected individual will have kidney disease due to an autosomal dominant inherited disorder is 1 in 2. Thus, when a parent and child have kidney disease, autosomal dominant disorders should be strongly considered. Once the inheritance pattern has been identified, it is important to evaluate the urine. The presence of blood or protein in the urine suggests a hereditary glomerular disorder such as Alport Syndrome. The presence of a bland urinary sediment suggests ADTKD. In the vast majority of patients with ADTKD, there is no proteinuria or trace proteinuria. Occasional individuals may have proteinuria up to 500 mg/d. A kidney biopsy is usually nonspecific in ADTKD, showing interstitial scarring with the absence of glomerular disease or an inflammatory infiltrate. These findings are not pathognomonic for ADTKD, and thus a definitive diagnosis cannot be made. For this reason, genetic analysis is the preferred diagnostic approach.

Why is it important to pursue a genetic diagnosis? 1) Once a genetic diagnosis is established, family members who wish to donate a kidney can be tested for the genetic mutation to see if they qualify as donors. In both ADTKD-*MUC1* and ADTKD-*UMOD*, affected individuals may have normal serum creatinine values past age 20, and there are at least three cases known to the authors of affected individuals being kidney donors to family members. 2) Identifying a genetic diagnosis is helpful in establishing follow-up and preventing kidney biopsies for diagnosis in other family members. 3) For ADTKD-*REN*, specific therapies are available, and for ADTKD-*UMOD*, family members may wish to consider taking allopurinol (see below). 3) Once a disease is diagnosed, family members

may wish to work with groups that are trying to identify treatments for these disorders. 4) ADTKD has affected many families for generations. Often, affected individuals simply want to know the specific cause of their disorder.

Rare inherited disorders may be difficult for the nephrologist to diagnose, as there are a large number of these conditions, and new ones continue to be identified. Both patients and nephrologists may initiate data searches on the Internet to identify the causes of such conditions. For some rare disorders, patient-led foundations or clinical centers may have a specific interest and may have developed excellent, informative websites. Unfortunately, many websites regarding these conditions may be outdated or inaccurate. Websites from many medical centers often provide limited, generic text that serves as a form of advertisement and are unhelpful. It is therefore important that patients and physicians have access to current information about these disorders. Resources that are highly reliable and provide pertinent accurate information when performing such a search include UpToDate, GeneReviews, and PubMed. Searching these sites will usually provide a clue to the diagnosis. If these sites are unhelpful, a search of the Internet may still be used. For ADTKD, we recommend the following websites: http://www.uptodate.com/contents/autosomal-dominant-tubulointerstitial-kidney-disease-medullary-cystic-kidney-disease, http://kdigo.org/home/conferences/adtkd/, http://rarediseases.org/rare-diseases/autosomal-dominant-interstitial-kidney-disease/, http://www.ukdcure.org/learn_more. https://ghr.nlm.nih.gov/condition/uromodulin-associated-kidney-disease, and http://www.wakehealth.edu/Nephrology/Medullary-Kidney-Disease/Research-Team-Mucin-1-Kidney-Disease.htm

The conditions causing ADTKD are rare, but, because of the autosomal dominant inheritance, a significant number of family members may be affected. Thus, obtaining a diagnosis in one family member will be beneficial to many other family members who may be affected. Once a diagnosis is made, it is important to contact other potentially affected family members and provide information regarding the specific familial condition. Often, unaffected family members believe the condition can “skip a generation” and live under a persistent fear that their children will develop kidney failure. Thus, providing information to all family members, including unaffected individuals is important. While it is important to inform other family members of the possibility they may have the condition, the decision for genetic testing is personal. At present, there are no specific treatments for ADTKD other than ADTKD-*REN*. Testing of children for genetic conditions in which a specific therapy is unavailable is discouraged.[2]

ADTKD-*UMOD*

ADTKD-*UMOD* is considered a rare disease, with less than 2,000 families identified worldwide with this disorder.

Clinical manifestations

The most common manifestations of ADTKD-*UMOD* include hypouricosuric hyperuricemia and chronic kidney disease. It is important to note that hyperuricemia is present in most, but not all individuals and families with this condition.[3] Affected

individuals frequently have an elevated serum urate level early in life, resulting from decreased urinary uric acid excretion.[4] In the early to late teen years, patients may develop gout. The symptoms are typical of those found in older individuals, with the big toe or ankle often being affected. Gout is often misdiagnosed by clinicians as over-exertion or a sports injury. As there is frequently a strong family history of gout, family members often make the diagnosis. As patients grow older, glomerular filtration rate declines. There is a large variation in the rate of progression of kidney disease that remains unexplained. The mean age for starting dialysis in our cohort is 47 years, with a range of 19 to >75.

Genetics and Pathophysiology

Mutations in the *UMOD* gene encoding uromodulin (also known as Tamm Horsfall glycoprotein) have been identified as the cause of ADTKD-*UMOD*.[5] Uromodulin is a membrane-anchored protein that is expressed only in tubular cells in the thick ascending limb of Henle.[6] The uromodulin protein has a very high cysteine content. As it traverses the endoplasmic reticulum, the cysteine residues form disulfide bonds that allow the protein to achieve its final conformation.[7] The protein is then transported to the apical surface of the tubular cell where it is anchored to the membrane initially. Uromodulin then undergoes extracellular enzymatic cleavage and is excreted in the urine.[8]

While uromodulin has been studied for over five decades,[9] its function remains unclear. A genome-wide association study suggested that uromodulin may have a very mild effect on the risk of kidney stone development.[10] Studies of uromodulin knock-out mice have shown that they are prone to urinary tract infection when their bladders are instilled with bacteria.[11] However, it is important to point out that in individuals who have *UMOD* mutations – and produce very little uromodulin – an increased risk of urinary tract infections or nephrolithiasis has not been reported.[12] Recent investigations have uncovered a more important role for uromodulin. Laboratory studies have shown that uromodulin facilitates the transport of the furosemide-sensitive NKCC2 transporter to the surface of the thick ascending limb.[13] In addition, Mutig et al. demonstrated that uromodulin enhances the phosphorylation of NKCC2, which increases NKCC2 activity and sodium absorption.[13] Approximately 15% of the general population has a minor genetic variant in the *UMOD* promoter that results in decreased uromodulin production as compared to the major variant found in 85% of the population. Due to increased sodium excretion, these individuals with the minor variant have lower blood pressure readings, better kidney function, and less tubulo-interstitial fibrosis later in life than the 85% of individuals who have the major variant and produce more uromodulin.[14] These findings point to the importance of uromodulin in modulating sodium reabsorption in the thick ascending limb. Decreased uromodulin function or production results in decreased NKCC2 translocation to the apical surface, decreased sodium reabsorption, and increased sodium excretion.

Affected individuals with ADTKD-*UMOD* have one normal *UMOD* allele and one mutant allele. They suffer from both decreased production of normal uromodulin as well as the production of abnormal uromodulin. Decreased production of normal uromodulin results in decreased transport of the furosemide-sensitive transporter to the apical surface of the TALH. Patients develop a mild natriuresis that is compensated for by increased proximal

tubular sodium uptake. This proximal tubular sodium uptake is coupled with increased proximal tubular urate uptake. In this manner, volume homeostasis is maintained, but patients develop hypouricosuric hyperuricemia, which leads to gout early in life.[15]

In addition to a decrease in normal uromodulin production, patients also suffer from intracellular deposition of mutant uromodulin, which is central to the pathogenesis of kidney disease. Mutations in the *UMOD* gene result in the addition or a deletion of a cysteine residue in approximately half of all mutations that have been identified.[16] In all cases, the mutations result in amino acid changes that prevent the uromodulin molecule from folding correctly. The mutant uromodulin deposits within the cell, leading to accelerated apoptosis and cell death.[17] Tubular cell death is followed by nephron dropout, renal fibrosis, and progressive chronic kidney disease leading to ESRD. Mutations that result in truncation or lack of synthesis of uromodulin do not cause ADTKD-*UMOD*,[16] and uromodulin knockout mice have no or mild kidney disease,[18] showing that the deposition of the mutant uromodulin appears central to the pathogenesis and loss of kidney function.

Diagnosis

Uromodulin kidney disease should be suspected in individuals with a family history of kidney disease and a bland urinary sediment. Sometimes the diagnosis can be made based on the appropriate clinical picture and knowledge that another family member has undergone genetic testing and has been identified with a *UMOD* mutation.[19] Otherwise, uromodulin genetic analysis is available at commercial clinical laboratories.[20] When ordering *UMOD* genetic analysis, providing the laboratory with the family mutation, if known, will lower the cost of genetic analysis.

Treatment

Gout and hyperuricemia in patients with ADTKD-*UMOD* is easily treated with allopurinol or febuxostat.[19] Any affected individuals who develop gout should be started on one of these agents to prevent future gout attacks and the development of gouty tophi. Early reports suggested that allopurinol might slow progression of CKD.[21] It has subsequently become apparent that allopurinol will not stop progression, and it remains unclear if it will slow progression. It is important that physicians discuss the risk/benefit ratio with the parents of affected children. Starting allopurinol early in life will prevent gout from developing later and life and may be helpful in slowing progression of kidney disease. These benefits must be balanced against the rare risk of severe allergic reaction to allopurinol. In addition, it is extremely important to warn all women of child-bearing age that allopurinol may possibly have some teratogenic effects and should be stopped prior to pregnancy.[22]

As kidney disease progression is slow and *UMOD* mutations affect only the kidneys, patients are excellent candidates for kidney transplantation. Family members wishing to donate should undergo *UMOD* mutational analysis prior to donation, even if they appear to have normal kidney function. Every effort should be made to have patients with ADTKD-*UMOD* undergo pre-emptive transplantation. It is important to note that the disease will not recur in the transplanted kidney.

Future directions

We are studying genetic variants in the promoter of the *UMOD* gene to determine if they are responsible for the wide variation in age of ESRD seen in individuals with ADTKD-*UMOD*. We are hoping to conduct a genome wide association study (GWAS) to determine other genetic factors that may affect the age of onset of kidney failure. This study will require DNA samples on approximately 1,000 individuals with ADTKD-*UMOD*. Please consider referring any families with known or suspected ADTKD-*UMOD* to us for participation in this study.

ADTKD-*MUC1*

ADTKD-*MUC1* is considered a rare disease, with less than 1,000 families identified worldwide with this disorder.[23]

Clinical manifestations

Affected individuals have slowly progressive chronic kidney disease as the sole manifestation. The deterioration of kidney function is highly variable both within and between families.[24] The mean age of onset of ESRD in our cohort is 43 years, ranging from 17 to >75. The variation can be quite significant even between an affected parent and child. We have seen some cases where the child is on dialysis in their 30's and the 60 year old affected parent only has stage III CKD. An elevated serum creatinine usually is first identified in the late teens or early twenties. Over time, the serum creatinine slowly increases. Patients have no other symptoms from this disease, and the urinary sediment is bland. The renal ultrasound is unremarkable. Hypertension, gout, anemia, and progressive deterioration of kidney size occur in a similar manner and with a similar frequency as found in patients with other forms of chronic kidney disease.[25] In some patients there is an acceleration in the loss of eGFR when it declines below 30 ml/min/1.73m^2.

Genetics

Identification of the genetic cause of ADTKD-*MUC1* was exceedingly difficult, and only recently was a mutation in the *MUC1* gene encoding mucin-1 identified as the genetic cause of this condition.[23] Mucin-1 is a mucoprotein with two components.[26] There is an intracellular and membrane-spanning domain with an extracellular component. The extracellular component is formed by a 20 – 125 repetitive sequence units of 20 amino acids. This segment is rich in serine, proline, and threonine residues, which allow for extensive glycosylation, giving mucin its adherent and protective properties. The other component of mucin-1 is an intracellular portion that associates with the membrane spanning domain and is responsible for cell signaling. Mucin-1 is found on the apical surface of many epithelial cells throughout the body, including in the gastro-intestinal tract, mammary glands, respiratory tract, and sebaceous glands of the skin. Mucin-1 is also expressed in the thick ascending limb and distal convoluted tubule.

Most families with ADTKD-*MUC1* have a cytosine insertion within a tract of seven cytosines within a repetitive 60 nucleic acid sequence that codes for the 20 amino acid repetitive amino acid sequence described above.[23] The cytosine insertion results in the

creation of a specific, self-terminating frameshift peptide. This peptide carries a very high positive chargeand deposits intracellularly. All patients with this disorder create the same specific frameshift peptide. No affected families have been found to have a missense or nonsense mutation that results in truncation of the protein or the creation of a different frameshift peptide. Thus, this specific frameshift peptide is central to the pathogenesis of ADTKD-*MUC1*. In affected individuals, this mutated protein is deposited in cells throughout the body, but for some reason, clinical consequences are limited to the kidney. Here, the frameshift peptide deposits within the cells and leads to accelerated apoptosis, tubular cell death, nephron dropout, and progressive CKD.

At present, only the cytosine insertion in the seven cytosine tract can be determined by genetic analysis. We believe that other mutations that produce the same frameshift peptide (e.g. a thymidine insertion instead of a cytosine insertion) may cause ADTKD-*MUC1* and are currently undiagnosed. In a group of 21 families with clinical characteristics of ADTKD-*MUC1*, we were able to identify the MUC1 cytosine insertion in 13.[23] One family linked to the region of the *MUC1* gene did not have the cytosine insertion. Thus, we believe that there are families without the cytosine insertion who have ADTKD-*MUC1*, likely generating the abnormal frameshift peptide via another mutation.

Diagnosis

Clinically approved (CLIA) genetic testing for ADTKD-*MUC1* is restricted to the diagnosis of the cytosine insertion. This test is available free of charge from the Broad Institute and can be obtained by contacting Anthony Bleyer, MD (ableyer@wakehealth.edu). It is important to note that testing for the *MUC1* mutation is not a straightforward mutational analysis, and this test cannot be performed at commercial clinical laboratories at this time. Investigators are working on other genetic methods to identify mutations in the *MUC1* gene.

Treatment

There is at present no specific therapy for ADTKD-*MUC1*. Optimal therapy of CKD – control of blood pressure and secondary changes of chronic kidney disease – are the only available treatments. As these patients will progress to ESRD at a slow rate, and as this condition affects no other organs, these patients are excellent candidates for kidney transplantation. It is extremely important that any potential donors within the family be tested for the *MUC1* mutation, even if they appear to have normal kidney function.

Future directions

There are many key aspects of pathophysiology that need to be understood. It is known that the MUC1 frameshift peptide is very highly positively charged and deposits within the cytoplasm of affected cells. However, we still need to determine the relative importance of the deposition of the abnormal protein vs. the loss of functioning normal mucin-1. How the MUC1 frameshift peptide leads to pathologic changes also needs to be identified. We are also interested in determining why deposition of the MUC1 frameshift peptide is only problematic in the kidney, even though this protein deposits in many cell types and tissues throughout the body.

From a clinical standpoint, it is unclear why there is such a wide variation in the age of onset of ESRD. This variation is seen between families, but also within families. We are trying to determine genetic and environmental factors that are responsible for these findings and are planning to perform a genome wide association study (GWAS) to identify genetic factors associated with the age of onset of kidney failure.

ADTKD-*REN*

ADTKD-*REN* is a rare cause of ADTKD, with less than twenty families reported worldwide.

Clinical manifestations

Affected individuals have one normal allele producing renin and another allele produces an abnormal renin precursor (preprorenin). Patients suffer from aberrant translocation of the abnormal renin precursor into the endoplasmic reticulum, which gradually reduces the viability of renin-expressing cells in kidney. In addition, the decreased production of renin due to the presence of only one normal renin allele results in signs of a relative decrease in renin production.

Renin augments the production of hemoglobin in childhood, and affected individuals suffer from anemia from the first year of life.[27] Hemoglobin levels range from 8 to 11 g/dl. Often, the cause of hypoproliferative anemia in these patients is unexplained. Serum erythropoietin levels are decreased. Some patients are clinically asymptomatic, while other patients receive erythropoietin, which increases hemoglobin levels. The anemia resolves as the child enters adolescence, likely due to the effects of steroid hormones on erythropoietin production. Other symptoms of hyporeninemia also may present in childhood but are subtle. Blood pressure levels are usually on the low side, and serum potassium levels are mildly elevated. Individuals also suffer from hypouricosuric hyperuricemia and may develop gout in their teenage years and are also prone to acute kidney failure in childhood. In a similar manner to patients receiving angiotensin converting enzyme inhibitors, volume depletion and decreased renin levels can lead to acute kidney injury in individuals with ADTKD-*REN*. Acute kidney injury sometimes occurs in childhood, when volume depletion results from febrile illnesses. Patients usually recover from the acute kidney injury event, but there is some baseline chronic kidney disease that is identified.

Genetics and pathophysiology

The *REN* gene produces the renin precursor preprorenin. Preprorenin contains a signal sequence that directs endoplasmic reticulum targeting, glycosylation, and cleavage of the preprotein to form renin. In ADTKD-*REN*, affected individuals have a mutation in the signal peptide or prosegment of preprorenin. This mutation affects the targeting to or processing of preprorenin in the endoplasmic reticulum and results in reduced prorenin and renin biosynthesis and secretion. These changes lead to stress in the endoplasmic reticulum, leading to accelerated apoptosis, cell death, nephron dropout, interstitial fibrosis, and progressive loss of kidney function.

Diagnosis relies on genetic testing. Renin and aldosterone levels are in the low normal range in most patients when stimulated, making this measurement inadequate for diagnosis. Genetic analysis of the *REN* gene should be used to make a diagnosis.

Treatment

Unlike other forms of ADTKD, there are several specific treatments available. First, as these patients are in a low renin state with mild hypovolemia, it is important to avoid the low sodium diet that is commonly prescribed in chronic kidney disease. These patients will develop worsening hypotension and are prone to acute kidney injury on a low sodium diet. To treat the hyperkalemia and mild hypotension, a higher sodium content diet or fludrocortisone[28] may be beneficial. Fludrocortisone corrects the hypotension, hyperkalemia, and the hyperuricemia but does not improve the hemoglobin levels. Importantly, the fludrocortisone may lower production of renin (and the mutated renin). Decreased production of the mutated renin MAY slow progression of chronic kidney disease.

Future directions

We are currently studying whether fludrocortisone slows progression of chronic kidney disease in individuals with ADTKD-*REN*.

ADTKD due to hepatocyte nuclear factor-1 beta mutations

Hepatocyte nuclear factor-1 beta (HNF-1 beta) is produced by the *TCF2* gene. Mutations in this gene were first identified as a cause of maturity onset diabetes of youth.[29] with renal manifestations later identified.

Clinical manifestations

Identifying individuals with HNF-1 beta mutations may be difficult due to the many, varied manifestations and the fact that these manifestations are not consistently present in all affected family members, making identification of inheritance patterns and diagnosis difficult. For example, a grandfather may have had chronic kidney disease leading to dialysis; his daughter may have mildly abnormal liver functions of unknown cause and a solitary kidney, and the grandchild may have bilateral cystic kidneys detected on fetal ultrasound. Thus, it is important to be familiar with the different clinical manifestations, realizing that only one or two may be present in an affected individual.

Non-renal manifestations of ADTKD due to HNF-1 beta mutations may include: 1) maturity onset diabetes of youth. While HNF1 alpha mutations are the most common cause, HNF1 beta mutations may also result in MODY. Patients typically present at an age < 25 years and are initially non-insulin dependent. Pancreatic atrophy often develops, and patients become insulin dependent later in life. 2) Abnormal liver function studies of unclear etiology. Patients often suffer from mild elevations in alanine amino-transferase and gamma-glutamyl transpeptidase. Liver biopsy frequently reveals normal tissue and does not aid in the diagnosis. Patients retain normal hepatic function.[30] 3) Genito-urinary tract malformations may occur. 4) Hyperuricemia and gout may occur in adolescence, 5) Hypomagnesemia

occurs in some individuals. Other conditions that may be associated with this form of ADTKD include autism, cromophobe renal cell carcinoma, and early onset hyperparathyroidism.

Renal manifestations may begin *in utero*. In a study of 62 cases of fetal bilateral echogenic kidneys[31], 18% of patients suffered from a *TCF2* mutation, with 15 of 18 having a complete heterozygous deletion. In adulthood, renal manifestations are common and often involve congenital anomalies of the kidney and urinary tract.[32] Patients may have numerous renal cysts, congenital solitary kidney, renal dysplasia, or hypoplastic kidneys. Most patients have some degree of chronic kidney disease. About 20% of patients will progress to ESRD. Urinalysis usually reveals less than 1 gram of proteinuria/24 hours and no hematuria. The renal manifestations are quite variable within families, which may make diagnosis difficult. Patients with this disorder can be diagnosed with genetic testing.

Pathophysiology

HNF 1 beta is encoded by the *TCF2* gene. Both the kidney and the pancreas express the homeodomain-containing transcription factors hepatocyte nuclear factor 1 alpha and 1 beta. These genes regulate transcription of RNA and are expressed both in the pancreas and the kidneys. Massa et al. inactivated HNF1beta in the murine matanephric mesenchyme and showed that this led to marked distortion of the tubule, characterized by absence of the proximal, distal tubule and loop of Henle.[33] Thus it is likely that mutations in HNF1beta affect tubular development.

Diagnosis

The key to diagnosis is the recognition of the variable presentation of each affected individual, even within families. Any of the above signs or symptoms may be present and vary within families. Mutational analysis of the *TCF2* gene is the best method of diagnosis. Faguer and colleagues have developed a 17 item score to help determine if mutational analysis should be performed.[34] This score includes items such as family history, renal morphology, and presence of the conditions discussed above.

Treatment

There are no specific therapies available for the underlying mutation. Treatment is supportive for chronic kidney disease. For individuals with early onset gout, one should consider agents such as allopurinol or febuxostat to prevent urate accumulation and tophus development. Screening for hyperglycemia, hypomagnesemia, hyperuricemia, and abnormal liver function tests should be carried out. A renal ultrasound should be performed to evaluate for morphologic abnormalities. Any related individual interested in kidney transplant donation should undergo mutational analysis.

Other causes of ADTKD

There are a number of other autosomal dominant genetic syndromes with a spectrum of genetic abnormalities that include kidney failure and renal structural anomalies as one of their components.

Mutations in SEC61A1 are another cause of ADTKD.[35] Two families have been identified with this condition. In one family, intrauterine growth retardation, dysplastic kidneys and anemia were present. In another family, chronic kidney disease, anemia, and neutropenia with abscess formation were documented.

Alagille syndrome is due to mutations in *JAG1* or *NOTCH2*.[36] The condition has a variable presentation. Features include: cholestasis due to decreased bile ducts, cardiac abnormalities, ocular disease, and a characteristic facial finding including prominent forehead, deep-set eyes and moderate hypertelorism, a pointed chin, and a straight nose. Cardiac abnormalities include pulmonic stenosis in two-thirds of patients and tetralogy of Fallot, atrial septal defect, aortic stenosis, and coarctation of the aorta. Skeletal manifestations include butterfly shaped thoracic vertebrae. Ocular abnormalities include a posterior embryotoxon (a defect in the anterior chamber of the eye) that is found in at least 75% of affected individuals. Renal manifestations include slowly progressive chronic kidney disease that can lead to dialysis. Some patients have renal tubular acidosis. Patients should be evaluated for renal artery stenosis, which has an increased prevalence in Alagille syndrome.

Townes-Brocks syndrome is due to SALL1 mutations and is characterized by an imperforate anus, dysplastic ears and thumb malformations. Chronic kidney disease also occurs in about half of affected individuals, sometimes associated with anatomic malformations such as reflux, cystic kidneys or renal hypoplasia.[37]

HDR syndrome (hypoparathyroidism, deafness, and renal anomalies) – also known as Barakat syndrome – is caused by haploinsufficiency of the *GATA3* gene. Similar to HNF-1 beta and Townes-Brocks syndrome, renal involvement is varied. Cystic kidneys, renal hypoplasia, proximal and distal renal tubular acidosis, and nephrocalcinosis may occur.[38] Approximately 10% of patients will develop ESRD, at ages ranging from the second decade to the seventh decade of life.[39]

Overall approach to genetic testing

UMOD mutations are the most common cause of ADTKD, and *UMOD* mutational analysis should be considered as the first genetic test if there is a family history of early gout in some members. If there is no family history of gout prior to CKD, mutational analysis for *MUC1* should be considered. This test is currently unavailable in clinical laboratories; please contact us for testing. Directed genetic mutational analysis for other conditions requires on the presence of associated clinical conditions. For questions on the approach to genetic testing, please contact ableyer@wakehealth.edu

ADTKD with negative genetic testing

We are aware of approximately 15 ADTKD families in whom the genetic diagnosis has not been established. If available, we initially examine kidney biopsy samples for immunohistochemical abnormalities of uromodulin, mucin-1, hepatocyte nuclear factor-1 beta, and SEC61A1 deposition. This analysis may point to mutations in already established genes that were missed by standard genetic analyses. If no genetic cause is identified, we then proceed with whole exome/genome sequencing that may provide the diagnosis.[40]

Summary

The most important consideration in the approach to ADTKD is to achieve a definitive diagnosis by genetic testing for affected families. ADTKD should be considered when CKD affects both a parent and child, together with the absence of proteinuria or hematuria. Genetic studies are the best method to make the diagnosis.

At this time we are recruiting as many patients with ADTKD as possible for observational and interventional studies. As these conditions are rare, we would appreciate if you would contact us regarding any families with a definitive diagnosis or potential diagnosis of ADTKD. We can help arrange genetic testing and provide free, clinical genetic testing for *MUC1* mutations.

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- There are three primary causes of ADTKD: mutations in the *UMOD* gene encoding uromodulin (Tamm Horsfall glycoprotein), mutations in the *REN* gene encoding renin, and mutations in the *MUC1* gene encoding mucin-1.
- These conditions should be suspected if both a parent and child have kidney disease, and if the urinalysis reveals a bland sediment.
- In all three conditions there is a variable rate of progression of chronic kidney disease, with the age of onset of end-stage kidney disease ranging from 17 to >75.
- These conditions should be diagnosed by genetic testing and not by kidney biopsy.
- In patients with ADTKD-*REN*, a low sodium diet should be avoided, and a high sodium diet or fludrocortisone should be considered as treatments.
- In patients with ADTKD-*UMOD*, allopurinol will prevent the development of gout and may slow progression of kidney disease.
- Treatment of ADTKD-*MUC1* is supportive.

Table 1

Characteristics of Three Major Causes of Autosomal Dominant Tubulo-Interstitial Kidney Disease.

	ADTKD-*UMOD*	**ADTKD-*MUC1***	**ADTKD-*REN***
Abbreviated name	Uromodulin Kidney Disease (ADTKD-UMOD)	Mucin-1 Kidney Disease (ADTKD-MUC1)	ADTKD-REN
Inheritance	Autosomal dominant	Autosomal Dominant	Autosomal Dominant
Urinary sediment	Bland	Bland	Bland
Gout	May occur in childhood; frequent	Occurs in advanced CKD, similar to other kidney diseases	May occur in childhood; frequent
Other symptoms	None	None	Anemia, mild hyperkalemia, mild hypotension, prone to acute kidney injury
Age of ESRD	47 (19 to > 75)	43 (17 to >75)	50 (30–>60)
Knockout mouse	No disease	No disease	Lethal mutation
Pathophysiology	Intracellular deposition of mutated uromodulin leading to CKD	Intracellular deposition of mutated mucin-1 leading to CKD	Intracellular deposition of mutated renin
Diagnosis	Genetic testing at commercial lab	Contact ableyer@wakehealth.edu	Genetic testing at research lab
Treatment	Allopurinol to prevent gout; may slow progression of CKD	No known treatment	High sodium diet or fludrocortisone